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Controlling Helix Handedness in Water-Soluble Quinoline Oligoamide Foldamers

Simon J. Dawson,[a,b] Ádám Mészáros,[c] Lilla Pethő,[c] Cinzia Colombo,[a,b] Márton Csékei,[c] András Kotschy,*[c] and Ivan Huc*[a,b]

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For biological applications, the control of the helix handedness of water-soluble quinoline-based oligoamide foldamers has been investigated by the installation of chiral end groups at either the C or N terminus. This has resulted in the development of monomer units capable of unequivocally inducing helical sense without impacting the aqueous solubility. Furthermore, we showed that very slow helix handedness inversion in water can be exploited. The incorporation of a chiral moiety with no handedness-induction properties allows the chromatographic separation of *P* and *M* helices as diastereoisomers with kinetically locked handedness.

Introduction

The chirality of secondary structures such as helices is a property fundamental to the complex molecular interactions involved in cellular processes, for example, at protein–protein interfaces. The importance of diastereomeric selectivity in biological target recognition highlights the need to investigate right-handed (*P*) or left-handed (*M*) conformers of helical foldamers as distinct entities, as such compounds are considered to be useful ligands for biopolymer recognition.[1] By extension, the ability to reliably induce helix handedness under biocompatible conditions is a must.

The induction of handedness in helical foldamers is an attractive concept, as it allows the display of functionality in a specific one-handed array along the face of a scaffold and, thus, the potential ability to recognize a particular biological surface with high selectivity. The induction of handedness is inherent in peptidic foldamers as chirality is imparted by the amino acid building blocks.[2] Aromatic amide backbones do not possess stereogenic centres and form racemic mixtures of *P* and *M* helices in solution.[3] Therefore, in this case, it is necessary to consider other methods for the control of handedness.

Helical aromatic oligoamide foldamers, such as those consisting of 8-amino-2-quinolinecarboxylic acid (Figure 1), feature properties that make them promising candidates for the recognition of protein and nucleic acid surfaces: they adopt well-defined, predictable conformations, they are medium sized (0.5–5.0 kDa), they are resistant to proteolytic degradation and have been shown to possess cell-penetrating properties.[4] However, as they do not closely resemble the biological structures they mimic, the challenge to design ligands for proteins and nucleic acids becomes all the more difficult. One rapid method for screening quinoline oligoamides for activity against a given biological surface relies on the fact that short sequences (<5 units) without any stereogenic centre exist as a mixture of interconverting *P* and *M* helical conformations. If binding to a target surface is helix sense dependent, then the equilibrium will be shifted towards the preferred conformer, and this process can be monitored by induced circular dichroism (ICD). Indeed, the *P* and *M* helices possess opposite sign CD bands that cancel each other. When equilibrium deviates from a 50:50 mixture, CD bands emerge. This technique has recently been used to screen short quinoline oligoamide sequences tethered to human carbonic anhydrase II (HCA) through a ligand (Figure 2), and a sequence was

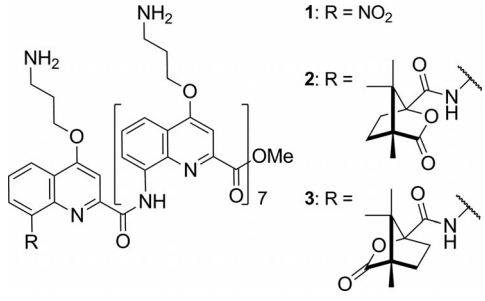

Figure 1. Cationic octamer and camphanyl inducing groups.

[a] Université de Bordeaux, CBMN (UMR 5248), Institut Européen de Chimie et Biologie,
2 rue Robert Escarpit, 33607 Pessac, France
E-mail: i.huc@iecb.u-bordeaux.fr
www.iecb.u-bordeaux.fr
[b] CNRS, CBMN (UMR5248), Institut Européen de Chimie et Biologie
2 Rue Robert Escarpit, 33607 Pessac
[c] Servier Research Institute of Medicinal Chemistry,
Záhony utca 7, 1031 Budapest, Hungary

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identified that not only possessed affinity for the protein surface but also induced the formation of a new HCA dimer.[5] The induction of helix handedness has also been observed between a fully cationic side-chain-functionalized tetramer and G-quadruplex DNA[6] and between helical capsules and their chiral guests.[7] In the former two cases, handedness induction is not required, because the biological target itself exerts control over helix sense.

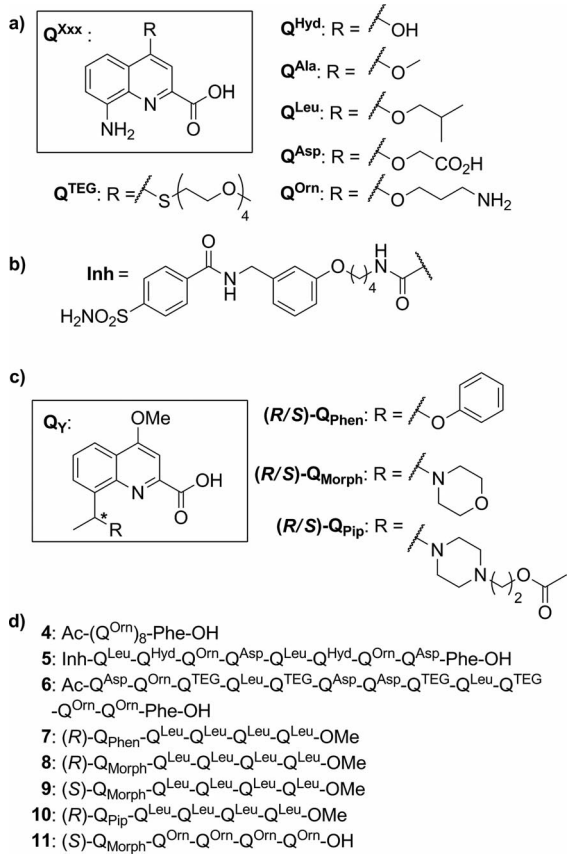


Figure 2. (a) Q^{Xxx} monomers, (b) HCA inhibitor structure, (c) Q_Y chiral monomers and (d) summary of foldamer sequences.

However, the kinetics of helix handedness inversion of 8-amino-2-quinolinecarboxylic acid oligoamides slow down as strand length increases.[8] This effect is so pronounced in protic solvents that handedness becomes kinetically stable for octameric sequences,[9] and a biological target is not required as a handedness inducer. An alternative is to induce helix handedness in the oligomer through the incorporation of a chiral unit either at an end[10] or middle[11] of the sequence or by the presence of a chiral side chain.[12] Both enantiomers can then be assessed independently for binding affinity to the target. This approach has been used in the assessment of G-quadruplex DNA binding of quinoline oligoamide foldamers. The systematic evolution of ligands by exponential enrichment (SELEX)[13] was used to identify G-rich aptamers with affinity for a fully cationic side-chain-functionalized octamer (**1**, Figure 1). The separate *P* and *M* helices of the octamer were then produced by installation of the (1*S*)-(–)-camphanyl (**2**) or (1*R*)-(+)-camphanyl (**3**) group, respectively, at the N terminus,[10i] and the aptamer candidates were then reassessed for binding, and one example indicated a preference for the *M* helix.[14]

However, the quantitative induction of helix handedness ($de > 99\%$) is a challenging objective, and success has been limited to a few cases.[6,10i,15] Although the camphanyl group can successfully induce handedness in aromatic oligoamide foldamers, its bulky and hydrophobic nature may be problematic with respect to the water solubility of the final compound and also to the function of the foldamer as an efficient ligand.[14] Therefore, it was clear to us that there was a need to further develop methods to control the helix handedness of quinoline oligoamide foldamers for applications in water.

Presented here are two methods that allow the preparation of isolated *P* and *M* helices of water-soluble quinoline oligoamides. Firstly, we investigated the concept that the incorporation of a chiral moiety with no handedness-induction properties could potentially allow chromatographic separation of *P* and *M* helices as diastereoisomers, as longer sequences (>6 units) are essentially kinetically "locked" into position under aqueous conditions. Secondly, we studied the effect of appending a chiral moiety onto the 8-position of a quinoline monomer unit (Q_Y, Figure 2), which could potentially allow it to act as an N-terminal handedness inducer.

These units were deliberately designed to permit solubility under both organic and aqueous conditions. This allowed us to incubate the foldamer in organic solvents and take advantage of the fast handedness-inversion kinetics to quickly reach equilibrium and then subsequently "lock" the handedness conformation in water.

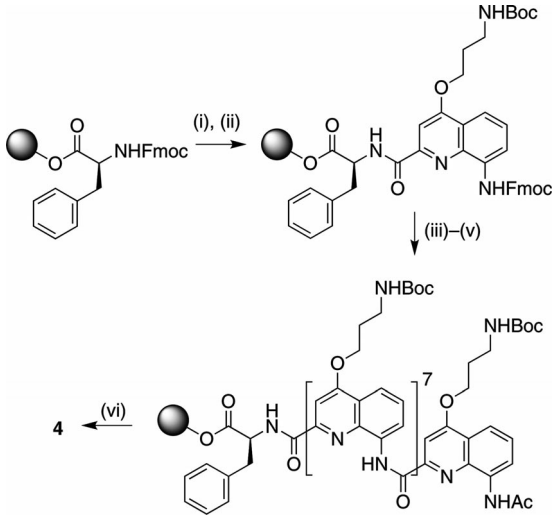
Results and Discussion

Separation of Diastereoisomers Arising from Helix Handedness

Previously, the installation of a C-terminal phenylalanine group was found to be a poor method for controlling helix handedness in organic solvents.[10b] However, it was noted that the resulting *P* and *M* diastereoisomers possessed strikingly different retardation factors on silica gel chromatography, which allowed their separation at low temperatures. Reequilibration of each isolated diastereoisomer to the racemic mixture then rapidly occurred at room temperature. We reasoned that if the same principle could be applied to reversed-phase (RP) chromatography with water-soluble oligomers, we could take advantage of the kinetic inertness under aqueous conditions to isolate diastereoisomers that would not racemize, provided they were exposed only to aqueous solvent mixtures.

Initial work focussed on the preparation of the all-cationic side-chain-functionalized octamer (**4**, Figure 2). Low-loading Wang resin was functionalized with Fmoc-Phe-OH (Fmoc = fluorenylmethyloxycarbonyl) by using the well-documented anhydride method.[16] Fmoc deprotection was then performed with piperidine in *N*,*N*-dimethylformamide (DMF; 20% v/v), and the first Fmoc-Q^{Orn} unit was in-

stalled through its acid chloride, which was formed by using 1-chloro-*N*,*N*,2-trimethyl-1-propenylamine (Scheme 1).[17] The oligoamide was then prepared by the microwave-assisted Fmoc solid-phase synthesis (SPS) strategy previously reported by our group (see Exp. Sect.).[18] Removal from the resin with concomitant side-chain *tert*-butyloxycarbonyl (Boc) deprotection was subsequently performed by treatment of the resin with 95:2.5:2.5 TFA/H_2O/*i*Pr_3SiH v/v/v (TFA = trifluoroacetic acid). The crude material was analyzed by RP-HPLC and indeed was found to consist of two well-separated main products (Figure 3) of approximately equal peak area; this was in concordance with the ^1H NMR analysis, which demonstrated the presence of 14 amide signals that correspond to two discrete octameric products (Figure 4, a).



Scheme 1. SPS of fully cationic-side-chain octamer **4**. Reagents and conditions: (i) 20% v/v piperidine in DMF, room temp., 10 min, repeat once; (ii) (a) Fmoc-$Q^{Orn(Boc)}$-OH, 1-chloro-*N*,*N*,2-trimethyl-1-propenylamine, CH_2Cl_2, r.t., 1 h; (b) product from (a), *i*Pr_2EtN, THF, microwave 50 W, ramp to 50 °C, hold 50 °C for 15 min, repeat once; (iii) 20% v/v piperidine in DMF, r.t., 10 min, repeat twice; (iv) repeat steps (ii)–(iii); (v) acetyl chloride, *i*Pr_2EtN, THF, microwave 50 W, ramp to 60 °C, hold 60 °C for 15 min, repeat once; (vi) TFA/*i*Pr_3SiH/H_2O (95:2.5:2.5), r.t., 2 h.

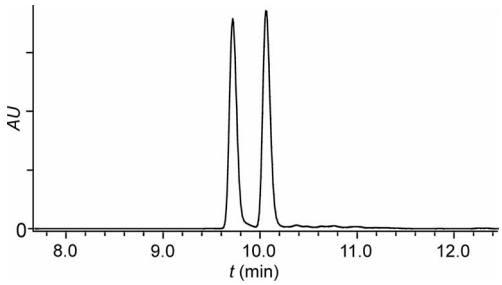


Figure 3. HPLC profile showing separation of the diastereoisomers of **4**. First eluting peak identified by CD (see Figure 5) as *P*-**4**, second eluting peak identified as *M*-**4**.

The crude mixture was purified by preparative RP-HPLC, and analysis of each product by ^1H NMR spectroscopy and mass spectrometry confirmed their identity as

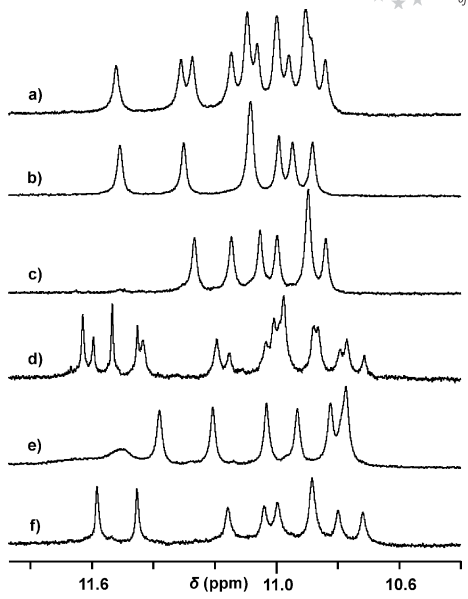


Figure 4. Carboxamide region of the ^1H NMR spectra of **4** and **5** in [D_6]DMSO at 298 K: (a) crude mixture of diastereoisomers of **4** after SPS (reflects the ratio of diastereoisomers in the TFA cleavage mixture), (b) (*P*)-**4**, (c) (*M*)-**4**, (d) crude mixture of diastereoisomers of **5** after SPS, (e) (*P*)-**5** and (f) (*M*)-**5**.

the expected octameric diastereoisomers. Analysis of the CD spectrum of each product was also important to confirm the separation of the *P* and *M* helices. Although the *P*-**4** and *M*-**4** helices are diastereomers and not enantiomers, the helical aromatic foldamer parts of their structures are mirror images and give rise to virtual "mirror image" spectra of opposing sign. Indeed, CD experiments (Figure 5) showed the expected deflections at 390–410 nm, the absorption region of the quinoline chromophores. By analogy to previous work,[10b] the first eluted diastereoisomer was determined to be the *P* helix (positive band near 400 nm), and the second was determined to be the *M* helix (negative band).

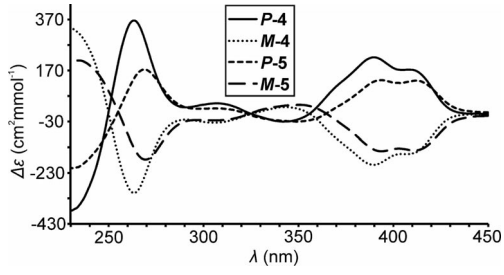


Figure 5. CD spectra of separated *P* and *M* diastereoisomers of 50–60 μM solutions of **4** and **5** in H_2O and H_2O/DMSO (99:1), respectively, at 293 K.

The stability of the separate diastereoisomers of **4** in water was assessed by HPLC, which revealed no detectable interconversion between handedness forms over a period of five days at room temperature. Unlike peptidic α helices, which tend to be destabilized when they consist exclusively of positively charged residues,[19] cationic aromatic oli-

goamide helices remain stable even when they possess multiple positive charges. This was in contrast to their behaviour in dimethyl sulfoxide (DMSO), in which a degree of racemization was observed after only two hours and complete equilibration after 2–3 d (see Supporting Information). Interestingly, in DMSO, it appears that the phenylalanine unit possesses a moderate ability to induce helix sense, and there is ca. 40% diastereomeric excess in favour of the *P* helix.

The ability to separate *P* and *M* helices by using a C-terminal group allows the N terminus to be left free for other purposes, that is, the incorporation of functionalities. This was of interest to us with respect to recent results concerning the attachment of foldamers to HCA through an N-terminal inhibitor moiety.[5] Therefore, we tested the separation of helix sense diastereoisomers in the context of HCA ligands and used SPS to prepare octamer **5**, which includes an N-terminal HCA inhibitor moiety and a C-terminal Phe unit (Figure 2). Once again, the crude HPLC demonstrated the presence of two major products assigned to the *P* and *M* helices. This was also reflected in the ^{1}H NMR spectrum (Figure 4, d). The separation of the two diastereoisomers by preparative HPLC was also straightforward, and both could be obtained in reasonable purity and afforded analogous CD profiles to those of **4** (Figure 5). Interestingly, the order of diastereoisomer elution was the same as previously, that is, the *P* helix eluted first.

The aqueous stability of the separate diastereoisomers of **5** was also assessed, although for solubility reasons this required the addition of a small proportion (0.5–1%) of DMSO. Once again, no interconversion between handedness forms could be detected over a period of five days at room temperature (see Supporting Information).

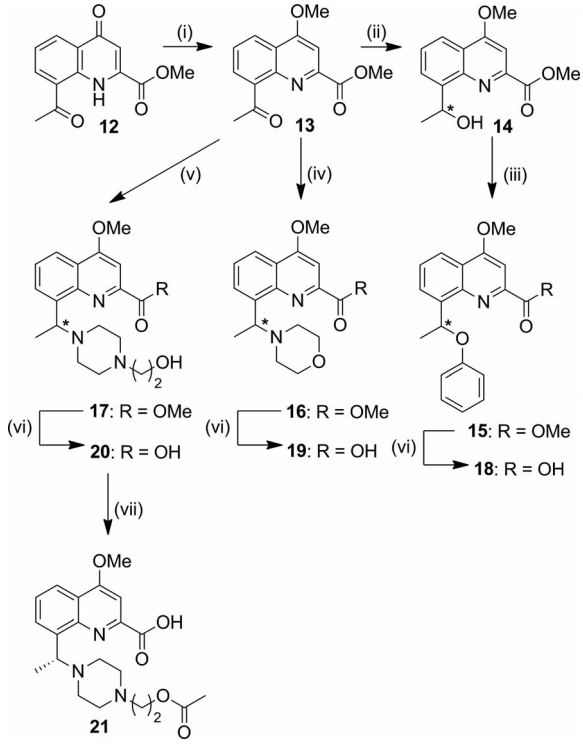
Considering the diverse nature of the side chains in comparison to those of the octamer **4**, this data suggested to us that this method could potentially be applied to a greater range of sequences. To determine whether this method could be used to access pure diastereoisomers of longer foldamers, we prepared the 12-mer **6** (Figure 2). HPLC analysis again revealed the presence of two distinct diastereoisomers, as confirmed by MS and ^{1}H NMR spectroscopy, but baseline separation could not be afforded with a number of different gradients and, thus, preparative HPLC was not attempted in this case.

In summary, the incorporation of a chiral centre at the C terminus afforded separable helix sense diastereoisomers of two octameric sequences with diverse side-chain functionality. This way, both *P* and *M* helices could be afforded by a single synthesis. The separated diastereoisomers were kinetically inert in water over long periods (days). This is important with respect to their use for targeting protein surfaces, as each diastereoisomer could be assessed separately for binding by techniques such as surface plasmon resonance (SPR) without the risk of racemization. Shorter sequences (≤5 units) can simply be presented to the target as a racemic mixture, and the interactions can be assessed by ICD, as this is permitted by their faster handedness-inversion kinetics.

Induction of Helix Handedness through an N-Terminal Quinoline-Based Chiral Building Block

We sought to further enhance our toolkit for the isolation of discrete helix handedness forms and to develop a method that could be applied regardless of the sequence, in particular, for longer oligomers that are not amenable to diastereomer separation. This led us to reconsider the possibility of using a terminal functional group with the ability to induce handedness. Our experiments with inducing groups at the N and C termini demonstrated incomplete handedness induction, except in the case of the large and hydrophobic camphanyl group.[10a–10c,10i] We speculated that bringing stereogenic centres as close as possible to the quinoline backbone might offer strong inducing properties and decided to introduce a chiral centre directly connected to the 8-position of an N-terminal quinoline unit. Furthermore, we chose groups that would potentially allow solubility in a range of solvents. This way, long foldamers could be designed to allow incubation in an organic solvent, in which inversion kinetics are relatively fast; after completion of the induction, transfer to water would then lock the conformation.

Three designs were proposed, all of which are accessible from a common ketone precursor **12** (Scheme 2), the synthesis of which has been described previously.[20] One face



Scheme 2. Synthesis of chiral quinoline monomers. Reagents and conditions: (i) Me_2SO_4, K_2CO_3, acetone, reflux, 1 h; (ii) $NaBH_4$, $C_2H_4Cl_2$, 55 °C, 8 h; (iii) phenol, di-*tert*-butyl azodicarboxylate (DBAD), PPh_3, toluene, 80 °C, 3 h; (iv) morpholine, $Na(OAc)_3BH$, $C_2H_4Cl_2$, 55 °C, 24 h; (v) 2-(1-piperazinyl)ethanol, $Na(CN)BH_3$, AcOH, $C_2H_4Cl_2$, 55 °C, 3 h; (vi) $LiOH·H_2O$, dioxane/H_2O, 1 h; (vii) Ac_2O, diisopropylethylamine (DIEA), $CHCl_3$, 4 h [performed on (*R*)-**20**].

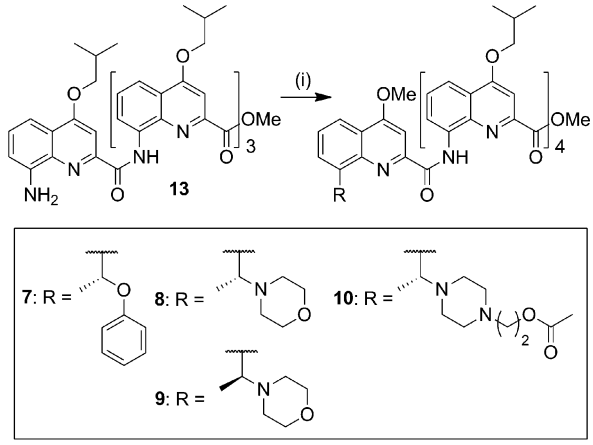
of the Q_{Phen} monomer (Figure 2) is hindered by the steric bulk of a pendant phenoxy group. This was also hoped to stabilize the preferred helix formation through stacking interactions.

The remaining two designs incorporated either morpholine or piperazine through the amine functionality. Although these would not be capable of stacking interactions with the aromatic foldamer backbone, they would be useful as solubilising groups. In addition, the installation of a piperazine moiety might also allow further functionalization of the foldamer through the terminal amine group.

The starting quinolinone **12** was functionalized with a simple methoxy group at the 4-position to yield the common ketone precursor. This was then either reduced and subsequently treated with phenol under Mitsunobu conditions to yield the racemic Q_{Phen} monomer or the morpholine or piperazinylethanol moiety was incorporated by direct reductive amination. The subsequent separation of each enantiomer from the racemic mixture by preparative chiral HPLC was followed by saponification to yield the free acids of the monomers. The terminal alcohol functionality of the Q_{Pip} monomer was then acetylated before activation as the acid chloride to avoid the possibility of side-reactions at this position. The configurations of both enantiomers of the Q_{Morph} monomer were confirmed by their crystal structures. The remaining monomers proved difficult to crystallize. Therefore, their configurations were inferred from their CD signs at 300 nm by comparison with those of the Q_{Morph} enantiomers (see Supporting Information).

To assess handedness induction by Q_{Pip}, Q_{Morph} and Q_{Phen}, we initially designed a pentameric sequence with side-chain functionality compatible with a range of organic solvents. We have previously demonstrated that adjusting the length of an oligomer and the solvents in which it is dissolved gave us the ability to "tune" the rate of helix handedness inversion.[8,9] In this case, a pentameric sequence in a nonpolar solvent such as chloroform would possess slow enough handedness-inversion kinetics on an NMR timescale that the separate diastereoisomers could be visualized as a distinct set of resonances. However, this behaviour would still be sufficiently fast that equilibration between handedness forms would be complete after minutes; thus, the degree of handedness induction could be accurately assessed. Therefore, quantitative induction could be initially determined by analysis of the ^{1}H NMR spectrum, which should show a single set of resonances. Analysis by CD would then confirm the induction of a single helix handedness form, as indicated by a deflection at the quinoline chromophore absorption region; the possibility that the separate diastereoisomers possess exactly overlapping NMR resonances is discounted.

The tetramer amine **13** (Scheme 3) was synthesized by the procedures previously reported by our group[21] and functionalized with a terminal chiral building block as the acid chloride. The tertiary amine groups of the Q_{Morph} and Q_{Pip} units could interfere with the activation. The prior protonation of these amines allowed the clean activation of acid functions into acid chlorides. No such problems were associated with the Q_{Phen} building block.



Scheme 3. Synthesis of pentamers bearing N-terminal handedness inducing groups from the tetramer amine precursor **13**. Reagents and conditions: (i) (a) chiral monomer unit, 1-chloro-*N*,*N*,2-trimethyl-1-propenylamine, CH_2Cl_2, room temp., 1 h; (b) product from (a), *i*Pr_2EtN, $CHCl_3$, r.t., 20 h. [the configuration of **10** was inferred from its CD spectrum (i.e., the resulting induction of *M* helix) and comparison between the CD spectra of Q_{Pip} and Q_{Morph}. See Supporting Information].

^{1}H NMR analysis of pentamer **7** indicated the presence of both *P* and *M* diastereoisomers in an almost 1:1 ratio, as demonstrated by the eight carboxamide resonances between δ = 11 and 12 ppm (Figure 6). This was confirmed by CD experiments (Figure 7), which showed negligible de-

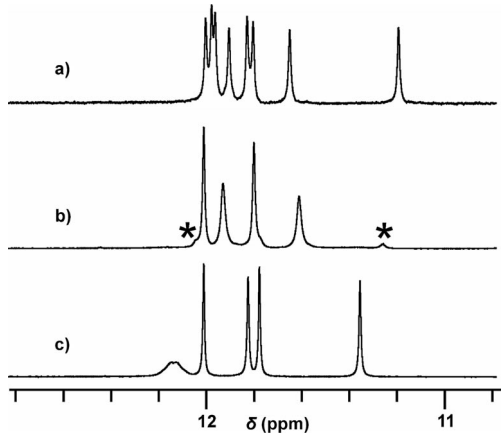


Figure 6. Carboxamide region of the ^{1}H NMR spectra of (a) **7**, (b) the unprotonated form of **8** (* shows a minor set of peaks) and (c) the hydrochloride salt of **8** in $CDCl_3$ at 298 K.

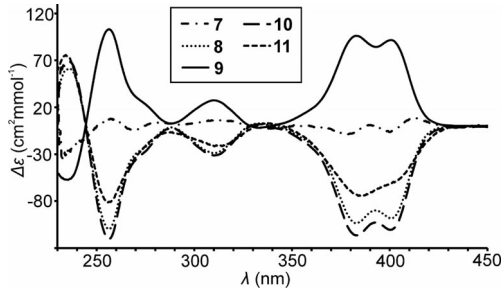


Figure 7. CD spectra of 50–60 μM solutions of **7**–**10** in $CHCl_3$ and **11** in H_2O at 293 K.

flection at 390–410 nm. In contrast, pentamers **8** and **9** with the *R* and *S* enantiomers of the Q_{Morph} monomer, respectively, were each found to afford an identical single set of ^{1}H NMR signals, which indicates quantitative handedness induction. This was also observed in $CD_3CN/CDCl_3$ (3:1), [D_3]MeOH and [D_6]DMSO. Compound **8** was found to retain one set of NMR signals in [D_6]DMSO for more than four weeks at room temperature and even after 24 h at 50 °C.

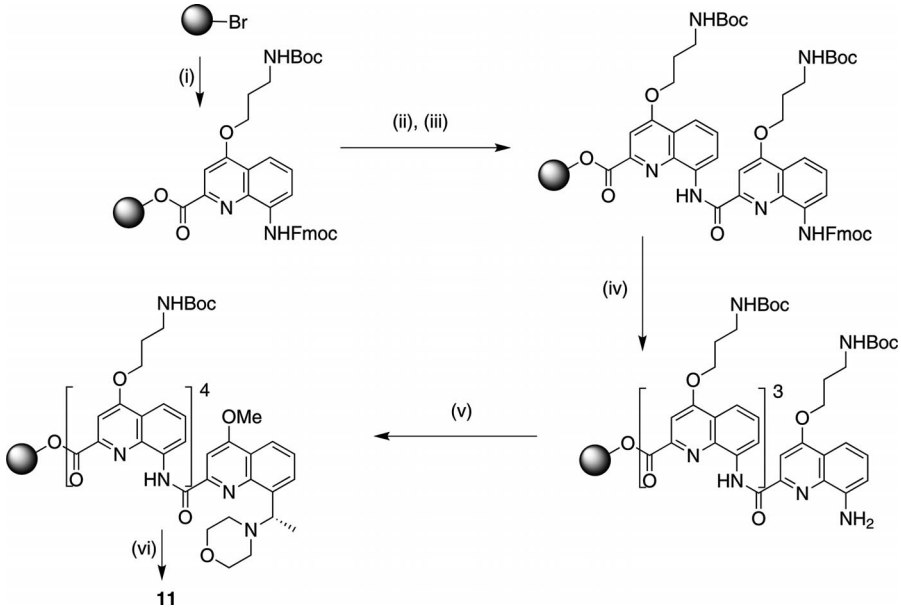
Analysis by CD confirmed single helix handedness, and intense bands were observed at 390–410 nm. Again, by analogy to previous work, the negative sign of these bands indicate a preferred *M* handedness for **8**, which possesses the (*R*)-Q_{Morph} monomer, and the inverse was observed for **9** [with the (*S*)-Q_{Morph} monomer], which indicates that *P* handedness is preferred. Interestingly, the protonation state of the morpholine unit appeared to slightly enhance handedness-induction efficiency; the ^{1}H NMR spectrum of the unprotonated form of **8** showed the presence of minor amide resonances (Figure 6), thought to be those of the unfavoured *P* diastereoisomer, which were eliminated on conversion to the hydrochloride salt. CD experiments (see Supporting Information) supported this, and the small reduction in intensity observed for the unprotonated form perhaps indicates a slight decrease in induction efficiency.

The Q_{Pip} monomer also demonstrated an ability to quantitatively induce helix handedness; compound **10** showed a negative CD deflection of approximately the same magnitude as that of **8** at 390–410 nm. This indicates that the monomer is of the *R* configuration and supports our earlier inference from comparison of the Q_{Pip} CD spectra with those of Q_{Morph}. As with the morpholine-functionalized monomer, the protonation state appeared to slightly affect induction efficiency (see Supporting Information).

To assess handedness-induction efficiency in water, we returned to the solid-phase synthesis methodology for the production of a simple pentameric sequence consisting of an N-terminal (*R*)-Q_{Morph} monomer plus four Q^{Orn} residues. Including the morpholine functionality, this sequence would be a pentacationic species after deprotection and, thus, was anticipated to be highly water-soluble at neutral pH or below. In addition, this pentameric sequence would also possess handedness-inversion kinetics fast enough in water to permit racemization and, thus, the assessment of handedness induction in this medium.

Low-loading Wang bromide resin was prepared by using the procedure of Morales and co-workers[22] and functionalized with the first quinoline monomer in the presence of Cs_2CO_3.

The Fmoc group was deprotected, and SPS was continued by using the methodology previously detailed in the literature (Scheme 4). The activation of the (*R*)-Q_{Morph} unit was preceded by protonation of its tertiary amine group to enable efficient coupling. The crude foldamer was removed from the resin with 50:48:2 TFA/CH_2Cl_2/*i*Pr_3SiH v/v/v and purified by RP-HPLC. ^{1}H NMR analysis of the product in both D_2O and [D_6]DMSO revealed the presence of a single set of signals, indicative of quantitative handedness induction, and this was confirmed by CD experiments, which showed the expected negative deflection (Figure 7). Compound **11** was found to remain as one set of NMR signals in D_2O even after 48 h at 40 °C.



Scheme 4. SPS of water-soluble pentamer with N-terminal helix sense inducing group. Reagents and conditions: (i) Fmoc-$Q^{Orn(Boc)}$-OH, Cs_2CO_3, *i*Pr_2EtN, DMF, microwave 50 W, ramp to 50 °C, hold 50 °C for 5 min, repeat once; (ii) 20% v/v piperidine in DMF, room temp., 10 min, repeat twice; (iii) (a) Fmoc-$Q^{Orn(Boc)}$-OH, 1-chloro-*N*,*N*,2-trimethyl-1-propenylamine, CH_2Cl_2, r.t., 1 h; (b) product from (a), *i*Pr_2EtN, THF, microwave 50 W, ramp to 50 °C, hold 50 °C for 15 min, repeat once; (iv) repeat steps (ii)–(iii); (v) (a) (*R*)-Q_{Morph}, 1-chloro-*N*,*N*,2-trimethyl-1-propenylamine, CH_2Cl_2, r.t., 1 h; (b) product from (a), *i*Pr_2EtN, $CHCl_3$, microwave 50 W, ramp to 50 °C, hold 50 °C for 30 min, then repeat at r.t., 20 h.

Conclusions

Two methods for the isolation of separate *P* and *M* helices of quinoline oligoamides have been assessed. The incorporation of a phenylalanine residue at the C terminus of two diversely functionalized water-soluble octamers in both cases afforded a mixture of the *P* and *M* diastereoisomers with strikingly different retention times. RP-HPLC separation of the diastereoisomers was straightforward, and each demonstrated a marked stability in water, which indicates the extremely slow kinetics of handedness inversion under these conditions, regardless of side-chain composition and even in the case of multicationic species. The facility of this method and the availability of the N terminus for further functionalization make it attractive when foldamer length (and therefore the resulting slow kinetics of handedness inversion) preclude the use of ICD to determine chirality-dependent interactions with biological targets such as protein surfaces.

Two chiral quinoline monomers offered quantitative induction of helix handedness in both organic and aqueous conditions when installed at the N termini of pentameric sequences. These units should provide solubility in a greater range of solvents than the camphanyl group and, owing to their smaller steric bulk, may be less likely to disrupt potential foldamer–biomolecule interactions. In addition, the piperazine moiety provides the opportunity for further functionalization of the foldamer after the chiral unit, for example, the tethering of fluorescent probes or small-molecule enzyme inhibitors.

These methods for handedness control will serve not only to aid investigation into the chirality dependence of foldamer–target interactions but also to facilitate the isolation of discrete, stable handedness forms of a foldamer sequence for use in biological and biophysical assays.

Experimental Section

General Methods: Low-loading Wang resin was purchased from Novabiochem. Ghosez reagent (1-chloro-*N*,*N*,2-trimethyl-1-propenylamine) was purchased from Sigma–Aldrich. *N*,*N*-Diisopropylethylamine was distilled from calcium hydride. Analytical grade organic solvents were used for solid-phase synthesis. Anhydrous tetrahydrofuran (THF) and $CHCl_2$ for solution and solid-phase synthesis were dispensed from an MBRAUN SPS-800 solvent purification system. HPLC-quality acetonitrile and MilliQ water were used for RP-HPLC analyses and purification. Reactions requiring anhydrous conditions were performed under nitrogen. ^{1}H NMR spectra were recorded at 300, 400 or 500 MHz, and ^{13}C NMR spectra were recorded at 75, 100 or 125 MHz. Chemical shifts are reported in ppm and are calibrated against the residual solvent signals of $CDCl_3$ (δ = 7.26, 77.2), [D_6]DMSO (δ = 2.50, 39.4) or D_2O (δ = 4.79 ppm). All coupling constants are reported in Hz. Signal multiplicities are abbreviated as s, singlet; br s, broad singlet; d, doublet; t, triplet; q, quartet; m, multiplet, dd, doublet of doublets. Silica gel chromatography was performed with Merck Kieselgel Si 60. Thin layer chromatography was performed with Merck Kieselgel Si 60 F254 plates. Chiral preparative HPLC was performed by using a Daicel Chiralpak AD column with isocratic ethanol/heptane mixtures as the eluent at either 100 (Q_{Phen} synthesis) or 50 mL min^{-1} (Q_{Morph} and Q_{Pip} syntheses). RP-HPLC analyses were performed at 1.5 mL min^{-1} by using a Macherey–Nagel Nucleodur C18 or C8 gravity column (4.6 × 100 mm, 3 μm). The mobile phase was composed of 0.1% (v/v) TFA/H_2O (solvent A) and 0.1% TFA/CH_3CN (solvent B) with the following gradients: 5–30% B over 13 min, then 30–100% B over 5 min (system A), 5–100% B over 13 min then 100% B for 5 min (system B) or 20–60% B over 25 min then 60–100% B for 5 min (system C). Monitoring was performed by UV detection at 214, 254 and 300 nm with a diode array detector. Semipreparative purifications of oligomers were performed at 4 mL min^{-1} by semipreparative HPLC by using a Macherey-Nagel Nucleodur C18 HTEC column (21 mm × 125 mm, 5 μm). The mobile phase was the same as for the analytic system with the following gradients: 5–26% B over 40 min (system D), 5–40% B over 20 min (system E) or 20–55% B over 35 min (system F). Monitoring was performed by UV detection at 254 and 300 nm with a diode array detector. High-resolution electrospray ionization time of flight (ESI-TOF) mass spectra were recorded in the positive ion mode with a Waters/Micromass Q-Tof Ultima spectrometer. X-ray diffraction experiments were performed with a high-flux RIGAKU FRX rotating anode at the Cu-K_α wavelength.

CCDC-990870 [for (1*R*)-**16**] and -990871 [for (1*S*)-**16**] contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Monomer Synthesis: Fmoc-Q^{Hyd}, Fmoc-Q^{Ala}, Fmoc-Q^{Leu}, Fmoc-Q^{Asp} and Fmoc-Q^{Orn} were synthesized by using the methods previously reported.[4,17] Fmoc-Q^{TEG} was provided by the Servier Research Institute of Medicinal Chemistry, Hungary.

Methyl 8-Acetyl-4-methoxyquinoline-2-carboxylate (13): Methyl 8-acetyl-4-hydroxyquinoline-2-carboxylate[20] (491 mg, 2.00 mmol) was dissolved in acetone (10 mL), and potassium carbonate (553 mg, 4.00 mmol) and dimethyl sulfate (182 μL, 2.00 mmol) were added. The mixture was stirred at reflux for 1 h and then cooled to room temp. Water was added, and the resulting precipitate was collected by filtration and washed with water to afford the title compound as a white solid (424 mg, 82%). ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 8.30 (dd, *J* = 8.3, 1.5 Hz, 1 H), 7.93 (dd, *J* = 7.1, 1.5 Hz, 1 H), 7.73 (dd, *J* = 8.3, 7.1 Hz, 1 H), 7.57 (s, 1 H), 4.13 (s, 3 H), 3.96 (s, 3 H), 2.88 (s, 3 H) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 202.9, 165.6, 163.5, 149.3, 145.2, 139.9, 130.6, 127.9, 125.2, 121.8, 101.1, 57.1, 53.4, 33.2 ppm. HRMS: calcd. for $C_{14}H_{13}NO_4$ [M + H]$^+$ 259.0845; found 260.0916.

Methyl 8-(1-Hydroxyethyl)-4-methoxyquinoline-2-carboxylate (14): Methyl 8-acetyl-4-methoxyquinoline-2-carboxylate (7.519 g, 29.00 mmol) was dissolved in dry 1,2-dichloroethane (200 mL), and sodium borohydride (3.292 g, 87.00 mmol) was added. The mixture was stirred at 55 °C for 8 h and then cooled to room temp. The mixture was diluted with dichloromethane (100 mL), and acetic acid was added to quench the reaction. The mixture was then washed with water and brine and extracted with CH_2Cl_2. The combined organic layers were dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (heptane/EtOAc) to afford the title compound as a white solid (5.096 g, 67%). ^{1}H NMR (500 MHz, [D_6]-DMSO): δ = 8.07 (dd, *J* = 8.3, 1.4 Hz, 1 H), 7.94 (d, *J* = 7.0 Hz, 1 H), 7.68 (dd, *J* = 8.1, 7.3 Hz, 1 H), 7.55 (s, 1 H), 5.84 (m, 1 H), 5.36 (d, *J* = 4.7 Hz, 1 H), 4.12 (s, 3 H), 3.96 (s, 3 H), 1.45 (d, *J* = 6.4 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, [D_6]DMSO): δ = 166.0, 163.4, 148.4, 146.5, 145.1, 128.2, 126.9, 121.6, 120.2, 100.5, 64.5, 56.9, 53.3, 26.2 ppm. HRMS: calcd. for $C_{14}H_{15}NO_4$ [M + H]$^+$ 261.1001; found 262.1072.

Methyl (1*R*)- and (1*S*)-4-Methoxy-8-[1-phenoxyethyl]quinoline-2-carboxylate (15): Methyl 8-(1-hydroxyethyl)-4-methoxyquinoline-2-carboxylate (4.734 g, 18.12 mmol), phenol (2.555 g, 27.15 mmol) and di-*tert*-butylazodicarboxylate (8.335 g, 36.20 mmol) were dissolved in dry toluene (400 mL), and polymer-bound triphenylphosphine (12.067 g, 36.20 mmol, 3 mmol/g) was added. The mixture was stirred at 80 °C under a nitrogen atmosphere for 3 h, filtered, and washed with ethyl acetate, and the filtrate was concentrated under reduced pressure. The crude product was purified by silica gel chromatography (heptane/EtOAc) to afford racemic methyl 4-methoxy-8-[1-phenoxyethyl]quinoline-2-carboxylate (3.388 g, 55%). The enantiomers were then separated by chiral chromatography (ethanol/heptane, 15:85) to obtain each enantiomer in *ee* ≥ 99.8%. The absolute configuration of the enantiomers was not determined; however, comparison of the CD spectra of the Q_{Phen} monomer precursors with those of the Q_{Morph} monomers (see Supporting Information) indicated that the first eluted enantiomer was 4-methoxy-8-[(1*S*)-1-phenoxyethyl]quinoline-2-carboxylate and the second eluted enantiomer was 4-methoxy-8-[(1*R*)-1-phenoxyethyl]-quinoline-2-carboxylate. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.11 (dd, *J* = 8.3, 1.4 Hz, 1 H), 7.83 (dd, *J* = 7.2, 1.2 Hz, 1 H), 7.65 (dd, *J* = 8.3, 7.3 Hz, 1 H), 7.62 (s, 1 H), 7.14 (m, 2 H), 6.84–6.78 (m, 3 H), 6.61 (q, *J* = 6.3 Hz, 1 H), 4.14 (s, 3 H), 3.99 (s, 3 H), 1.68 (d, *J* = 6.3 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 165.5, 163.1, 157.4, 148.5, 144.6, 141.4, 129.5, 127.9, 126.7, 121.3, 120.8, 120.5, 115.3, 100.6, 70.0, 56.5, 52.9, 23.6 ppm. HRMS: calcd. for $C_{20}H_{19}NO_4$ [M + H]$^+$ 337.1314; found 338.1389 for first eluted enantiomer and 338.1396 for second eluted enantiomer.

Methyl (1*R*)- and (1*S*)-4-Methoxy-8-(1-morpholinoethyl)quinoline-2-carboxylate (16): Methyl 8-acetyl-4-methoxyquinoline-2-carboxylate (1.919 g, 7.40 mmol) was dissolved in dry 1,2-dichloroethane (110 mL), and morpholine (3.87 mL, 44.40 mmol) and sodium triacetoxyborohydride (4.705 g, 22.20 mmol) were added. The mixture was stirred at 55 °C for 24 h, then diluted with water (150 mL) and extracted with CH_2Cl_2. The combined organic layers were dried with Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (heptane/EtOAc) to afford racemic methyl 4-methoxy-8-(1-morpholinoethyl)quinoline-2-carboxylate (1.847 g, 76%). The enantiomers were then separated by chiral chromatography (ethanol/heptane, 15:85 with 0.05% v/v diethylamine). The first eluted enantiomer was determined to be methyl 4-methoxy-8-[(1*S*)-1-morpholinoethyl]quinoline-2-carboxylate by X-ray diffraction (See Supporting Information), and the second eluted enantiomer was determined to be methyl 4-methoxy-8-[(1*R*)-1-morpholinoethyl]quinoline-2-carboxylate, also by X-ray diffraction (see Supporting Information). ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 8.10 (dd, *J* = 8.3, 1.4 Hz, 1 H), 7.93 (dd, *J* = 7.2, 1.3 Hz, 1 H), 7.70 (dd, *J* = 8.1, 7.5 Hz, 1 H), 7.55 (s, 1 H), 4.95 (q, *J* = 6.8 Hz, 1 H), 4.12 (s, 3 H), 3.96 (s, 3 H), 3.56 (m, 4 H), 2.48 (m, 2 H), 2.29 (m, 2 H), 1.33 (d, *J* = 6.8 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 166.1, 163.4, 148.4, 146.3, 143.0, 128.6, 128.1, 121.8, 120.3, 100.5, 67.0, 56.9, 56.8, 53.3, 51.4, 20.5 ppm. HRMS (racemate): calcd. for $C_{18}H_{22}N_2O_4$ [M + H]$^+$ 330.1580; found 331.1639.

Methyl (1*R*)- and (1*S*)-8-{1-[4-(2-Hydroxyethyl)piperazin-1-yl]-ethyl}-4-methoxyquinoline-2-carboxylate (17): Methyl 8-acetyl-4-methoxyquinoline-2-carboxylate (3.370 g, 13.00 mmol) was dissolved in anhydrous 1,2-dichloroethane (200 mL), and then 2-(1-piperazinyl)ethanol (14.36 mL, 117.00 mmol), glacial acetic acid (2 mL, 35 mmol) and sodium cyanoborohydride (2.042 g, 32.50 mmol) were added. The mixture was stirred at 55 °C for 3 h and then diluted with saturated NaCl (200 mL) and extracted with CH_2Cl_2. The combined organic layers were dried with Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (CH_2Cl_2/MeOH) to afford racemic methyl 8-{1-[4-(2-hydroxyethyl)piperazin-1-yl]ethyl}-4-methoxyquinoline-2-carboxylate (2.631 g, 54%). The enantiomers were separated by chiral chromatography (ethanol/heptane, 15:85 with 0.05% v/v diethylamine) to obtain the first eluted enantiomer in 99.8%*ee* and the second eluted enantiomer in 94.4%*ee*. The absolute configuration of the enantiomers was not determined; however, comparison of the CD spectrum of the Q_{Pip} monomer precursors with those of the Q_{Morph} monomers (see Supporting Information) indicated that the first eluted enantiomer was methyl 8-{(1*R*)-1-[4-(2-hydroxyethyl)piperazin-1-yl]ethyl}-4-methoxyquinoline-2-carboxylate and the second eluted enantiomer was methyl 8-{(1*S*)-1-[4-(2-hydroxyethyl)piperazin-1-yl]ethyl}-4-methoxyquinoline-2-carboxylate. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.08 (dd, *J* = 8.3, 1.4 Hz, 1 H), 7.91 (dd, *J* = 7.2, 1.4 Hz, 1 H), 7.69 (dd, *J* = 8.2, 7.4 Hz, 1 H), 7.55 (s, 1 H), 4.95 (q, *J* = 6.7 Hz, 1 H), 4.31 (t, *J* = 5.4 Hz, 1 H), 4.12 (s, 3 H), 3.96 (s, 3 H), 3.42 (m, 2 H), 2.38 (br. s, 4 H), 2.32 (m, 2 H), 2.30 (br. s, 4 H), 1.33 (d, *J* = 6.7 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 166.1, 163.4, 148.3, 146.3, 143.4, 128.5, 128.1, 121.8, 120.2, 100.4, 60.8, 58.9, 56.9, 56.4, 55.4, 54.1, 53.3, 50.6, 20.8 ppm. HRMS: calcd. for $C_{20}H_{27}N_3O_4$ [M + H]$^+$ 373.2002; found 374.2064 for first eluted enantiomer and 374.2053 for second eluted enantiomer.

General Method for Q_Y Monomer Precursor Saponification: The corresponding ester was dissolved in dioxane/water 5:1 (10 mL/mmol) and lithium hydroxide monohydrate (3 equiv.) was added. The mixture was stirred at room temp. until no further conversion was observed by TLC. The mixture was then neutralized with 1.25 M HCl in ethanol (3 equiv.) and concentrated under reduced pressure. The crude product was purified by preparative reversed-phase chromatography by using an Armen Spot liquid chromatography system with a Gemini-NX® 10 μM C18, 250 mm × 50 mm i.d. column from Phenomenex at a flow rate of 118 mL min^{-1} with UV diode array detection (210–400 nm); 5 mM aqueous ammonium formate solution and acetonitrile or water and acetonitrile were used as eluents.

(*R*/*S*)-Q_{Phen} (18): ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 13.33 (br s, 1 H), 8.10 (dd, *J* = 8.3, 1.5 Hz, 1 H), 7.73 (dd, *J* = 7.2, 1.2 Hz, 1 H), 7.63 (dd, *J* = 8.3, 7.2 Hz, 1 H), 7.63 (s, 1 H), 7.14 (m, 2 H), 6.86 (m, 2 H), 6.80 (m, 1 H), 6.77 (q, *J* = 6.3 Hz, 1 H), 4.13 (s, 3 H), 1.65 (d, *J* = 6.3 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, [D$_6$]-DMSO): δ = 166.3, 163.2, 157.4, 149.1, 144.4, 141.6, 129.4, 127.8, 126.6, 121.3, 120.7, 120.4, 115.3, 100.2, 70.0, 56.5, 23.7 ppm. HRMS: calcd. for $C_{19}H_{17}NO_4$ [M + H]$^+$ 323.1158; found 324.1229 and 324.1228.

(*R*/*S*)-Q_{Morph} (19): ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 8.11 (dd, *J* = 8.4, 1.4 Hz, 1 H), 7.92 (dd, *J* = 7.2, 1.3 Hz, 1 H), 7.70 (dd, *J* = 8.3, 7.3 Hz, 1 H), 7.59 (s, 1 H), 4.91 (q, *J* = 6.7 Hz, 1 H), 4.15 (s, 3 H), 3.61 (m, 4 H), 2.55 (m, 2 H), 2.35 (m, 2 H), 1.36 (d, *J* = 6.7 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 165.4, 163.9, 149.9, 144.2, 140.7, 128.9, 127.5, 121.2, 120.2, 100.0, 66.2, 57.5, 56.7, 50.7, 19.5 ppm. HRMS: calcd. for $C_{17}H_{20}N_2O_4$ [M + H]$^+$ 316.1423; found 317.1502 [(*S*)-Q_{Morph}) and 317.1506 [(*R*)-Q_{Morph}].

(1*R*)- and (1*S*)-8-{1-[4-(2-Hydroxyethyl)piperazin-1-yl]ethyl}-4-methoxyquinoline-2-carboxylic Acid (20): ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 8.09 (dd, *J* = 8.3, 1.4 Hz, 1 H), 7.88 (dd, *J* = 7.3, 1.3 Hz, 1 H), 7.66 (dd, *J* = 8.2, 7.3 Hz, 1 H), 7.56 (s, 1 H), 4.94 (q, *J* = 6.7 Hz, 1 H), 4.12 (s, 3 H), 3.48 (t, *J* = 6.2 Hz, 2 H), 2.58 (br s, 4 H), 2.49–2.23 (m, 6 H), 1.38 (d, *J* = 6.7 Hz, 3 H) ppm. ^{13}C

NMR (125 MHz, [D$_6$]DMSO): δ = 166.2, 163.5, 151.9, 144.4, 140.3, 128.5, 127.0, 121.0, 120.2, 100.0, 59.8, 58.0, 57.5, 56.5, 52.8, 49.4, 19.6 ppm. HRMS: calcd. for $C_{19}H_{25}N_3O_4$ [M + H]$^+$ 359.1845; found 360.1931 and 360.1937.

(*R*)-Q$_{Pip}$ (21): 8-{(1*R*)-1-[4-(2-Hydroxyethyl)piperazin-1-yl]ethyl}-4-methoxyquinoline-2-carboxylic acid (300 mg) was dissolved in $CHCl_3$, and the solution was stirred at room temp. under N_2. *i*Pr$_2$EtN (0.872 mL, 5.00 mmol, 6 equiv.) was then added, followed by Ac_2O (0.237 mL, 2.50 mmol, 3 equiv.), and the mixture was stirred at room temp. for 4 h under N_2. The solvents were evaporated under reduced pressure, and the crude residue was dissolved in THF/H_2O (1:1, 6.0 mL) and stirred for 3 h at room temp. 1 M HCl was then added dropwise to bring the mixture to pH 2, and the solvents were evaporated under reduced pressure. The crude residue was purified by silica gel chromatography (100% CH_2Cl_2 to CH_2Cl_2/MeOH, 85:5) to yield the title compound as a white foam (225 mg, 67%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.30 (dd, *J* = 8.4, 1.3 Hz, 1 H), 7.99 (s, 1 H), 7.80 (m, 1 H), 7.70 (dd, *J* = 8.3, 7.4 Hz, 1 H), 4.32 (s, 3 H), 4.29 (m, 1 H), 4.21 (t, *J* = 5.8 Hz, 2 H), 2.94–2.84 (m, 6 H), 2.76 (m, 2 H), 2.70 (m, 2 H), 2.07 (s, 3 H), 1.61 (d, *J* = 6.8 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 171.0, 168.4, 153.0, 138.1, 134.1, 132.2, 128.0, 122.5, 101.2, 64.0, 61.7, 57.8, 56.2, 52.2, 21.0, 18.2 ppm. HRMS: calcd. for $C_{21}H_{27}N_3O_5$ [M + H]$^+$ 401.1951; found 402.2041.

Compound 4: Synthesized on a 0.022 mmol scale (50 mg of Wang resin, loading 0.44 mmol g^{-1}) by using the general methods previously reported.[18] The crude mixture of diastereoisomers was purified by RP-HPLC (system D) to yield each pure diastereoisomer as a yellow solid. (*P*)-**4**: (corresponding to the first analytical peak, 5.0 mg, 21%). RP-HPLC (C18, system A) R_t = 9.83 min. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 11.51 (s, 1 H), 11.30 (s, 1 H), 11.08 (s, 1 H), 10.99 (s, 1 H), 10.94 (s, 1 H), 10.87 (s, 1 H), 8.49 (s, 1 H), 7.95–8.29 (m, CHAr), 7.34–7.89 (m, 13 H), 7.08–7.23 (m, 3 H), 6.99 (s, 1 H), 6.87 (s, 1 H), 6.78 (m, 1 H), 6.46–6.65 (m, 9 H), 6.34 (s, 1 H), 6.25 (m, 2 H), 5.97 (s, 1 H), 3.78–4.49 (m, 16 H), 3.03–3.17 (m, 16 H) ppm. HRMS: calcd. for $C_{115}H_{117}N_{25}O_{19}$ [M + H]$^+$ 2151.8958; found 2152.9098. (*M*)-**4**: (corresponding to the second analytical peak, 4.5 mg, 19%). RP-HPLC (C18, system A): R_t = 10.11 min. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 11.27 (s, 1 H), 11.14 (s, 1 H), 11.06 (s, 1 H), 11.00 (s, 1 H), 10.90 (s, 1 H), 10.84 (s, 1 H), 8.47 (s, 1 H), 7.96–8.22 (m, CHAr), 7.34–7.82 (m, 13 H), 7.06–7.23 (m, 3 H), 6.97 (s, 1 H), 6.86 (s, 1 H), 6.76 (m, 3 H), 6.51 (s, 1 H), 6.39 (m, 3 H), 6.31 (s, 1 H), 6.20 (s, 1 H), 5.96 (s, 1 H), 4.07–4.46 (m, 16 H), 3.11 (m, 16 H), 2.22 (m, 16 H) ppm. HRMS: calcd. for $C_{115}H_{117}N_{25}O_{19}$ [M + H]$^+$ 2151.8958; found 2152.9098.

Compound 5: Synthesized on a 0.019 mmol scale (50 mg of Wang resin, loading 0.38 mmol g^{-1}) by using the general methods previously reported.[5,18] The crude mixture of diastereoisomers was purified by RP-HPLC (system F) to yield each pure diastereoisomer as a pale yellow solid. (*P*)-**5**: (corresponding to the first analytical peak) 2.2 mg (9%). RP-HPLC (C18, system C) R_t = 14.37 min. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 11.61 (s, 1 H), 11.54 (s, 1 H), 11.44 (s, 1 H), 11.20 (s, 1 H), 11.02 (s, 1 H), 10.98 (s, 1 H), 10.87 (s, 1 H), 10.77 (s, 1 H), 9.14 (t, *J* = 6.1 Hz, 1 H), 8.13–7.33 (m, 25 H), 7.22–7.06 (m, 4 H), 6.93 (m, 2 H), 6.85–6.63 (m, 6 H), 6.46 (m, 3 H), 6.17 (m, 3 H), 5.99 (s, 1 H), 5.95 (br. s, 1 H), 5.05–4.61 (m, 7 H), 4.40 (m, 2 H), 4.32–4.15 (m, 5 H), 3.94 (m, 3 H), 3.68 (m, 3 H), 1.37–1.27 (m, 8 H), 1.21–1.16 (m, 6 H), 1.06 (m, 4 H) ppm. HRMS: calcd. for $C_{126}H_{114}N_{22}O_{27}S$ [M]$^+$ 2398.7945; found 2398.7935. (*M*)-**5**: (corresponding to the second analytical peak) 2.8 mg (11%). RP-HPLC (C18, system C) R_t = 14.53 min. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 11.58 (s, 1 H), 11.45 (s, 1 H), 11.16 (s, 1 H), 11.03 (s, 1 H), 10.99 (s, 1 H), 10.88 (s, 1 H), 10.80 (s, 1 H), 10.72 (s, 1 H), 9.13 (t, *J* = 5.9 Hz, 1 H), 8.05–7.31 (m, 27 H), 7.20–7.05 (m, 5 H), 6.91 (s, 1 H), 6.84–6.62 (m, 6 H), 6.58 (s, 1 H), 6.55 (s, 1 H), 6.36 (m, 3 H), 6.14 (s, 1 H), 6.12 (s, 1 H), 5.99 (s, 1 H), 5.92 (br s, 1 H), 4.98–4.69 (m, 7 H), 4.39 (m, 2 H), 4.23–4.11 (m, 5 H), 3.93 (m, 3 H), 3.65 (m, 3 H), 1.35–1.26 (m, 8 H), 1.20–1.16 (m, 6 H), 1.05 (m, 4 H) ppm. HRMS: calcd. for $C_{126}H_{114}N_{22}O_{27}S$ [M]$^+$ 2398.7945; found 2398.7971.

Compound 6: Synthesized on a 0.022 mmol scale (50 mg of Wang resin, loading 0.44 mmol g^{-1}) by using the general methods previously reported[18] to yield 55 mg of crude material (67% crude yield) as a yellow solid. RP-HPLC (C8, system B): major peaks at R_t = 6.82 and 6.91 min. ^{1}H NMR (300 MHz, [D$_6$]DMSO): ca.1:1 ratio of diastereoisomers: δ = 11.11 (s, 1 H), 10.93 (s, 2 H), 10.83 (s, 1 H), 10.77 (s, 2 H), 10.73 (s, 1 H), 10.69 (s, 1 H), 10.25–10.41 (m, 10 H), 9.93 (m, 4 H), 8.30 (s, 2 H), 7.67–6.60 (m, 72 H), 6.52 (s, 1 H), 6.35 (m, 13 H), 4.82 (m, 9 H), 4.63 (m, 6 H), 4.38 (m, 5 H), 3.97–3.49 (m, 122 H), 3.39–3.09 (m, 50 H), 2.34–2.09 (m, 17 H), 1.27 (m, 24 H) ppm. ESI-MS: *m*/*z* = 1862.67 [M + 2H]$^{2+}$, 1242.27 [M + 3H]$^{3+}$.

Compound 7: Q$_{Phen}$ (11.6 mg, 0.036 mmol) was dissolved in anhydrous CH_2Cl_2 (550 μL), and the solution was stirred at room temp. under N_2. 1-Chloro-*N*,*N*,2-trimethyl-1-propenylamine (9.5 μL) was added, and the mixture was stirred for 1 h at room temp. and then evaporated to dryness with a vacuum manifold. Compound **13**[21] (30 mg, 0.030 mmol) was dissolved in anhydrous $CHCl_3$ (230 μL), to which was added *i*Pr$_2$EtN (12.6 μL, 0.072 mmol), and the mixture was stirred at 0 °C under N_2. The acid chloride was then added dropwise in anhydrous $CHCl_3$ (230 μL) over ca. 5 min, and the mixture was stirred at room temp. for 15 h. It was then diluted with $CHCl_3$ and washed with a saturated solution of $NaHCO_3$, 0.1 M HCl, H_2O and brine, and the organic phase was dried with $MgSO_4$. The crude residue was then purified by silica gel chromatography (100% cyclohexane to cyclohexane/EtOAc, 7:3) to yield the title compound as a pale yellow solid (28 mg, 72%). ^{1}H NMR (300 MHz, $CDCl_3$): ca. 55:45 ratio of diastereoisomers: δ = 11.97 (s, 1 H), 11.94 (s, 1 H), 11.93 (s, 1 H), 11.87 (s, 1 H), 11.79 (s, 1 H), 11.77 (s, 1 H), 11.61 (s, 1 H), 11.16 (s, 1 H), 8.72 (m, 2 H), 8.55 (m, 2 H), 8.27 (m, 2 H), 8.16 (m, 1 H), 8.08 (m, 7 H), 7.92 (m, 1 H), 7.81 (m, 1 H), 7.75–7.57 (m, 5 H), 7.53 (s, 1 H), 7.48 (s, 1 H), 7.43–7.28 (m, 5 H), 7.03 (m, 4 H), 6.82 (m, 4 H), 6.70 (m, 2 H), 6.57 (s, 1 H), 6.45–6.26 (m, 7 H), 6.14 (t, *J* = 7.2 Hz, 1 H), 5.75 (m, 1 H), 5.65 (m, 1 H), 4.49–3.38 (m, 8 H), 4.27 (m, 2 H), 3.95–3.79 (m, 10 H), 3.70 (m, 2 H), 3.20 (s, 3 H), 3.15 (s, 1 H), 2.53 (m, 2 H), 2.40–2.17 (m, 6 H), 1.43–1.11 (m, 48 H), 0.91 (d, *J* = 5.9 Hz, 3 H), 0.34 (d, *J* = 6.4 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.9, 163.8, 163.7, 163.1, 163.0, 162.3, 162.2, 161.9, 161.7, 161.6, 161.3, 161.0, 160.6, 157.9, 151.0, 150.1, 149.6, 148.9, 141.1, 139.1, 138.6, 138.4, 134.1, 134.0, 133.8, 133.7, 132.5, 129.1, 128.4, 127.8, 127.6, 127.1, 127.0, 126.9, 125.6, 122.7, 122.5, 122.2, 122.0, 121.9, 120.0, 119.6, 117.1, 117.0, 116.9, 116.5, 116.2, 115.8, 115.6, 114.8, 100.3, 99.6, 99.4, 98.7, 98.3, 97.8, 97.6, 97.2, 75.6, 75.4, 75.2, 75.0, 74.9, 70.0, 68.7, 56.2, 52.1, 28.4, 28.3, 28.2, 28.1, 26.9, 21.4, 19.5, 19.4, 19.3, 16.8 ppm. HRMS: calcd. for $C_{76}H_{75}N_9O_{12}$ [M + H]$^+$ 1305.5535; found 1306.5644.

General Method to Couple Tertiary Amine-Based Chiral Monomer Units, Exemplified by Compound 8: (*R*)-Q$_{Morph}$ (17.5 mg, 0.055 mmol) was suspended in THF (1 mL), and conc. HCl (5.4 μL, 0.055 mmol) was added. The mixture was stirred at room temp. for 20 min, and then the solvents were evaporated under reduced pressure (coevaporated twice with toluene). The resulting hy-

drochloride salt was dissolved in anhydrous CH_2Cl_2 (850 μL), and the solution was stirred at room temp. under N_2. Chloro-*N*,*N*,2-trimethyl-1-propenylamine (15.0 μL) was then added, and the mixture stirred for 1 h at room temp. and then evaporated to dryness with a vacuum manifold. Compound **13**[21] (46 mg, 0.046 mmol) was dissolved in anhydrous $CHCl_3$ (350 μL), to which was added *i*Pr_2EtN (19.2 μL, 0.110 mmol), and the mixture was stirred at 0 °C under N_2. The acid chloride was then added dropwise in anhydrous $CHCl_3$ (350 μL) over ca. 5 min, and the mixture was stirred at room temp. for 15 h. It was then diluted with $CHCl_3$ and washed with a saturated solution of $NaHCO_3$, 0.1 M HCl, H_2O and brine, and the organic phase was dried with $MgSO_4$. The crude residue was then purified by silica gel chromatography (100% cyclohexane to cyclohexane/EtOAc, 7:3) to yield the title compound as a pale yellow solid (43 mg, 72%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 12.10 (m, 1 H), 11.98 (s, 1 H), 11.79 (s, 1 H), 11.74 (s, 1 H), 11.32 (s, 1 H), 8.72 (dd, *J* = 7.6, 1.0 Hz, 1 H), 8.47 (dd, *J* = 7.6, 1.2 Hz, 1 H), 8.34 (dd, *J* = 8.1, 0.9 Hz, 1 H), 8.18–7.91 (m, 6 H), 7.80–7.63 (m, 3 H), 7.52–7.35 (m, 4 H), 7.16 (m, 3 H), 6.94 (s, 1 H), 6.88 (s, 1 H), 6.59 (s, 1 H), 4.93 (m, 1 H), 4.44 (m, 4 H), 4.22 (m, 1 H), 4.06–3.92 (m, 4 H), 3.82 (m, 3 H), 3.70 (m, 1 H), 3.49 (m, 1 H), 3.19 (m, 5 H), 2.53 (m, 1 H), 2.36 (m, 7 H), 1.92 (m, 1 H), 1.24 (m, 24 H), 0.35 (d, *J* = 6.8 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.3, 164.0, 163.7, 163.3, 163.2, 162.4, 161.9, 161.7, 161.4, 161.0, 151.8, 150.6, 150.2, 149.1, 145.4, 145.0, 139.0, 138.4, 137.9, 137.7, 135.8, 134.0, 133.6, 133.4, 131.3, 131.3, 129.1, 128.2, 127.7, 127.4, 127.0, 126.9, 125.5, 124.1, 122.7, 122.3, 122.2, 121.8, 121.7, 117.4, 117.2, 117.0, 116.9, 116.5, 116.1, 100.4, 99.8, 99.3, 98.2, 97.9, 75.7, 75.6, 75.4, 75.1, 63.2, 58.8, 56.6, 52.1, 51.3, 50.1, 34.3, 30.3, 28.4, 28.3, 28.2, 28.1, 19.5, 19.4, 19.3, 19.2, 14.8 ppm. HRMS: calcd. for $C_{74}H_{78}N_{10}O_{12}$ $[M + H]^+$ 1298.5801; found 1299.5896.

Compound 9: Synthesized on a 0.042 mmol scale by using the general method described above to yield the title compound as a pale yellow solid (32 mg, 59%). ^{1}H NMR ($CDCl_3$): δ = 12.10 (m, 1 H), 11.97 (s, 1 H), 11.79 (s, 1 H), 11.74 (s, 1 H), 11.32 (s, 1 H), 8.72 (m, 1 H), 8.47 (m, 1 H), 8.35 (m, 1 H), 8.18–7.91 (m, 6 H), 7.80–7.63 (m, 3 H), 7.49–7.35 (m, 4 H), 7.17 (m, 1 H), 6.98 (s, 1 H), 6.94 (s, 1 H), 6.88 (s, 1 H), 6.58 (s, 1 H), 4.94 (m, 1 H), 4.44 (m, 4 H), 4.23 (m, 1 H), 4.03–3.92 (m, 4 H), 3.83 (m, 3 H), 3.70 (m, 1 H), 3.49 (m, 1 H), 3.20 (m, 5 H), 2.55 (m, 1 H), 2.35 (m, 7 H), 1.92 (m, 1 H), 1.26 (m, 24 H), 0.35 (d, *J* = 6.1 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.3, 164.0, 163.7, 163.3, 163.2, 162.4, 161.9, 161.7, 161.4, 161.0, 151.8, 150.6, 150.2, 149.2, 145.4, 145.0, 139.0, 138.4, 137.9, 137.7, 134.0, 133.6, 133.4, 131.3, 131.3, 129.1, 128.2, 127.7, 127.4, 127.0, 125.5, 125.3, 124.1, 122.7, 122.3, 122.2, 121.8, 121.7, 117.4, 117.2, 117.0, 116.9, 116.5, 116.1, 100.4, 99.8, 99.3, 99.2, 98.2, 97.9, 75.7, 75.6, 75.4, 75.1, 63.2, 58.8, 56.6, 52.1, 51.4, 50.1, 30.3, 29.7, 28.4, 28.3, 28.2, 28.1, 19.5, 19.4, 19.3, 19.2, 14.9 ppm. HRMS: calcd. for $C_{74}H_{78}N_{10}O_{12}$ $[M + H]^+$ 1298.5801; found 1299.5878.

Compound 10: Synthesized on a 0.043 mmol scale by using the general method described above to yield the title compound as a pale yellow solid (34 mg, 57%). ^{1}H NMR ($CDCl_3$): δ = 12.37 (br s, 1 H), 11.95 (s, 1 H), 11.79 (s, 1 H), 11.73 (s, 1 H), 11.25 (br s, 1 H), 8.73 (m, 1 H), 8.49 (m, 1 H), 8.40 (m, 1 H), 8.16–7.96 (m, 5 H), 7.76–7.60 (m, 4 H), 7.52 (m, 1 H), 7.42 (m, 2 H), 7.34 (m, 1 H), 7.15 (m, 1 H), 6.87 (s, 1 H), 6.86 (s, 1 H), 6.56 (s, 1 H), 5.15 (br s, 1 H), 4.42 (m, 4 H), 4.22 (m, 1 H), 3.98–3.78 (m, 7 H), 3.56 (m, 1 H), 3.20 (m, 7 H), 2.98 (m, 2 H), 2.54 (m, 1 H), 2.32 (m, 5 H), 1.86 (m, 3 H), 1.24 (m, 24 H), 0.39 (m, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.7, 164.3, 163.9, 163.8, 163.2, 163.1, 162.3, 162.0, 161.5, 160.9, 152.7, 150.0, 149.1, 145.3, 144.7, 139.0, 138.3, 137.5, 134.0, 133.7, 133.5, 129.8, 129.1, 128.2, 127.8, 127.3, 126.9, 126.1, 125.5, 125.3, 124.8, 122.7, 122.6, 122.1, 121.7, 121.5, 117.5, 117.1, 116.7, 116.6, 116.4, 116.0, 115.7, 100.3, 99.9, 99.7, 98.1, 97.6, 75.6, 75.3, 75.0, 58.7, 57.6, 56.6, 55.2, 52.1, 30.3, 28.3, 28.2, 28.1, 21.5, 20.7, 19.5, 19.4, 19.3, 19.2, 14.3 ppm. HRMS: calcd. for $C_{78}H_{85}N_{11}O_{13}$ $[M + H]^+$ 1383.6328; found 1384.6437.

Compound 11: Synthesized on a 0.019 mmol scale (50 mg of Wang resin, loading 0.38 mmol g^{-1}) by using the general method previously reported.[18] The crude material was purified by RP-HPLC (C18, system E) to afford the title compound as a pale yellow solid (6 mg, 17%). RP-HPLC (system A): R_t = 7.58 min. ^{1}H NMR (D_2O/H_2O): δ = 11.17 (s, 1 H), 11.12 (s, 1 H), 11.03 (s, 1 H), 10.80 (s, 1 H), 8.24 (m, 1 H), 7.93 (m, 3 H), 7.81–7.71 (m, 6 H), 7.52 (m, 4 H), 7.43–7.20 (m, 5 H), 7.13 (s, 1 H), 7.05 (s, 1 H), 6.95 (m, 1 H), 6.46 (s, 1 H), 5.85 (m, 1 H), 3.39 (m, 6 H), 2.92 (m, 2 H), 2.74–2.16 (m, 14 H), 0.01 (d, *J* = 6.7 Hz, 3 H) ppm. HRMS: calcd. for $C_{69}H_{72}N_{14}O_{12}$ $[M + H]^+$ 1288.5454; found 1289.5561.

Supporting Information (see footnote on the first page of this article): CD data, NMR and HPLC-based studies of helix stability, ^{1}H and ^{13}C NMR spectra and details of X-ray diffraction experiments.

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