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Improved solid-phase synthesis and study of arylopeptoids with conformation-directing side chains

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ABSTRACT

The development of an improved methodology for iterative solid-phase synthesis of *para*- and *meta*-arylopeptoids (oligomeric *N*-substituted aminomethyl benzamides) using benzoyl chloride building blocks is described. This methodology has enabled the synthesis of arylopeptoids with *tert*-butyl and phenyl side chains, which allows for complete control over the amide conformation: the *tert*-butyl results in a 100% *cis* amide conformation while the phenyl side chain results in a 100% *trans* amide conformation. The method has furthermore enabled the first synthesis and preliminary conformational studies of arylopeptoids bearing (*S*)-*N*-(1-phenylethyl) side chains.

1. Introduction

During the last decade, aryl-based foldamers have proven to be well suited for structural and functional mimicry of biopolymers.[1] Among these, aromatic oligoamides built from aromatic amino acids in a 'one-way sequence' have been a main area of interest.[2] Most research efforts have been focused on species with free backbone amide protons for which the folding propensities are mainly due to intramolecular hydrogen bonds along the artificial backbone; by contrast, their *N*-substituted counterparts remain less developed. Until recently only *N*-alkylated benzanilides (Fig. 1, left),[3] and *N*-alkylated naphthanilides (Fig. 1, mid) had been studied.[3b] These oligomers have only the amide functionalities in common with peptide backbones; they contain no aliphatic carbons and the amide protons are absent. The hydrogen bonding capability of the peptide backbone plays a central role in the formation of secondary structures but for these artificial oligomers the lack of amide proton significantly decreases the capability of intra- and intermolecular hydrogen bonding.

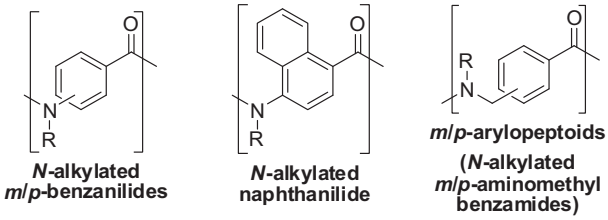

Fig. 1. *N*-Alkylated aromatic oligoamides.

Nevertheless, it has been demonstrated that these unnatural aromatic backbones can be driven into stable secondary structures by solvophobic and/or aromatic interactions. Indeed, *N*-alkylated benzanilides have been reported to adopt crescent or helical structures,[3g] and have been used as α-helix mimetics for inhibition of protein–protein p53–hDM2 interactions.[3a] The arylopeptoids (oligomeric *N*-substituted aminomethyl benzamides, Fig. 1, right) may, however, represent an intriguing addition to *N*-alkylated aromatic oligoamide foldamers. Although first reported back in the mid 1990s in connection with the development of peptoids[4,5] (oligomeric *N*-alkylated glycines),[6] the potential of this type of oligomers remained

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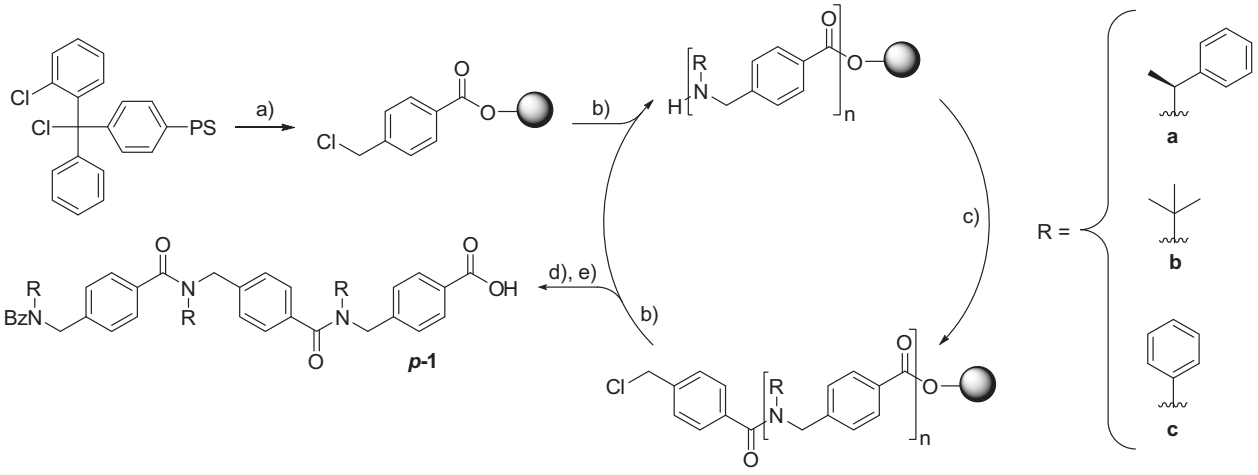
unexplored until very recently.[7,8] If control of their backbone conformations can be achieved, the presence of aliphatic carbons in their backbones relative to *N*-alkylated benzanilides and naphthanilides may allow for sampling of a larger conformational space. The additional methylene group together with the tertiary amide should also allow this artificial polyamide to retain the favorable characteristics of peptoids, such as large potential for diversity and straightforward synthesis using submonomer methods. These characteristics are, for example, crucial for the development of large libraries for discovering new inhibitors of protein–protein interactions.[9] Thus, drawing from our experiences within development of convenient methods for peptoid synthesis,[10] we have reported the first solution-phase synthesis of *para*- and *meta*-arylopeptoids.[7b] The optimized submonomer coupling-substitution cycles were carried out using bromomethylbenzoyl bromide building blocks in THF at 0 °C followed by reactions with primary amines in THF at rt. This method allowed for gram-scale synthesis of selected arylopeptoids and we furthermore undertook the first conformational studies of arylopeptoids by NMR. Thus, we found that increasing the bulkiness of simple alkyl side chains greatly favored the *cis* amide bond conformation. To allow rapid synthesis of large and diversified libraries, we recently added an efficient solid-phase methodology to the toolbox of arylopeptoid synthesis.[7a] While the *N*-alkylated benzanilides and naphthanilides have exclusively been synthesized using building blocks activated as acid chlorides, this method utilizes benzoic acid building blocks and peptide-type coupling reagents. Thus, having excluded the use of bromomethyl benzoic acid building blocks due to their instability under basic conditions, the optimized iterative submonomer method is based on COMU-mediated coupling of chloromethylbenzoic acid building blocks in NMP at rt followed by reaction with primary amines in DMSO at 50 °C. Although broadly applicable, this method was found to be inadequate when attempting to install the bulky (*S*)-*N*-(1-phenylethyl) (*spe*) side chains, which have been used extensively in conformational studies of peptoids.[11,12] The method also failed when attempting to install the highly bulky *tert*-butyl side chain. The *tert*-butyl side chain is of interest since we have shown that it invokes a 100% *cis* amide conformation.[7b] The method was also unsuccessful when attempting to couple the COMU-activated benzoic acid building blocks to intermediates derived from use of aniline in the substitution reactions. This hindered insertion of a side chain that was expected to give rise to a high proportion of *trans* amide conformation.[3b,13] Herein we report that the use of chloromethyl benzoyl chlorides rather than COMU-activated benzoic acids in the acylation steps represents a solution to these limitations. We also report further conformational studies of these arylopeptoids, primarily by NMR.

2. Development of synthetic methods

2.1. Method A: direct adaptation from COMU-method

During our preceding solution-phase studies it was demonstrated that installation of the highly bulky *tert*-butyl side chains was possible when using acyl bromides in the coupling steps.[7b] We therefore speculated that the solution to the limitations of our developed solid-phase methodology could be the use of acid chlorides in place of the corresponding COMU-activated (chloromethyl)benzoic acids in the coupling steps. The required building blocks, 3- and 4-(chloromethyl)benzoyl chloride are both commercially available. As in our preceding solid phase studies we chose to synthesize *para*-trimers with free acids at the *C*-terminus as model targets for testing this hypothesis (Scheme 1 and Table 1). A 2-chlorotrityl chloride polystyrene resin with a listed loading of 1.50 mmol g^{-1} was used; employing the same attachment procedure a loading of 1.23±0.03 mmol g^{-1} chloromethylbenzoic acid was obtained.[7a] Using incorporation of the bulky *spe* side chain as a starting point, we replaced the use of 1.0 M COMU-activated 4-(chloromethyl)benzoic acid (3.0 equiv) in NMP with the use of 0.50 M 4-(chloromethyl)benzoyl chloride (3.0 equiv) in CH_2Cl_2 in the coupling steps. Apart from the higher dilution, which was necessary to facilitate mixing, all other reaction conditions were left unchanged. The new acid chloride based method proved very efficient for installing the bulky *spe* side chains and the desired model trimer *p*-**1a** was isolated in an excellent 97% crude purity (Table 1, entry 1). No optimization was needed and we therefore assumed that this directly adapted method (method A) would also be efficient for installing other side chains derived from the use of reactive and less bulky amines. We then found that the method furnished model trimer *p*-**1b** carrying *tert*-butyl side chains in 80% crude purity (entry 2). Although obtained in a much less impressive 28% crude purity, the method was likewise able to provide model trimer *p*-**1c** derived from the use of unreactive aniline in the substitution steps (entry 3). Thus, for installation of side chains derived from highly bulky *tert*-butyl amine and unreactive aniline additional optimization studies were required.



Scheme 1. Acid chloride based solid-phase synthesis of model arylopeptoid trimers using conditions directly adapted from COMU-mediated synthesis (method A). Key: (a) $ClCH_2ArCOOH$ (1.2 equiv, 0.14 M), DIPEA (6.0 equiv), CH_2Cl_2, rt, 1 h. (b) R-NH_2 (20 equiv, 2.0 M), DMSO, 50 °C, 1 h. (c) $ClCH_2ArCOCl$ (3.0 equiv, 0.5 M), DIPEA (6.0 equiv), CH_2Cl_2, rt, 20 min. (d) BzCl (3.0 equiv, 0.5 M), DIPEA (6.0 equiv), CH_2Cl_2, rt, 20 min. (e) HFIP/CH_2Cl_2 1:4, rt, 1 h. See Table 1 for yields.

Table 1
Results for acid chloride based solid-phase synthesis of model trimer arylopeptoids using conditions directly adapted from COMU-mediated synthesis (method A)

Entry	Trimer	Crude yield (%)	Crude purity (%)[a]
1	*p*-**1a**	78	97
2	*p*-**1b**	74	80
3	*p*-**1c**	51	28

[a] Determined by analytical HPLC.

2.2. Method B: adaptation for *tert*-butyl side chains

The reaction conditions for installing *tert*-butyl side chains were optimized by synthesizing trimer *p*-**1b** as a model target, with 80% crude purity and 74% crude yield being the starting points (Table 2, entry 1). We rapidly established that increasing the reaction time during the substitution steps had no effect on the crude purity and crude yield (entry 2). Optimization efforts were therefore concentrated on the coupling and capping steps. By increasing the reaction time of these steps from 20 min to 40 min an increase in crude purity to 90% was obtained (entry 3). A similar improvement could also be achieved by increasing the concentration and equivalents of acid chlorides to 1.0 M and 6.0 equiv, respectively, while keeping the reaction time at 20 min (entry 4). Combination of these two findings, i.e., use of 6.0 equiv acid chloride at 1.0 M for 40 min provided the optimal conditions (method B) with 94% crude purity and a crude yield of 89% (entry 5). Increasing the reaction times further to 1 h did not result in any improvement (entry 6).

Table 2
Optimization of substitution step (b) and coupling/capping step (c)/(d) for synthesis of *p*-**1b** (method B)

Entry	Substitution step (b)		Coupling/capping steps (c)/(d)			Crude yield (%)	Crude purity (%)[a]
	^{t}BuNH$_2$ ([c])	Time (h)	ArCOCl (equiv/[c])	DIPEA (equiv)	Time (min)		
1	2.0	1	3.0/0.5	6.0	20	74	80
2	2.0	2	3.0/0.5	6.0	20	77	79
3	2.0	1	3.0/0.5	6.0	40	83	90
4	2.0	1	6.0/1.0	12.0	20	87	91
5	2.0	1	6.0/1.0	12.0	40	89	94
6	2.0	1	6.0/1.0	12.0	60	90	94

[a] Determined by analytical HPLC.

2.3. Method C: adaptation for phenyl side chains

Next, we turned to optimizing the conditions for installing phenyl side chains with 28% crude purity and 51% crude yield of the model trimer *p*-**1c** as starting points (Table 3, entry 1). Opposite to the *tert*-butyl optimization, a dramatic improvement to 58% crude purity was observed when increasing the reaction time from 1 h to 2 h during the substitution reactions (entry 2). On the contrary, increased reaction time for the coupling and capping steps had no effect on the crude purity and crude yield (entry 3) and we therefore focused the optimizing efforts on the substitution step.

Thus, increasing the reaction time to 3 h further improved the crude purity (75%, entry 4). The use of a more concentrated solution of aniline in the substitution steps (4.0 M/1 h, entry 5) also resulted in improved crude purity to 58%. Combination of these two parameters again furnished the optimal conditions (method C). Thus, the use of 4.0 M aniline for 3 h (entry 7) provided the best compromise between crude purity (87%) and crude yield (75%) since shortening the reaction time to 2 h gave a lower crude purity (82%, entry 6) while a reaction time of 4 h resulted in a decreased crude yield (64%, entry 8) even though the crude purity was improved slightly (90%). This observed decrease in crude yield is presumably a result of increased aminolysis of the arylopeptoid chains from the 2-chlorotrityl linker caused by the extended reaction times of the substitution steps.

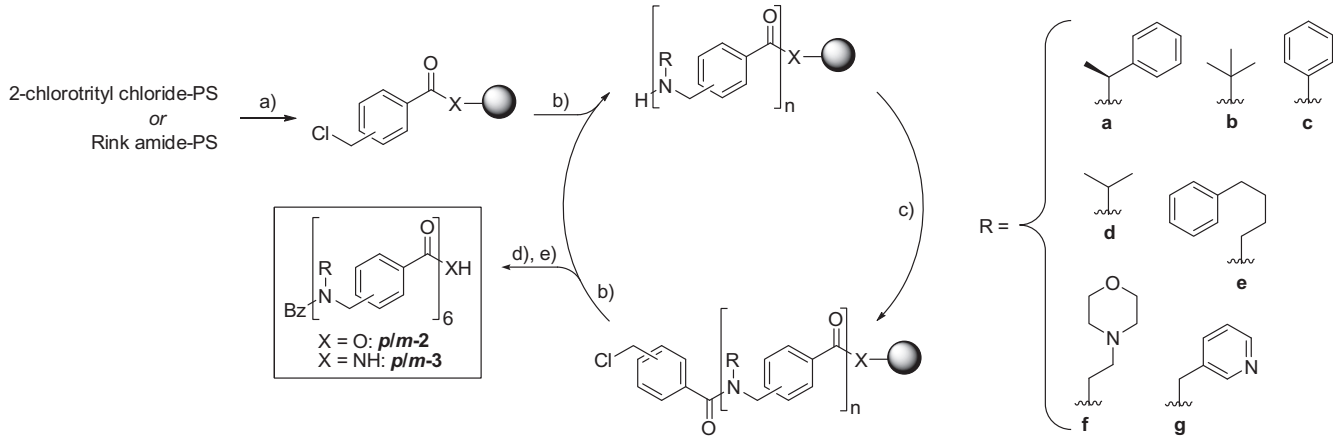
3. Solid-phase synthesis of arylopeptoids

With optimized methods in hand we then synthesized a range of representative model *para*- and *meta*-homohexamers with free acids (*p*/*m*-**2**) or primary amides (*p*/*m*-**3**) at the *C*-terminus (Scheme 2 and Table 4). The syntheses of *p*/*m*-**2** were performed on the 2-chlorotrityl polystyrene resin used in the above optimization studies, while a rink amide polystyrene resin with a listed loading of 0.74 mmol g^{-1} was used for synthesis of *p*/*m*-**3**. For incorporation of the highly bulky *tert*-butyl side chains we used the optimized conditions from Table 2, entry 4 (method B) and for installation of phenyl side chains we used the optimized conditions from Table 3, entry 7 (method C). For installation of all other side chains we used the initial conditions (method A). Thus, using method A we first synthesized model hexamers *p*/*m*-**2a**, which are decorated with *spe* side chains (Table 4, entries 1 and 2). The desired oligomers were isolated in excellent

Table 3
Optimization of substitution step (b) and coupling/capping step (c)/(d) for synthesis of *p*-**1c** (method C)

Entry	Substitution step (b)		Coupling/capping steps (c)/(d)			Crude yield (%)	Crude purity (%)[a]
	PhNH$_2$ ([c])	Time (h)	ArCOCl (equiv/[c])	DIPEA (equiv)	Time (min)		
1	2.0	1	3.0/0.5	6.0	20	51	28
2	2.0	2	3.0/0.5	6.0	20	60	58
3	2.0	2	3.0/0.5	6.0	40	59	58
4	2.0	3	3.0/0.5	6.0	20	66	75
5	4.0	1	3.0/0.5	6.0	20	63	58
6	4.0	2	3.0/0.5	6.0	20	72	82
7	4.0	3	3.0/0.5	6.0	20	75	87
8	4.0	4	3.0/0.5	6.0	20	64	90

[a] Determined by analytical HPLC.



Scheme 2. Solid-phase submonomer synthesis of arylopeptoid hexamers with free acids or primary amides at the *C*-terminus. Key: (a) X=O: 2-chlorotrityl chloride polystyrene resin, $ClCH_2ArCOOH$ (1.2 equiv, 0.14 M), DIPEA (6.0 equiv), CH_2Cl_2, rt, 1 h. X=NH: rink amide polystyrene resin, piperidine/NMP 1:4, rt, 2 and 15 min; then $ClCH_2ArCOCl$ (3.0 equiv, 0.5 M), DIPEA (6.0 equiv), CH_2Cl_2, rt, 20 min (b) method A and B: R-NH_2 (20 equiv, 2.0 M), DMSO, 50 °C, 1 h. method C: R-NH_2 (20 equiv, 4.0 M), DMSO, 50 °C, 3 h. (c) method A and C: $ClCH_2ArCOCl$ (3.0 equiv, 0.5 M), DIPEA (6.0 equiv), CH_2Cl_2, rt, 20 min. method B: $ClCH_2ArCOCl$ (6.0 equiv, 1.0 M), DIPEA (12.0 equiv), CH_2Cl_2, rt, 40 min. (d) method A and C: BzCl (3.0 equiv, 0.5 M), DIPEA (6.0 equiv), CH_2Cl_2, rt, 20 min. method B: BzCl (6.0 equiv, 1.0 M), DIPEA (12.0 equiv), CH_2Cl_2, rt, 40 min. (e) X=O: HFIP/CH_2Cl_2 1:4, rt, 1 h. X=NH: TFA/water 95:5, rt, 2 h (2×10 min for *p*/*m*-**3a**). See Table 4 for yields and purities.

Table 4
Results for solid-phase submonomer synthesis of arylopeptoid hexamers

Entry	Hexamer	X	Method	Crude yield (%)	Crude purity (%)[a]	Purified yield (%)[b]
1	*p*-**2a**	O	A	73	95	54
2	*m*-**2a**	O	A	89	97	68
3	*p*-**3a**	NH	A	128	79[c]	67
4	*m*-**3a**	NH	A	137	68[c]	65
5	*p*-**2b**	O	B	94	91	64
6	*m*-**2b**	O	B	87	97	65
7	*p*-**3b**	NH	B	98	—[d]	—[d]
8	*m*-**3b**	NH	B	101	—[d]	—[d]
9	*p*-**2c**	O	C	56	78	32
10	*m*-**2c**	O	C	66	76	36
11	*p*-**3c**	NH	C	111	70	43
12	*m*-**3c**	NH	C	113	71	54
13	*p*-**2d**	O	A	76	99	—[d]
14	*p*-**3d**	NH	A	128	97	69
15	*p*-**2e**	O	A	68	84	46
16	*p*-**3e**	NH	A	97	85	52
17	*p*-**2f**	O	A	97	94	65
18	*p*-**3f**	NH	A	119	90	62
19	*p*-**2g**	O	A	98	59	23
20	*p*-**3g**	NH	A	94	60	26

[a] Determined by analytical HPLC.
[b] Yield of product isolated in >99% purity after preparative HPLC.
[c] Cleavage time reduced to 2×10 min in order to minimize decomposition.
[d] HPLC purification and/or analysis hindered due to poor solubility.

crude purities (95–97%) and good purified yields (54–68%). Their counterparts *p*/*m*-**3a** with primary amides at the *C*-terminus were initially isolated as highly complex mixtures containing less than 20% of the desired products after cleavage for 2 h with 95% TFA. This degradation is likely due to the cleavage of *spe* side chains by formation of benzyl carbocations during the harsh cleavage step and we found that the problem could be minimized by shortening the cleavage procedure to only 2×10 min, which enabled *p*/*m*-**3a** to be isolated in good crude purities (68–79%, entries 3 and 4) and good yields (65–67%). Method B successfully provided hexamers *p*/*m*-**2b** with *tert*-butyl side chains and a free acid at the *C*-terminus in excellent crude purities (91–97%) and good purified yields (64–65%, entries 5 and 6). The crude products from synthesis of the corresponding hexamers *p*/*m*-**3b** with primary amides at the *C*-terminus were unfortunately found to be completely insoluble in any useful organic solvent, which hindered analysis (entries 7 and 8). We speculate that the insolubility is due to at least partial removal of the *tert*-butyl side chains caused by the harsh conditions used in the cleavage step thus giving rise to insoluble oligomeric aminomethyl benzamides with free backbone amide protons. Synthesis of shorter oligomers and/or shortening the cleavage procedure did not offer a solution to these insolubility issues.

Hexamers carrying phenyl side chains were synthesized using method C and the desired model hexamers *p*/*m*-**2c** (entries 9 and 10) and *p*/*m*-**3c** (entries 11 and 12) with free acids and primary amides at the *C*-terminus, respectively, were all obtained in good crude purities (70–78%). The purified yields of *p*/*m*-**2c** (32–36%) were slightly lower than for *p*/*m*-**3c** (43–54%), which, as mentioned above, is presumably due to slow aminolysis of the arylopeptoid chains from the 2-chlorotrityl linker during the extended reaction times of the substitution steps.

To enable direct comparison with our preceding COMU-based method,[7a] the *para*-hexamers *p*-**2d**–**g** and *p*-**3d**–**g**, which carry isopropyl, 4-phenylbutyl, 2-morpholinoethyl, or pyridinylmethyl side chains were synthesized using the directly adapted method A (entries 13–20). The corresponding *meta*-hexamers were not synthesized since, in general, little or no difference is observed in the crude purities and purified yields between *para*-oligomers and *meta*-oligomers. Method A provided all the hexamers in increased crude purities (4–21%) and purified yields (2–14%) relative to the COMU-based method. The most dramatic increase was observed for hexamers that carry isopropyl side chains (*p*-**2d** and *p*-**3d**: 17–21% increase in crude purity and 7–14% increase in purified yield) while the smallest overall difference was observed for the hexamers that carry pyridinylmethyl side chains (*p*-**2g** and *p*-**3g**: 7–9% increase in crude purity and 2–4% increase in purified yield).

The initial methods for synthesizing arylopeptoids using DIC-activated benzoic acids reported by Zuckermann and co-workers,[6] and by Lokey and Combs,[8] were limited to the synthesis of arylopeptoids with either primary amides or free acids at the *C*-terminus, respectively. Our preceding method using COMU-activated benzoic acids compared favorably with these methods and was furthermore adaptable to the synthesis of arylopeptoids with both primary amides and free acids at the *C*-terminus. The acid chloride based method we have developed herein represents a further improvement since the yields are higher than those obtained in our COMU-based method and it also allows for installation of side chains that were not previously possible.

4. NMR studies of model monomers with *tert*-butyl and phenyl side chains

We previously undertook the first conformational studies of arylopeptoids by means of NMR where we studied *para*- and *meta*-arylopeptoids carrying simple aliphatic side chains of increasing bulk.[7b] Arylopeptoids that carried the less bulky methyl, ethyl, and isopropyl side chains produced NMR spectra with very broad signals in $CDCl_3$ at rt, indicating that these series underwent conformational changes in the intermediate time regime on the NMR time scale. Partly overlapping sets of signals for carbons and/or protons in close proximity to the amide nitrogen(s) were observed due to the presence of *cis*/*trans* mixtures. Arylopeptoids decorated with the highly bulky *tert*-butyl side chain represented a particularly interesting case since only single, sharp sets of signals were observed in NMR spectra. NOESY experiments revealed that these single sets of signals corresponded to a 100% *cis* conformation.[7b] Amongst all the new side chains we have introduced since then, only the phenyl side chain introduced in this paper likewise gives rise to very sharp signals in NMR spectra. In order to investigate this intriguing observation, we synthesized model monomers *p*/*m*-**4b** with a *tert*-butyl side chain and *p*/*m*-**4c**, which carry a phenyl side chain using method B and C, respectively (Fig. 2). Model monomers *p*/*m*-**4b** were synthesized as a reference and NOESY spectra confirmed the presence of 100% *cis* conformation by the existence of a correlation between the benzylic protons of the backbone and the aromatic protons of the capping group representing the next arylopeptoid residue in line. Accordingly, no correlations between the *tert*-butyl group and the aromatic protons of the capping group were observed. On the contrary, for the model monomers *p*/*m*-**4c** carrying a phenyl side chain, we observed no correlation between the benzylic protons of the backbone and the aromatic protons of the *N*-terminus benzamide. Instead, correlations between the aromatic protons from the phenyl side chain and aromatic protons of the *N*-capping group were observed, which intriguingly reveal that the sharp sets of signals in NMR of arylopeptoids with phenyl side chains are due to a 100% *trans* conformation. This finding is in full agreement with the results found in conformational studies of closely resembling *N*-alkylated benzanilide monomers.[3b] The same conformational preference has also been observed in related *N*-methyl-*N*-phenylacetamides.[14] *Ab initio* molecular orbital calculations indicated that this preference was due to the *N*-phenyl group being less bulky than the *N*-methyl group and to electronic repulsion between the carbonyl lone-pair electrons and the phenyl π-electrons.[14b] Overall, the *tert*-butyl and phenyl side chains allow for complete control over the amide conformation in arylopeptoids with the former side chain resulting in 100% *cis* while the latter invokes a 100% *trans* conformation.

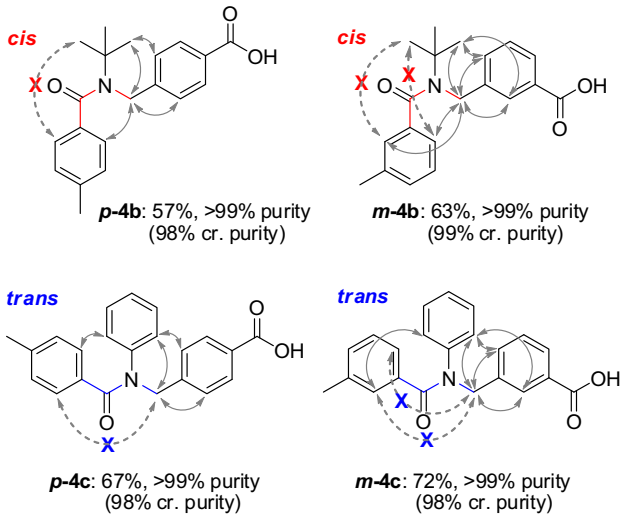
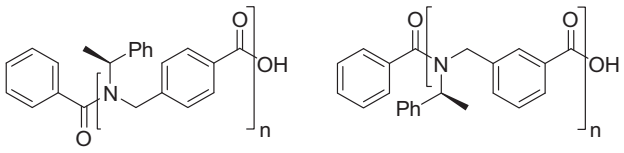


Fig. 2. Model monomer arylopeptoids *p*/*m*-**4b** and *p*/*m*-**4c** and observed NOESY correlations.

5. Conformational studies of arylopeptoids with *spe* side chains

The *spe* side chain has been used extensively in conformational studies of peptoids,[5,10b,11,12] and we were consequently interested in investigating the influence of the *spe* side chain upon the conformational preference of arylopeptoids. A library of arylopeptoids bearing the *spe* side chain was therefore obtained by complementing the synthesis of trimer *p*-**1a** and hexamers *p*/*m*-**2a** described above with the synthesis of monomers *p*/*m*-**5a**, trimer *m*-**1a**, and nonamers *p*/*m*-**6a** (Fig. 3). These were all synthesized in good purified yields (47–67%) using method A and it is of note that even the nonamers were isolated in at least 95% crude purity.



***p*-5a** (n = 1): 64% (99% cr. purity) ***m*-5a** (n = 1): 67% (99% cr. purity)
***p*-1a** (n = 3): 62% (97% cr. purity) ***m*-1a** (n = 3): 71% (99% cr. purity)
***p*-2a** (n = 6): 54% (95% cr. purity) ***m*-2a** (n = 6): 68% (97% cr. purity)
***p*-6a** (n = 9): 47% (95% cr. purity) ***m*-6a** (n = 9): 50% (97% cr. purity)

Fig. 3. Library of arylopeptoids carrying *spe* side chains. The yields are of purified products isolated in >99% purity.

NMR spectra of all the synthesized *para*- and *meta*-arylopeptoids that carry the *spe* side chain were recorded at 15–50 mM in $CDCl_3$ and no distinct length-dependant changes to the spectra were observed. The spectra were characterized by broad peaks and seemingly showed only the presence of a single amide conformation. These features resembled spectra previously obtained from arylopeptoids with isopropyl chains, which were established to exist as a ~83:17 *cis*/*trans* mixture below rt.[7b] In order to further investigate these observations, the model monomers *p*/*m*-**4a** (Fig. 4) mimicking the *para*- and *meta*-arylopeptoid backbones were synthesized in 64–68% purified yield (both obtained in 99% crude purity) also using method A. The NMR spectra of *p*/*m*-**4a** in $CDCl_3$ were then recorded in the temperature range 272–308 K (Fig. 4 and SD). Two distinct signals originating from the presence of a *cis*/*trans* mixture were clearly observed below rt in both cases. Signal splitting was not observed above rt, indicating a fast exchange between the two conformers. At 272 K we measured the ratios 83:17 and 81:19 between the two conformations of *p*-**4a** and *m*-**4a**, respectively, which represents a moderate conformational heterogeneity (see SD).

NOESY, HSQC, and COSY spectra recorded at 278 K did not provide basis for definite assignment of the conformations due to overlap in the crowded aromatic region of the spectra. However, we note that there are some indications that the major conformation corresponds to a *trans* amide conformation: (1) in the NOESY of *p*-**4a** at 278 K, the *spe* side chain methine proton of the major conformation displays correlations with three distinct sets of aromatic protons while the benzylic protons of the backbone only correlate with a single set of aromatic protons (see SD). Assuming that the aromatic functionalities in the *cis* and *trans* isomers are able to rotate freely, this set of correlations observed for the major

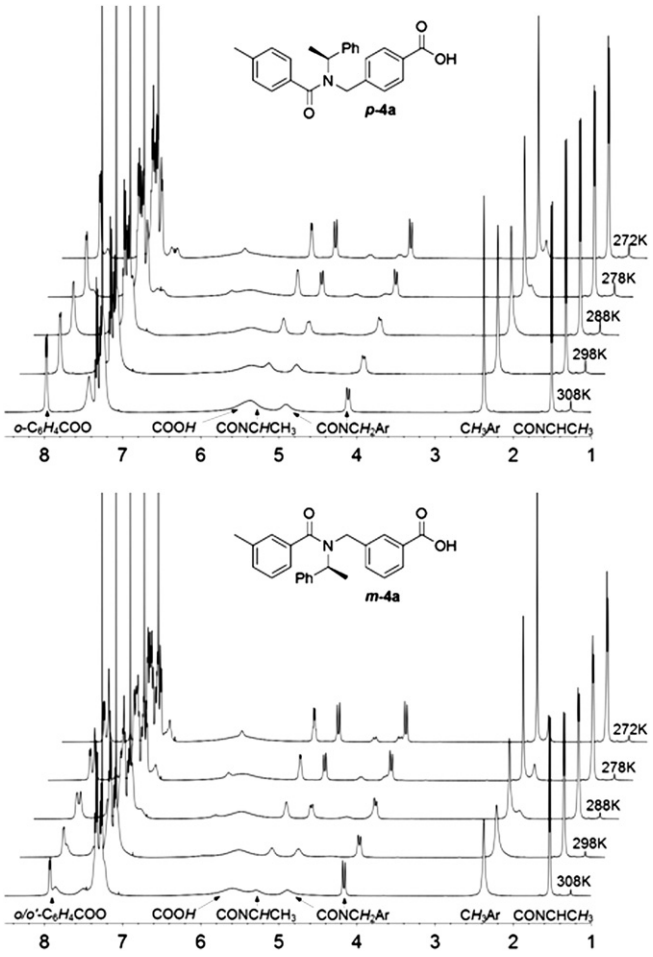


Fig. 4. NMR temperature studies of model monomers *p*-**4a** (top) and *m*-**4a** (bottom) in $CDCl_3$ at 500 MHz.

isomer may only be observed if the isomer corresponds to a *trans* amide conformation. (2) In ^{1}H NMR of peptoids carrying *spe* side chains, the *spe* side chain methine proton corresponding to a *trans* amide configuration appears upfield (~5 ppm) relative to that of a *cis* amide configuration (~6 ppm).[10b,15] In *p*/*m*-**4a** at 272 K (Fig. 4 and SD), a similar displacement of signals is observed with the major signal (~5.3 ppm) observed upfield relative to the minor signal (~6.2 ppm). (3) Likewise, in HSQC spectra of peptoids carrying *spe* side chains, the *spe* side chain methine carbon corresponding to a *trans* amide configuration appears slightly downfield (~54 ppm) relative to that of a *cis* amide configuration (~51 ppm).[10b,15] In the HSQC spectrum of *m*-**4a** at 278 K (see SD), a similar displacement of signals is again observed with the major signal (~57 ppm) observed downfield relative to the minor signal (~53 ppm).

The library of arylopeptoids carrying *spe* side chains, shown in Fig. 3, was also used to record the first circular dichroism (CD) spectra of arylopeptoids (see SD). The spectra were obtained in $CDCl_3$ to facilitate comparison with CD spectra of *N*-alkyl poly(*m*-benzamide)s[16] however, whilst the spectra were not dissimilar, the limited solvent transparency of $CDCl_3$ was an issue for interpretation. Since these CD spectra are the first reported for arylopeptoids then further CD investigation is required to be able to relate the spectral features to the conformational preference of arylopeptoids. A detailed circular dichroism investigation, supported by other spectroscopic techniques, will be reported in due course.

6. Conclusions

We have developed an improved solid-phase submonomer synthetic pathway to *para*- and *meta*-arylopeptoids (oligomeric *N*-substituted aminomethyl benzamides) using benzoyl chlorides in the coupling steps rather than the corresponding benzoic acids activated with peptide-type coupling reagents. Compared to our previous COMU-based technique, the arylopeptoids were obtained in higher crude purities and purified yields. Furthermore, the new methodology has enabled the access to side chains that were previously not accessible. Thus, we were able to synthesize arylopeptoids decorated with *tert*-butyl and phenyl side chains and show that they allow for an extraordinary complete control over the amide conformation with the first side chain resulting in 100% *cis* while the latter invokes a 100% *trans* conformation. We will continue to explore the potential of these side chains in detail by synthesis of both heterooligomers and longer homooligomers since they allow for design of aromatic oligoamides with full control over the amide conformations. In particular, oligomers with alternating *cis* and *trans* amides would be very exciting architectures to study. The improved method presented in this paper furthermore enabled synthesis and preliminary study of arylopeptoids carrying the (*S*)-*N*-(1-phenylethyl) (*spe*) side chains, which has been used extensively to explore the conformational preference of peptoids. We will likewise continue to study arylopeptoids with this side chain in order to increase the understanding of the conformational preference of arylopeptoids.

7. Experimental section

7.1. General experimental methods

CH_2Cl_2 used as solvent in reactions was dried over 4 Å molecular sieves. All other chemicals and solvents obtained from commercial sources (Alfa Aesar, Fluka, Merck and Sigma–Aldrich) were used as received. 2-Chlorotrityl chloride copoly(styrene-1% DVB) resin (100–200 mesh) with a listed loading of 1.50 mmol/g and rink amide copoly(styrene-1% DVB) resin (100–200 mesh) with a listed loading of 0.74 mmol/g were purchased from Merck. Primary amines (2.0 or 4.0 M) in DMSO used in the substitution steps were prepared from the neat, free amines. Melting points were determined on a Mettler Toledo MP70 melting point system and are referenced to the melting points of benzophenone and benzoic acid. Routine NMR spectra were recorded on a Bruker Avance 300 MHz spectrometer and temperature studies were recorded on a Bruker Avance 500 MHz instrument. Chemical shifts are referenced to the residual solvent peak and *J* values are given in hertz. The following multiplicity abbreviations are used: (s) singlet, (d) doublet, (m) multiplet, and (br) broad. Where applicable, assignments were based on COSY, HMBC, HSQC, and *J*-mod-experiments. IR spectra were recorded on a Shimadzu FTIR-8400S spectrometer equipped with a Pike Technologies MIRacle™ ATR and wavenumbers (ν) are expressed in cm^{-1}. HRMS of all arylopeptoids except for *p*/*m*-**3a**, *p*/*m*-**3c**, *p*/*m*-**5a**, and *p*/*m*-**6a** were recorded on a Micromass LCT apparatus equipped with an AP-ESI probe calibrated with Leu-Enkephalin. HRMS of *p*/*m*-**3c**, *p*/*m*-**5a** and *p*/*m*-**6a** were recorded on a Micromass Q-Tof Micro (3000 V) apparatus. The known arylopeptoids *p*-**2d**–**g** and *p*-**3d**–**g** were synthesized using method A and were purified (>99% purity) by preparative HPLC as previously described.[7a] See SD for details concerning analytical and preparative HPLC.

7.2. General procedure for attachment to trityl resin

2-Chlorotrityl chloride resin (100 mg, 1.50 mmol g^{-1}; thus 0.150 mmol) was washed with CH_2Cl_2 (2×2 mL). The resin was

swelled in CH_2Cl_2 (2 mL) for 5 min and drained. To a suspension of 3- or 4-(chloromethyl)benzoic acid (30.7 mg, 0.18 mmol) in CH_2Cl_2 (1.3 mL) at rt was added DIPEA (0.126 mL, 0.72 mmol). The resulting solution was added to the resin and the resulting mixture was agitated for 1 h at rt after which time a loading of 0.123±0.003 mmol was obtained.[7a] The resin was drained and washed with CH_2Cl_2 (3×2 mL) and DMSO (3×2 mL).

7.3. General procedure for attachment to rink amide resin

Rink amide resin (162 mg, 0.74 mmol g^{-1}; thus 0.120 mmol) was washed with CH_2Cl_2 (2×2 mL) and NMP (5×2 mL). Piperidine/NMP 1:4 (1.0 mL) was added and the resin was agitated for 2 min and drained. Further piperidine/NMP 1:4 (1.0 mL) was added and the resin was agitated for 15 min, drained and washed with NMP (3×2 mL) and CH_2Cl_2 (3×2 mL). To a solution of 3- or 4-(chloromethyl)benzoyl chloride (71 mg, 0.38 mmol) in CH_2Cl_2 (0.76 mL) at rt was DIPEA (0.132 mL, 0.76 mmol). The mixture was added to the resin and the resulting mixture was agitated for 20 min at rt. The resin was drained and washed with CH_2Cl_2 (3×2 mL) and DMSO (3×2 mL). The resin was drained and washed with CH_2Cl_2 (3×2 mL) and DMSO (3×2 mL).

7.4. General procedure for coupling step, methods A and C

To a solution of 3- or 4-(chloromethyl)benzoyl chloride (71 mg, 0.38 mmol) in CH_2Cl_2 (0.76 mL) at rt was added DIPEA (0.132 mL, 0.76 mmol). The mixture was added to the resin and the resulting mixture was agitated for 20 min at rt. The resin was drained and washed with CH_2Cl_2 (3×2 mL) and DMSO (3×2 mL).

7.5. General procedure for coupling step, method B

To a solution of 3- or 4-(chloromethyl)benzoyl chloride (143 mg, 0.76 mmol) in CH_2Cl_2 (0.76 mL) at rt was added DIPEA (0.264 mL, 1.52 mmol). The mixture was added to the resin and the resulting mixture was agitated for 40 min at rt. The resin was drained and washed with CH_2Cl_2 (3×2 mL) and DMSO (3×2 mL).

7.6. General procedure for substitution step, methods A and B

A solution of the primary amine (20 equiv, 2 M) in DMSO (1.3 mL) was added to the resin and the mixture was agitated at 50 °C for 1 h. The resin was drained and washed with DMSO (3×2 mL) and CH_2Cl_2 (3×2 mL).

7.7. General procedure for substitution step, method C

A solution of the primary amine (20 equiv, 4 M) in DMSO (0.65 mL) was added to the resin and the mixture was agitated at 50 °C for 3 h. The resin was drained and washed with DMSO (3×2 mL) and CH_2Cl_2 (3×2 mL).

7.8. General procedure for capping step, methods A and C

To a solution of benzoyl chloride, 3-methylbenzoyl chloride or 4-methylbenzoyl chloride (0.38 mmol) in CH_2Cl_2 (0.76 mL) at rt was added DIPEA (0.132 mL, 0.76 mmol). The solution was added to the resin and the resulting mixture was agitated for 20 min at rt. The resin was drained and washed with CH_2Cl_2/DIPEA 4:1 (3×1 mL, only for arylopeptoids that contain side chains with basic functionalities), CH_2Cl_2 (3×2 mL), NMP (3×2 mL), and CH_2Cl_2 (3×2 mL).

7.9. General procedure for capping step, method B

To a solution of benzoyl chloride, 3-methylbenzoyl chloride or 4-methylbenzoyl chloride (0.76 mmol) in CH_2Cl_2 (0.76 mL) at rt was added DIPEA (0.264 mL, 1.52 mmol). The solution was added to the resin and the resulting mixture was agitated for 40 min at rt. The resin was drained and washed with CH_2Cl_2/DIPEA 4:1 (3×1 mL, only for arylopeptoids that contain side chains with basic functionalities), CH_2Cl_2 (3×2 mL), NMP (3×2 mL), and CH_2Cl_2 (3×2 mL).

7.10. General procedure for cleavage from trityl resin

The resin was cleaved in HFIP/CH_2Cl_2 1:4 (1 mL) with agitation for 1 h. The resin was drained and washed with CH_2Cl_2 (5×2 mL). The solvents were evaporated under reduced pressure and the residue was evaporated with CH_2Cl_2 (3×5 mL) yielding the crude product, which was purified by preparative HPLC (see SD for details).

7.11. General procedure for cleavage from rink amide resin

The resin was cleaved in TFA/water 95:5 (2 mL) with agitation for 2 h (2×10 min for *p*/*m*-**3a**). The resin was drained and washed with TFA (2 mL) and CH_2Cl_2 (5×2 mL). The solvents were evaporated under reduced pressure and the residue was evaporated with CH_2Cl_2 (3×5 mL) yielding the crude product, which was purified by preparative HPLC (see SD for details).

7.12. Spectroscopic and characterization data for arylopeptoids

*7.12.1. Arylopeptoid trimer p-**1a**.* Synthesized using method A (78% crude yield, 97% crude purity). Data for *p*-**1a**: colorless solid (65 mg, 62%, >99% purity). Mp=123–126 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.04–7.84 (m, 2H), 7.64–7.10 (m, 30H), 5.40–5.06 (br m, 3H, 3× CONC*H*CH_3), 5.06–4.72 (br m, 3H, 3× CONC*H*HAr), 4.24–3.92 (m, 3H, 3× CONCH*H*Ar), 1.62–1.38 (m, 9H, 3× CONCHC*H*$_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=173.0, 172.8, 170.5 (4C_q), 140.6, 139.8, 139.7, 136.4, 134.8, 128.2 (10C_q), 130.1, 129.7, 128.7, 128.6, 127.8, 127.7, 127.5, 127.0, 126.9, 126.5, 126.3 (32CH), 57.4 (br, 3× CH, 3× CONCHCH$_3$), 45.3 (br, 3× CH_2, 3× CONCH_2Ar), 18.2 (br, 3CH_3, 3× CONCHC*H*$_3$) ppm. ν_{max}/cm^{-1} (ATR) 2992 (COOH), 2909 (CH), 1713 (C=O acid), 1632, 1611 (C=O amide), 1494, 1445, 1404, 1328 (OH), 1209, 1147, 1027. HRMS (TOF MS ES$^+$) calcd for $C_{55}H_{52}N_3O_5$ [M+H]$^+$ *m*/*z* 834.3901, found 834.3895.

*7.12.2. Arylopeptoid trimer m-**1a**.* Synthesized using method A (90% crude yield, 99% crude purity). Data for *m*-**1a**: colorless solid (75 mg, 71%, >99% purity). Mp=97–100 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.99–7.77 (m, 2H), 7.68–6.95 (m, 30H), 5.45–5.04 (br m, 3H, 3× CONC*H*CH_3), 5.04–4.70 (br m, 3H, 3× CONC*H*HAr), 4.23–3.88 (m, 3H, 3× CONCH*H*Ar), 1.62–1.34 (m, 9H, 3× CONCHC*H*$_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=173.2 (C_q), 173.0 (C_q), 172.9 (C_q), 170.2 (C_q), 139.7, 139.4, 139.1, 136.4, 136.3, 136.2, 129.7 (10C_q), 129.7, 128.7, 128.6, 128.4, 127.8, 127.0, 126.4, 125.2, 124.9 (32CH), 57.4 (br, 3× CH, 3× CONCHCH$_3$), 45.3 (br, 3× CH_2, 3× CONCH_2Ar), 18.1 (br, 3CH_3, 3× CONCHC*H*$_3$) ppm. ν_{max}/cm^{-1} (ATR) 2991 (COOH), 1717 (C=O acid), 1627, 1600 (C=O amide), 1495, 1447, 1406, 1329 (OH), 1306, 1160, 1027. HRMS (TOF MS ES$^+$) calcd for $C_{55}H_{52}N_3O_5$ [M+H]$^+$ *m*/*z* 834.3901, found 834.3910.

*7.12.3. Arylopeptoid trimer p-**1b**.* Synthesized using method B (89% crude yield, 94% crude purity). Data for *p*-**1b**: colorless solid (61 mg, 70%, >99% purity). Mp=96–99 °C (dec). ^{1}H NMR (300 MHz, $CDCl_3$): δ=9.56–9.34 (br s, 1H, COO*H*), 8.06–7.98 (m, 2H), 7.36–7.15 (m, 11H), 7.13–7.01 (m, 4H), 4.64 (s, 2H, CONCH_2Ar), 4.52 (s, 2H,

CONCH_2Ar), 4.50 (s, 2H, CONCH_2Ar), 1.50 (s, 9H, CON^{t}Bu), 1.44 (s, 9H, CON^{t}Bu), 1.43 (s, 9H, CON^{t}Bu) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=174.4 (C_q), 173.9 (C_q), 173.8 (C_q), 170.3 (C_q), 145.6 (C_q), 141.0 (C_q), 140.9 (C_q), 138.3 (C_q), 137.4 (C_q), 137.2 (C_q), 130.5 (2CH), 129.2 (CH), 128.7 (C_q), 128.3 (2CH), 126.4 (4CH), 126.3 (2CH), 126.2 (4CH), 125.9 (2CH), 58.6 (C_q), 58.6 (C_q), 58.5 (C_q), 51.5 (CH_2, CONCH_2Ar), 51.3 (2CH_2, 2× CONCH_2Ar), 28.7 (3CH_3, CON^{t}Bu), 28.6 (6CH_3, 2× CON-^{t}Bu) ppm. ν_{max}/cm^{-1} (ATR) 2988 (COOH), 2967 (CH), 1717 (C=O acid), 1623 (C=O amide), 1394, 1360, 1259, 1197, 1162, 1117, 1018. HRMS (TOF MS ES$^+$) calcd for $C_{43}H_{40}N_3O_5$ $[M+H]^+$ *m*/*z* 690.3901, found 690.3901.

*7.12.4. Arylopeptoid trimer p-**1c**.* Synthesized using method C (75% crude yield, 87% crude purity). Data for *p*-**1c**: colorless solid (48 mg, 51%, >99% purity). Mp=97–100 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.08–7.86 (br m, 3H, *o*-C_6H_4COO and COO*H*), 7.43–7.37 (m, 2H), 7.29–7.04 (m, 24H), 6.91–6.85 (m, 2H), 6.78–6.70 (m, 4H), 5.18 (s, 2H, CONCH_2Ar), 5.01 (s, 4H, 2× CONCH_2Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=170.8 (C_q), 170.8 (C_q), 170.6 (C_q), 170.5 (C_q), 143.3 (C_q), 143.1 (C_q), 142.9 (C_q), 142.8 (C_q), 139.2 (C_q), 139.1 (C_q), 135.4 (C_q), 134.6 (C_q), 134.5 (C_q), 130.4 (2CH), 129.7 (CH), 129.1 (2CH), 129.0, 129.0 (6CH), 128.9 (2CH), 128.6 (2CH), 128.6 (C_q), 128.3 (2CH), 127.9, 127.8 (4CH), 127.7 (2CH), 127.6 (4CH), 127.5 (2CH), 126.9 (CH), 126.8, 126.8 (2CH), 53.7 (CH_2, CONCH_2Ar), 53.3 (2CH_2, 2× CONCH_2Ar) ppm. ν_{max}/cm^{-1} (ATR) 3065 (COOH), 2947 (CH), 1715 (C=O acid), 1639, 1612, 1594 (C=O amide), 1493, 1386, 1319 (OH), 1299, 1279, 1214, 1177, 1019. HRMS (TOF MS ES$^+$) calcd for $C_{49}H_{40}N_3O_5$ $[M+H]^+$ *m*/*z* 750.2962, found 750.2969.

*7.12.5. Arylopeptoid hexamer p-**2a**.* Synthesized using method A (73% crude yield, 95% crude purity). Data for *p*-**2a**: colorless solid (106 mg, 54%, >99% purity). Mp=143–146 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.12–8.00 (br s, 1H, COO*H*), 8.00–7.84 (m, 2H), 7.64–6.88 (m, 57H), 5.42–5.06 (br m, 6H, 6× CONC*H*CH_3), 5.06–4.72 (br m, 6H, 6× CONC*H*HAr), 4.24–3.92 (m, 6H, 6× CONCH*H*Ar), 1.62–1.35 (m, 18H, 6× CONCHC*H*$_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=173.1, 173.0 (7C_q), 140.5, 136.2, 134.6 (19C_q), 130.1, 129.7, 128.7, 128.6, 127.8, 127.7, 127.5, 127.0, 126.4, 126.3 (59CH), 57.3 (br, 6CH, 6× CONCHCH$_3$), 45.2 (br, 6CH_2, 6× CONCH_2Ar), 18.1 (br, 6CH_3, 6× CONCHCH_3) ppm. ν_{max}/cm^{-1} (ATR) 3060 (COOH), 2978 (CH), 1714 (C=O acid), 1635, 1627, 1612 (C=O amide), 1446, 1404, 1329 (OH), 1209, 1172. HRMS (TOF MS ES$^+$) calcd for $C_{103}H_{98}N_6O_8$ $[M+2H]^{2+}$ *m*/*z* 773.3718, found 773.3719.

*7.12.6. Arylopeptoid hexamer m-**2a**.* Synthesized using method A (89% crude yield, 97% crude purity). Data for *m*-**2a**: colorless solid (132 mg, 68%, >99% purity). Mp=101–104 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.98–7.72 (m, 2H), 7.66–6.84 (m, 57H), 5.42–5.02 (br m, 6H, 6× CONC*H*CH_3), 5.02–4.68 (br m, 6H, 6× CONC*H*HAr), 4.20–3.84 (m, 6H, 6× CONCH*H*Ar), 1.60–1.32 (m, 18H, 6× CONCHC*H*$_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=172.9, 172.8 (7C_q), 139.8, 139.7, 139.5, 136.5, 136.4, 136.4, 129.9 (19C_q), 129.6, 128.6, 128.5, 128.3, 127.7, 127.0, 126.3, 125.3, 125.1, 124.8 (59CH), 57.4 (br, 6CH, 6× CONCHCH$_3$), 45.3 (br, 6CH_2, 6× CONCH_2Ar), 18.2 (br, 6CH_3, 6× CONCHCH_3) ppm. ν_{max}/cm^{-1} (ATR) 3038 (COOH), 2986 (CH), 1715 (C=O acid), 1635 (C=O amide), 1493, 1448, 1405, 1329 (OH), 1305, 1201, 1172, 1027. HRMS (TOF MS ES$^+$) calcd for $C_{103}H_{98}N_6O_8$ $[M+2H]^{2+}$ *m*/*z* 773.3718, found 773.3710.

*7.12.7. Arylopeptoid hexamer p-**3a**.* Synthesized using method A (128% crude yield, 79% crude purity), performing the final cleavage in 2×10 min. Data for *p*-**3a**: colorless solid (125 mg, 67%, >99% purity). Mp=130–133 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.78–6.86 (m, 59H), 6.32–5.98 (br m, 2H, CONH_2), 5.37–5.04 (br m, 6H, 6× CONC*H*CH_3), 5.04–4.77 (br m, 6H, 6× CONC*H*HAr), 4.24–3.84 (m, 6H, 6× CONCH*H*Ar), 1.72–1.36 (m, 18H, 6× CONCHC*H*$_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=172.8, 172.7, 172.7 (7C_q), 140.6, 139.8, 139.8, 136.5, 134.9, 131.2 (19C_q), 129.6, 128.7, 128.6, 127.8, 127.7, 127.6, 127.4, 126.9, 126.9, 126.4, 126.3 (59CH), 57.3 (br, 6CH, 6× CONCHCH$_3$), 45.2 (br, 6CH_2, 6× CONCH_2Ar), 18.2 (br, 6CH_3, 6× CONCHCH_3) ppm. ν_{max}/cm^{-1} (ATR) 3067, 2979 (COOH), 1678, 1630, 1616 (C=O amide), 1495, 1437, 1404, 1328, 1171, 1027. HRMS (TOF MS ES$^+$) calcd for $C_{103}H_{99}N_7O_7$ $[M+2H]^{2+}$ *m*/*z* 772.8803, found 772.8804.

*7.12.8. Arylopeptoid hexamer m-**3a**.* Synthesized using method A (137% crude yield, 68% crude purity), performing the final cleavage in 2×10 min. Data for *m*-**3a**: colorless solid (120 mg, 65%, >99% purity). Mp=114–117 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.67–6.80 (m, 59H), 6.30–5.98 (br m, 2H, CONH_2), 5.38–5.02 (br m, 6H, 6× CONC*H*CH_3), 5.02–4.57 (br m, 6H, 6× CONC*H*HAr), 4.28–3.82 (m, 6H, 6× CONCH*H*Ar), 1.72–1.30 (m, 18H, 6× CONCHC*H*$_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=172.9, 172.7, 170.1 (7C_q), 139.9, 139.8, 139.6, 136.5 (19C_q), 129.7, 128.7, 128.5, 127.8, 127.8, 126.9, 126.3, 125.3, 125.0, 124.8 (59CH), 57.4 (br, 6CH, 6× CONCHCH$_3$), 45.4 (br, 6CH_2, 6× CONCH_2Ar), 18.2 (br, 6CH_3, 6× CONCHCH_3) ppm. ν_{max}/cm^{-1} (ATR) 2984 (CH), 1683, 1630 (C=O amide), 1584, 1494, 1448, 1405, 1329, 1305, 1202, 1170, 1157, 1027. HRMS (TOF MS ES$^+$) calcd for $C_{103}H_{99}N_7O_7$ $[M+2H]^{2+}$ *m*/*z* 772.8803, found 772.8803.

*7.12.9. Arylopeptoid hexamer p-**2b**.* Synthesized using method B (94% crude yield, 91% crude purity). Data for *p*-**2b**: colorless solid (101 mg, 64%, >99% purity). Mp=125–128 °C (dec). ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.02–7.96 (m, 2H), 7.96–7.81 (br s, 1H, COO*H*), 7.33–7.13 (m, 17H), 7.13–7.00 (m, 10H), 4.63 (s, 2H, CONCH_2Ar), 4.56–4.44 (m, 10H, 5× CONCH_2Ar), 1.49 (s, 9H, CON^{t}Bu), 1.45–1.39 (m, 45H, 5× CON^{t}Bu) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=174.3 (C_q), 173.9 (C_q), 173.7 (C_q), 173.7 (2C_q), 173.6 (C_q), 169.3 (C_q), 145.4 (C_q), 141.0, 141.0, 140.9 (5C_q), 138.4 (C_q), 137.5 (2C_q), 137.4 (C_q), 137.4 (C_q), 137.3 (C_q), 130.3 (2CH), 129.1 (CH), 128.9 (C_q), 128.3 (2CH), 126.5, 126.4 (10CH), 126.2, 126.2, 126.1 (12CH), 125.9 (2CH), 58.5 (C_q), 58.5, 58.4, 58.4 (5C_q), 51.5 (CH_2, CONCH_2Ar), 51.3 (5CH_2, 5× CONCH_2Ar), 28.6 (18CH_3, 6× CON^{t}Bu) ppm. ν_{max}/cm^{-1} (ATR) 2982 (COOH), 2934 (CH), 1717 (C=O acid), 1635, 1610 (C=O amide), 1391, 1362, 1256, 1196, 1112. HRMS (TOF MS ES$^+$) calcd for $C_{79}H_{98}N_6O_8$ $[M+2H]^{2+}$ *m*/*z* 629.3718, found 629.3710.

*7.12.10. Arylopeptoid hexamer m-**2b**.* Synthesized using method B (87% crude yield, 97% crude purity). Data for *m*-**2b**: colorless solid (103 mg, 65%, >99% purity). Mp=107–110 °C (dec). ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.92–7.86 (m, 2H), 7.62–7.51 (br s, 1H, COO*H*), 7.41–7.36 (m, 2H), 7.31–7.09 (m, 25H), 4.59 (s, 2H, CONCH_2Ar), 4.50 (s, 2H, CONCH_2Ar), 4.47 (s, 4H, 2× CONCH_2Ar), 4.44 (s, 2H, CON-CH_2Ar), 4.43 (s, 2H, CONCH_2Ar), 1.48 (s, 9H, CON^{t}Bu), 1.39 (s, 9H, CON^{t}Bu), 1.38–1.34 (m, 27H, 3× CON^{t}Bu), 1.34 (s, 9H, CON^{t}Bu) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=174.3 (C_q), 173.8 (C_q), 173.7 (C_q), 173.5 (3C_q), 168.7 (C_q), 140.2 (C_q), 140.0 (2C_q), 140.0 (2C_q), 139.9 (C_q), 139.2 (C_q), 139.0 (C_q), 139.0 (C_q), 139.0 (C_q), 138.8 (C_q), 138.3 (C_q), 130.6 (C_q), 130.6, 129.2, 128.8, 128.7, 128.3, 127.5, 127.0, 126.9, 126.9, 126.8, 126.7, 125.9, 124.7, 124.6, 124.1, 124.1, 124.0, 124.0, 123.9 (29CH), 58.5 (2C_q), 58.4 (C_q), 58.4 (C_q), 58.4 (C_q), 58.4 (C_q), 51.3, 51.2, 51.1 (6CH_2, 6× CONCH_2Ar), 28.7, 28.6, 28.6, 28.5 (18CH_3, 6× CON^{t}Bu) ppm. ν_{max}/cm^{-1} (ATR) 2976, 2915 (CH), 1717 (C=O acid), 1635 (C=O amide), 1393, 1256, 1093, 1167. HRMS (TOF MS ES$^+$) calcd for $C_{79}H_{98}N_6O_8$ $[M+2H]^{2+}$ *m*/*z* 629.3718, found 629.3724.

*7.12.11. Arylopeptoid hexamer p-**2c**.* Synthesized using method C (56% crude yield, 78% crude purity). Data for *p*-**2c**: colorless solid (55 mg, 32%, >99% purity). Mp=130–133 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.03–7.98 (m, 2H), 7.42–7.36 (m, 2H), 7.29–7.02 (m, 43H), 6.90–6.85 (m, 2H), 6.78–6.68 (m, 10H), 6.45–6.10 (br s, 1H, COO*H*), 5.17 (s, 2H, CONCH_2Ar), 5.02–4.94 (m, 10H, 5× CONCH_2Ar)

ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=170.6 (C_q), 170.5 (C_q), 170.4 (C_q), 170.4 (3C_q), 170.1 (C_q), 143.2, 143.2, 143.0, 142.9, 142.9, 139.3, 139.2, 139.1, 139.1, 135.5, 134.7, 134.6, 134.6, 128.7 (19C_q), 130.3, 129.7, 129.1, 129.0, 128.9, 128.9, 128.6, 128.3, 127.8, 127.7, 127.6, 127.5, 126.9, 126.8 (59CH), 53.6 (CH_2, CONCH_2Ar), 53.3 (5CH_2, 5× CONCH_2Ar) ppm. ν_{max}/cm^{-1} (ATR) 3043 (COOH), 2930, 2853 (CH), 1717 (C=O acid), 1640, 1611, 1594 (C=O amide), 1493, 1383, 1318 (OH), 1299, 1279, 1184, 1152, 1112, 1019. HRMS (TOF MS ES$^+$) calcd for $C_{91}H_{74}N_6O_8$ [M+2H]$^{2+}$ *m*/*z* 689.2779, found 689.2784.

*7.12.12. Arylopeptoid hexamer m-**2c**.* Synthesized using method C (66% crude yield, 76% crude purity). Data for *m*-**2c**: colorless solid (63 mg, 36%, >99% purity). Mp=97–100 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.02–7.94 (m, 2H), 7.58–7.52 (m, 1H), 7.29–7.02 (m, 44H), 6.89–6.84 (m, 2H), 6.78–6.68 (m, 10H), 6.62–6.38 (br s, 1H, COO*H*), 5.16 (s, 2H, CONCH_2Ar), 5.00 (s, 2H, CONCH_2Ar), 4.97 (s, 8H, 4× CONCH_2Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=170.7, 170.6, 170.5, 170.4, 170.4 (6C_q), 169.6 (C_q), 143.0, 143.0, 142.9, 142.8, 137.8, 137.1, 137.0, 135.9, 135.9, 135.9, 135.8, 135.8, 135.5, 130.0 (19C_q), 133.2, 129.9, 129.8, 129.8, 129.6, 129.1, 129.0, 128.8, 128.7, 128.6, 128.6, 128.6, 128.0, 127.9, 127.8, 127.6, 127.6, 127.6, 126.8, 126.8 (59CH), 53.5, 53.4, 53.4, 53.4, 53.3 (6CH_2, 6× CONCH_2Ar) ppm. ν_{max}/cm^{-1} (ATR) 3050 (COOH), 1715 (C=O acid), 1614, 1594, 1583 (C=O amide), 1494, 1383, 1302, 1280, 1198, 1172. HRMS (TOF MS ES$^+$) calcd for $C_{91}H_{74}N_6O_8$ [M+2H]$^{2+}$ *m*/*z* 689.2779, found 689.2784.

*7.12.13. Arylopeptoid hexamer p-**3c**.* Synthesized using method C (111% crude yield, 70% crude purity). Data for *p*-**3c**: colorless solid (71 mg, 43%, >99% purity). Mp=114–117 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.77–7.71 (m, 2H), 7.40–7.34 (m, 2H), 7.28–7.02 (m, 43H), 6.89–6.83 (m, 2H), 6.78–6.67 (m, 10H), 6.50–6.02 (br m, 2H, CONH_2), 5.14 (s, 2H, CONCH_2Ar), 5.03–4.94 (m, 10H, 5× CONCH_2Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=170.6 (C_q), 170.4 (C_q), 170.4 (4C_q), 169.7 (C_q), 143.1, 143.0, 142.9, 141.9, 139.3, 139.2, 139.2, 139.1, 135.6, 134.7, 134.6, 132.0 (19C_q), 129.7, 129.1, 129.0, 128.9, 128.6, 128.5, 127.8, 127.8, 127.7, 127.6, 127.5, 126.9, 126.8 (59CH), 53.6 (CH_2, CONCH_2Ar), 53.3 (5CH_2, 5× CONCH_2Ar) ppm. ν_{max}/cm^{-1} (ATR) 3684 (CONH_2), 2988, 2972, 2901 (CH), 1642, 1636 (C=O amide), 1493, 1383, 1279, 1075, 1052. HRMS (TOF MS ES$^+$) calcd for $C_{91}H_{73}N_7O_7Na_2$ [M+2Na]$^{2+}$ *m*/*z* 710.7683, found 710.7657.

*7.12.14. Arylopeptoid hexamer m-**3c**.* Synthesized using method C (113% crude yield, 71% crude purity). Data for *m*-**3c**: colorless solid (89 mg, 54%, >99% purity). Mp=94–97 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.79–7.71 (m, 2H), 7.44–7.38 (m, 1H), 7.36–7.00 (m, 44H), 6.88–6.83 (m, 2H), 6.76–6.64 (m, 10H), 6.50–6.26 (br m, 2H, CONH_2), 5.11 (s, 2H, CONCH_2Ar), 4.98 (s, 2H, CONCH_2Ar), 4.94–4.91 (m, 8H, 4× CONCH_2Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=170.8 (C_q), 170.6 (C_q), 170.4 (C_q), 170.4 (3C_q), 170.1 (C_q), 143.0, 143.0, 142.9, 137.8, 137.2, 137.1, 137.0, 135.9, 135.9, 135.8, 135.5, 133.1 (19C_q), 132.2, 129.9, 129.8, 129.8, 129.2, 129.0, 128.8, 128.7, 128.6, 128.6, 128.6, 128.0, 127.9, 127.8, 127.7, 127.7, 127.6, 127.2, 126.9, 126.9, 126.8 (59CH), 53.7 (CH_2, CONCH_2Ar), 53.4 (CH_2, CONCH_2Ar), 53.4 (4CH_2, 4× CONCH_2Ar) ppm. ν_{max}/cm^{-1} (ATR) 3067 (COOH), 1641, 1594, 1583 (C=O amide), 1494, 1383, 1302, 1280, 1204, 1173. HRMS (TOF MS ES$^+$) calcd for $C_{91}H_{73}N_7O_7Na_2$ [M+2Na]$^{2+}$ *m*/*z* 710.7683, found 710.7676.

*7.12.15. Arylopeptoid model monomer p-**4a**.* Synthesized using method A (80% crude yield, 99% crude purity) at twice the scale described in the general methods. Data for *p*-**4a**: colorless solid (60 mg, 64%, >99% purity). Mp=73–76 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.04–7.78 (m, 3H, *o*-C_6H_4COO and COO*H*), 7.54–7.15 (m, 11H), 5.52–5.16 (br m, 1H, CONC*H*CH_3), 5.07–4.65 (br m, 1H, CONC*H*HAr), 4.11 (d, *J*=16.0 Hz, 1H, CONCH*H*Ar), 2.38 (s, 3H, C*H*$_3$Ar), 1.51 (d, *J*=7.0 Hz, 3H, CONCHC*H*$_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=173.4 (C_q, *C*ON), 171.3 (C_q, *C*OO), 145.0 (C_q, *p*-C_6H_4COO), 140.0 (C_q, *p*-C_6H_4CON), 139.8 (C_q, *ipso*-CHCH$_3$$C_6H_5$), 133.2 ($C_q$, *ipso*-$C_6H_4$CON), 130.2 (2CH, *o*-$C_6H_4$COO), 129.3 (2CH), 128.7 (2CH), 128.0 (C_q, *ipso*-C_6H_4COO), 127.8 (CH), 127.1 (4CH), 126.5 (2CH), 45.2 (br, CH_2, CONCH_2Ar [from HSQC correlation]), 21.4 (CH_3, *C*H$_3$Ar), 18.1 (br, CH_3, CONCHC*H*$_3$) ppm. The peak for CONCHCH$_3$ was presumably too broad to be detected. ν_{max}/cm^{-1} (ATR) 3030 (COOH), 2984 (CH), 1714, 1689 (C=O acid), 1634, 1612, 1595 (C=O amide), 1447, 1410, 1331 (OH), 1282, 1209, 1176, 1111, 1018. HRMS (TOF MS ES$^+$) calcd for $C_{24}H_{24}NO_3$ [M+H]$^+$ *m*/*z* 374.1751, found 374.1744.

*7.12.16. Arylopeptoid model monomer m-**4a**.* Synthesized using method A (85% crude yield, 99% crude purity) at twice the scale described in the general methods. Data for *m*-**4a**: colorless solid (64 mg, 68%, >99% purity). Mp=58–61 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.94–7.73 (br s, 1H, COO*H*), 8.00–7.75 (m, 2H, *o*-C_6H_4COO and *o*′-C_6H_4COO), 7.64–6.98 (m, 11H), 5.45–5.10 (br m, 1H, CONC*H*CH_3), 5.08–4.75 (br m, 1H, CONC*H*HAr), 4.17 (d, *J*=15.8 Hz, 1H, CONCH*H*Ar), 2.38 (s, 3H, C*H*$_3$Ar), 1.54 (d, *J*=7.0 Hz, 3H, CONCHC*H*$_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=173.5 (C_q, *C*ON), 171.3 (C_q, *C*OO), 139.7, 139.1, 138.7, 136.1, 129.4 (5C_q), 132.6, 130.5, 128.8, 128.7, 128.5, 127.8, 127.0, 123.2 (13CH), 56.8 (br, CH, CONCHCH$_3$ [from HSQC correlation]), 45.0 (br, CH_2, CONCH_2Ar [from HSQC correlation]), 21.4 (CH_3, *C*H$_3$Ar), 18.1 (br, CH_3, CONCHC*H*$_3$) ppm. ν_{max}/cm^{-1} (ATR) 3059, 3026 (COOH), 2979, 2923 (CH), 1715, 1692 (C=O acid), 1632, 1593, 1583 (C=O amide), 1494, 1451, 1409, 1331 (OH), 1283, 1198, 1168, 1081, 1027. HRMS (TOF MS ES$^+$) calcd for $C_{24}H_{24}NO_3$ [M+H]$^+$ *m*/*z* 374.1751, found 374.1755.

*7.12.17. Arylopeptoid model monomer p-**4b**.* Synthesized using method B (77% crude yield, 98% crude purity) at twice the scale described in the general methods. Data for *p*-**4b**: colorless solid (47 mg, 57%, >99% purity). Mp=181–184 °C (dec). ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.09–8.04 (m, 2H, *o*-C_6H_4COO), 7.36–7.31 (m, 2H, *m*-C_6H_4COO), 7.30–7.26 (m, 2H, *o*-C_6H_4CON), 7.11–7.06 (m, 2H, *m*-C_6H_4CON), 4.68 (s, 2H, CONCH_2Ar), 2.29 (s, 3H, C*H*$_3$Ar), 1.50 (s, 9H, CON^{t}Bu) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=174.3 (C_q, *C*ON), 171.0 (C_q, *C*OO), 146.5 (C_q, *p*-C_6H_4COO), 139.3 (C_q, *p*-C_6H_4CON), 135.9 (C_q, *ipso*-C_6H_4CON), 130.5 (2CH, *o*-C_6H_4COO), 129.0 (2CH, *m*-C_6H_4CON), 128.3 (C_q, *ipso*-C_6H_4COO), 126.3 (2CH, *m*-C_6H_4COO), 126.1 (2CH, *o*-C_6H_4CON), 58.3 (C_q, CON^{t}Bu), 51.6 (CH_2, CONCH_2Ar), 28.8 (3CH_3, CON^{t}Bu), 21.3 (CH_3, *C*H$_3$Ar) ppm. ν_{max}/cm^{-1} (ATR) 2979 (COOH), 2895 (CH), 1703 (C=O acid), 1609, 1600 (C=O amide), 1393, 1356, 1254, 1245, 1187, 1114. HRMS (TOF MS ES$^+$) calcd for $C_{20}H_{24}NO_3$ [M+H]$^+$ *m*/*z* 326.1751, found 326.1752.

*7.12.18. Arylopeptoid model monomer m-**4b**.* Synthesized using method B (81% crude yield, 99% crude purity) at twice the scale described in the general methods. Data for *m*-**4b**: colorless solid (52 mg, 63%, >99% purity). Mp=197–200 °C (dec). ^{1}H NMR (300 MHz, $CDCl_3$/εMeOH): δ=7.86–7.77 (m, 2H, *o*-C_6H_4COO and *o*′-C_6H_4COO), 7.35–7.28 (m, 2H, *m*-C_6H_4COO and *p*-C_6H_4COO), 7.10–6.98 (m, 4H, *o*-C_6H_4CON, *o*′-C_6H_4CON, *m*-C_6H_4CON, and *p*-C_6H_4CON), 4.54 (s, 2H, CONCH_2Ar), 2.16 (s, 3H, C*H*$_3$Ar), 1.39 (s, 9H, CON^{t}Bu) ppm. ^{13}C NMR (75 MHz, $CDCl_3$/εMeOH): δ=174.5 (C_q, *C*ON), 168.3 (C_q, *C*OO), 139.9 (C_q, *m*′-C_6H_4COO), 138.5 (C_q, *ipso*-C_6H_4CON), 138.1 (C_q, *m*′-C_6H_4CON), 130.7 (C_q, *ipso*-C_6H_4COO), 130.4 (CH, *p*-C_6H_4COO), 129.7 (CH), 128.4 (CH), 128.2 (CH), 127.4 (CH, *o*′-C_6H_4CON), 126.3 (CH), 122.5 (CH), 58.2 (C_q, CON^{t}Bu), 51.2 (CH_2, CONCH_2Ar), 28.4 (3CH_3, CON^{t}Bu), 20.9 (CH_3, *C*H$_3$Ar) ppm. ν_{max}/cm^{-1} (ATR) 2971 (COOH), 2781, 2622 (CH), 1708 (C=O acid), 1591, 1569 (C=O amide), 1428, 1404, 1250, 1119. HRMS (TOF MS ES$^+$) calcd for $C_{20}H_{24}NO_3$ [M+H]$^+$ *m*/*z* 326.1751, found 326.1744.

*7.12.19. Arylopeptoid model monomer p-**4c**.* Synthesized using method C (82% crude yield, 98% crude purity) at twice the scale described in the general methods. Data for *p*-**4c**: colorless solid

(58 mg, 67%, >99% purity). Mp=62–65 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.70–8.35 (br s, 1H, COO*H*), 8.06–8.00 (m, 2H, *o*-C_6H_4COO), 7.45–7.39 (m, 2H, *m*-C_6H_4COO), 7.27–7.22 (m, 2H, *o*-C_6H_4CON), 7.20–7.07 (m, 3H, CONC$_6H_5$), 7.00–6.94 (m, 2H, *m*-C_6H_4CON), 6.94–6.89 (m, 2H, CONC$_6H_5$), 5.20 (s, 2H, CONCH_2Ar), 2.25 (s, 3H, CH_3Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=171.4 (C_q, *C*OO), 170.8 (C_q, *C*ON), 143.6 (C_q, *p*-C_6H_4COO), 143.4 (C_q, CONC$_6H_5$), 140.2 (C_q, *p*-C_6H_4CON), 132.4 (C_q, *ipso*-C_6H_4CON), 130.4 (2CH, *o*-C_6H_4COO), 129.1 (2CH, CONC$_6H_5$), 129.0 (2CH, *o*-C_6H_4CON), 128.5 (C_q, *ipso*-C_6H_4COO), 128.4 (2CH, *m*-C_6H_4CON), 128.3 (2CH, *m*-C_6H_4COO), 127.5 (2CH, CONC$_6H_5$), 126.8 (CH, CONC$_6H_5$), 53.8 (CH_2, CONCH_2Ar), 21.3 (CH_3, CH_3Ar) ppm. ν_{max}/cm^{-1} (ATR) 3023, 1671 (C=O acid), 1643 (C=O amide), 1495, 1428, 1376, 1307, 1281, 1227, 1157. HRMS (TOF MS ES$^+$) calcd for $C_{22}H_{20}NO_3$ [M+H]$^+$ *m*/*z* 346.1438, found 346.1439.

*7.12.20. Arylopeptoid model monomer m-**4c**.* Synthesized using method C (85% crude yield, 98% crude purity) at twice the scale described in the general methods. Data for *m*-**4c**: colorless solid (63 mg, 72%, >99% purity). Mp=177–180 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=10.85–10.55 (br s, 1H, COO*H*), 8.03–7.97 (m, 2H, *o*-C_6H_4COO and *o*′-C_6H_4COO), 7.67–7.60 (m, 1H, *p*-C_6H_4COO), 7.45–7.37 (m, 1H, *m*-C_6H_4COO), 7.25 (s, 1H, *o*′-C_6H_4CON), 7.20–6.97 (m, 6H, *o*-C_6H_4CON, *m*-C_6H_4CON, *p*-C_6H_4CON, and CONC$_6H_5$), 6.96–6.90 (m, 2H, CONC$_6H_5$), 5.20 (s, 2H, CONCH_2Ar), 2.22 (s, 3H, CH_3Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=171.5 (C_q, *C*OO), 171.1 (C_q, *C*ON), 143.1 (C_q, CONC$_6H_5$), 137.9 (C_q, *m*′-C_6H_4COO), 137.6 (C_q, *m*′-C_6H_4CON), 135.3 (C_q, *ipso*-C_6H_4CON), 133.7 (CH, *p*-C_6H_4COO), 130.6 (CH), 129.9 (CH, *o*′-C_6H_4COO), 129.6 (C_q, *ipso*-C_6H_4COO), 129.5 (CH, *o*′-C_6H_4CON), 129.2 (CH, *o*-C_6H_4COO), 129.1 (2CH, CONC$_6H_5$), 128.7 (2CH, *m*-C_6H_4COO), 127.6 (2CH, CONC$_6H_5$), 127.5 (CH), 126.8 (CH, CONC$_6H_5$), 125.8 (CH), 53.5 (CH_2, CONCH_2Ar), 21.1 (CH_3, CH_3Ar) ppm. ν_{max}/cm^{-1} (ATR) 3023, 1671 (C=O acid), 1643 (C=O amide), 1495, 1428, 1376, 1307, 1281, 1227, 1157. HRMS (TOF MS ES$^+$) calcd for $C_{22}H_{20}NO_3$ [M+H]$^+$ *m*/*z* 346.1438, found 346.1434.

*7.12.21. Arylopeptoid monomer p-**5a**.* Synthesized using method A (85% crude yield, 99% crude purity) at twice the scale described in the general methods. Data for *p*-**5a**: colorless solid (58 mg, 64%, >99% purity). Mp=66–69 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=9.55–9.25 (br s, 1H, COO*H*), 8.08–7.90 (m, 2H), 7.66–7.10 (m, 12H), 5.45–5.13 (br m, 1H, CONC*H*CH$_3$), 5.12–4.78 (br m, 1H, CONC*H*HAr), 4.13 (d, *J*=16.1 Hz, 1H, CONCH*H*Ar), 1.52 (d, *J*=7.0 Hz, 3H, CONCHCH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=173.1 (C_q), 171.3 (C_q), 144.9 (C_q), 139.7 (C_q), 136.3 (C_q), 130.2 (2CH), 129.7 (CH), 128.7 (4CH), 128.0 (C_q), 127.9 (CH), 127.1 (4CH), 126.4 (2CH), 56.8 (br, CH, CONCHCH$_3$ [from HSQC correlation]), 45.1 (br, CH_2, CONCH_2Ar [from HSQC correlation]), 18.1 (br, CH_3, CONCHCH_3) ppm. ν_{max}/cm^{-1} (ATR) 3066 (COOH), 2984, 2939 (CH), 1714, 1694, 1683 (C=O acid), 1635, 1612, 1595, 1575 (C=O amide), 1495, 1447, 1410, 1330 (OH), 1280, 1208, 1175, 1108, 1027. HRMS (TOF MS ES$^+$) calcd for $C_{23}H_{21}NO_3Na$ [M+Na]$^+$ *m*/*z* 382.1419, found 382.1425.

*7.12.22. Arylopeptoid monomer m-**5a**.* Synthesized using method A (85% crude yield, 99% crude purity) at twice the scale described in the general methods. Data for *m*-**5a**: colorless solid (61 mg, 67%, >99% purity). Mp=56–59 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=10.10–9.65 (br s, 1H, COO*H*), 7.99–7.78 (m, 2H), 7.70–7.18 (m, 12H), 5.55–5.11 (br m, 1H, CONC*H*CH$_3$), 5.10–4.58 (br m, 1H, CONC*H*HAr), 4.17 (d, *J*=15.9 Hz, 1H, CONCH*H*Ar), 1.54 (d, *J*=7.0 Hz, 3H, CONCHCH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=173.1 (C_q), 171.4 (C_q), 139.9 (C_q), 139.4 (C_q), 136.6 (C_q), 132.6 (CH), 129.6 (CH), 129.5 (C_q), 128.7 (6CH), 128.5 (CH), 127.8 (CH), 127.1 (2CH), 126.4 (2CH), 44.9 (br CH_2, CONCH_2Ar [from HSQC correlation]), 18.1 (br, CH_3, CONCHCH_3) ppm. The peak for CONCHCH$_3$ was presumably too broad to be detected. ν_{max}/cm^{-1} (ATR) 3050 (COOH), 2991 (CH), 1713, 1691 (C=O acid), 1634, 1606, 1591 (C=O amide), 1495, 1447, 1410, 1329 (OH), 1248, 1193, 1077, 1027. HRMS (TOF MS ES$^+$) calcd for $C_{23}H_{21}NO_3Na$ [M+Na]$^+$ *m*/*z* 382.1419, found 382.1434.

*7.12.23. Arylopeptoid nonamer p-**6a**.* Synthesized using method A (71% crude yield, 95% crude purity). Data for *p*-**6a**: colorless solid (135 mg, 47%, >99% purity). Mp=148–151 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.02–7.80 (m, 2H), 7.62–6.88 (m, 84H), 6.70–6.50 (br s, 1H, COO*H*), 5.40–5.04 (br m, 9H, 9× CONC*H*CH$_3$), 5.04–4.68 (br m, 9H, 9× CONC*H*HAr), 4.22–3.88 (m, 9H, 9× CONCH*H*Ar), 1.62–1.34 (m, 27H, 9× CONCHCH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=172.9, 172.8 (10C_q), 140.6, 139.8, 136.5, 134.8 (28C_q), 130.1, 129.6, 128.7, 128.6, 127.8, 127.7, 127.5, 127.0, 126.5, 126.3 (86CH), 57.3 (br, 9CH, 9× CONCHCH$_3$), 45.2 (br, 9CH_2, 9× CONCH_2Ar), 18.2 (br, 9CH_3, 9× CONCHCH_3) ppm. ν_{max}/cm^{-1} (ATR) 3064 (COOH), 2985 (CH), 1713 (C=O acid), 1632, 1612 (C=O amide), 1494, 1433, 1403, 1329 (OH), 1209, 1168, 1027. HRMS (TOF MS ES$^+$) calcd for $C_{151}H_{141}N_9O_{11}Na_3$ [M+3Na]$^{3+}$ *m*/*z* 775.0148, found 775.0109.

*7.12.24. Arylopeptoid nonamer m-**6a**.* Synthesized using method A (84% crude yield, 97% crude purity). Data for *m*-**6a**: colorless solid (142 mg, 50%, >99% purity). Mp=129–132 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.97–7.70 (m, 2H), 7.70–6.86 (m, 84H), 6.85–6.65 (br s, 1H, COO*H*), 5.40–5.02 (br m, 9H, 9× CONC*H*CH$_3$), 5.02–4.68 (br m, 9H, 9× CONC*H*HAr), 4.20–3.84 (m, 9H, 9× CONCH*H*Ar), 1.62–1.30 (m, 27H, 9× CONCHCH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=173.0, 172.9, 172.9 (10C_q), 139.7139.6, 136.5, 136.4, 136.3, 130.0 (28C_q), 129.7, 128.7, 128.5, 128.3, 127.8, 126.9, 126.4, 125.3, 125.2, 124.9 (86CH), 57.4 (br, 9CH, 9× CONCHCH$_3$), 45.3 (br, 9CH_2, 9× CONCH_2Ar), 18.2 (br, 9CH_3, 9× CONCHCH_3) ppm. ν_{max}/cm^{-1} (ATR) 2987 (COOH), 2908 (CH), 1716 (C=O acid), 1634, 1601 (C=O amide), 1493, 1447, 1404, 1329 (OH), 1305, 1201, 1156, 1028. HRMS (TOF MS ES$^+$) calcd for $C_{151}H_{141}N_9O_{11}Na_3$ [M+3Na]$^{3+}$ *m*/*z* 775.0148, found 775.0168.

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Supplementary data

Methods used for analytical and preparative HPLC; HPLC profiles and NMR spectra of all synthesized arylopeptoids; NOESY spectra of *p*/*m*-**4b** and *p*/*m*-**4c**; temperature NMR studies of *p*/*m*-**4a**; CD spectra of arylopeptoids with *spe* side chains in $CDCl_3$. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.12.049.

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