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Aromatic Oligoamides with a Rare *ortho*-Connectivity: Synthesis and Study of *ortho*-Arylopeptoids

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Even though aromatic oligoamides composed of aromatic amino acids in a "one-way sequence" attract ever increasing research interest, backbones connected through *ortho*-linked aromatics remain rare. Herein, we present the first synthesis and study of *N*-alkylated *ortho*-aminomethyl-benzamides termed "*ortho*-arylopeptoids". The *ortho*-arylopeptoids may, with a few exceptions, be synthesized either in solution or on solid-phase using unique and highly efficient submonomer methods with similar levels of high generality and efficiency to those previously demonstrated for *meta*- and *para*-arylopeptoids. NMR studies indicated a more restricted rotation about the amide bonds in *ortho*-arylopeptoids, presumably due to a more congested backbone structure resulting from the *ortho*-connectivity pattern. Intriguingly, *tert*-butyl and phenyl side chains offer complete control over the amide conformations; whereas arylopeptoid residues with *tert*-butyl side chains adopt a 100 % *cis* amide conformation, the opposite 100 % *trans* amide conformation was observed in arylopeptoids with phenyl side chains. The *tert*-butyl moiety can furthermore serve as a protecting group during synthesis, which can later be removed to allow the amide to adopt a 100 % *trans* conformation instead.

Introduction

Structural and functional mimicry of biopolymers is a research area of high interest, and aryl-based foldamers have proven to be well-suited for this purpose.[1] Aromatic oligoamides assembled from aromatic amino acids in a "one-way sequence" constitutes a subgroup of these foldamers that receives ever increasing attention.[2] The most well-studied foldamers of this genre include benzanilides,[3] pyridylamides,[3c,3k,4] and oligoamides of quinolines[5] and naphthyridines (Figure 1, top row).[6] The lack of aliphatic backbone carbon atoms in these constructs necessitates comparably more rigorous coupling conditions during their syntheses but results in the formation of relatively rigid structures. These may be further stabilized by the capacity of their backbone amide protons to participate in intramolecular hydrogen bonding. Accordingly, spherand or crown ether-like structures,[3n,3q] crescent or helical structures,[3i,3r–3t,4a–4d,5,6] rod-like structures,[3g,3h,3p] as well as their use as α-helix mimetics[3c,3e,3h,3k,3m,4e–4f] and G-quadruplex ligands[5j] have all been reported. Increased structural diversity at the expense of reduced rigidity may be achieved by insertion of aliphatic carbon atoms into the aromatic oligoamide backbone, which has been demonstrated in aminomethylbenzamides,[7] aminomethylpyrid-

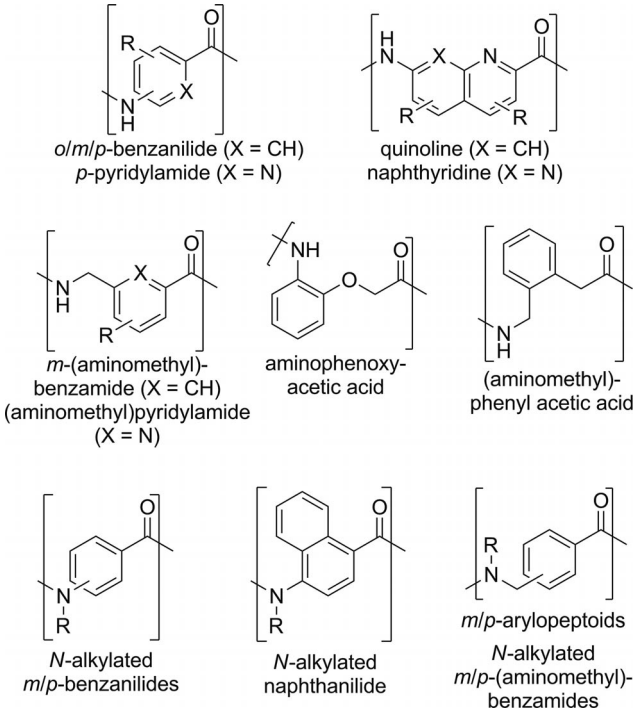

Figure 1. "One-way sequence" aromatic oligoamides.

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ylamides,[8] oligoamides of aminophenoxy acetic acid,[9] and oligoamides of aminomethylphenyl acetic acid (Figure 1, mid row).[10]

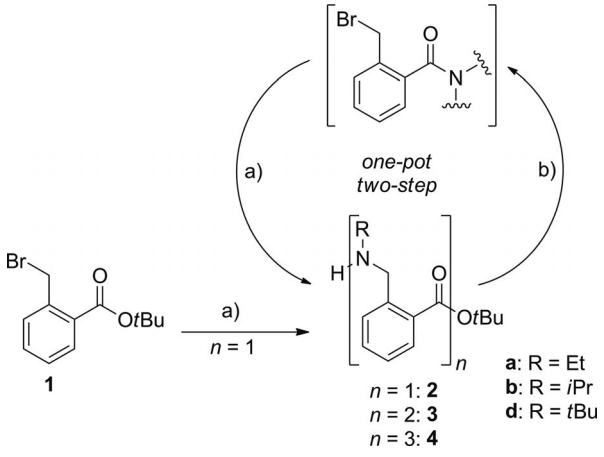
The syntheses of these oligoamides involve comparatively more reactive aliphatic amines and carboxylic acids and therefore require less demanding coupling conditions. However, although the formation of crescent or helical structures has been documented,[9,10] they remain less well studied. A different approach that may greatly increase the structural diversity of aromatic oligoamides is alkylation of the backbone amide nitrogen atoms (Figure 1, bottom row), in this case at the expense of losing the possibility for backbone participation in intramolecular hydrogen bonding. This strategy has been applied in *N*-alkylated benzanilides,[3d,11] and *N*-alkylated naphthanilides,[3d] which do not contain any aliphatic backbone carbon atoms. Interestingly, even in the absence of backbone amide protons, crescent or helical structures,[11g] as well as the use as α-helix mimetics[11b] of these oligoamides have still been reported. We focus on this intriguing strategy in our research program on *N*-alkylated *meta*- and *para*-aminobenzamides termed "*meta*-arylopeptoids" and "*para*-arylopeptoids", respectively.[12] Interestingly, this strategy has recently been extended to heteroaromatic backbones.[13] The *N*-alkylated *meta*- and *para*-aminomethyl-benzamides were originally conceived as a subclass of the peptidomimetic peptoids,[14,15] (*N*-alkylated glycines and β-alanines) in which each backbone residue is "extended" with a phenyl ring. However, after being briefly mentioned for the first time in a few patents back in the mid and late 90's,[16] they had, until recently, only received further attention in a single letter in 2007.[17] Since then, we have begun to unveil the potential of this promising class of aromatic oligoamides by developing greatly improved synthetic methods and undertaking the first conformational studies. Thus, we have recently developed the first convenient solution-phase synthesis of *meta*- and *para*-arylopeptoids using bromomethyl benzoyl bromides in the coupling steps,[12c] and two solid-phase methodologies based on the use of either COMU-activated chloromethylbenzoic acids[12b] or chloromethylbenzoyl chlorides[12a] in the coupling steps. These methods all rely on "submonomer" approaches wherein the arylopeptoid residues are created in an iterative manner directly on the growing oligoamide chains using a unique acylation-substitution cycle. In principle, any primary amine may be used in the substitution steps for installing the side chains, whereby a great diversity of arylopeptoids may be envisioned. Overall, only inexpensive, commercially available reagents are required and the combination of our methods makes it possible both to synthesize large and diversified libraries of *meta*- and *para*-arylopeptoids as well as to access target *meta*- and *para*-arylopeptoids on a gram scale.

However, in spite of the ever increasing research efforts on "one-way sequence" aromatic oligoamides, the demonstration of backbones connected through *ortho*-linked aromatics is, to the best of our knowledge, limited to as few as three examples.[3v,9,10] Inspired by the sparse literature precedence, we herein present the first synthesis and study of an entirely new type of aromatic oligoamides with *ortho* connection patterns in their backbone aromatics: *ortho*-arylopeptoids.

Results and Discussion

Solution-Phase Synthesis

We initiated our work on *ortho*-arylopeptoids by studying the feasibility of solution-phase submonomer synthesis (Scheme 1). We opted for the use of *tert*-butyl 2-(bromomethyl)benzoate (**1**)[18] as starting material because the *tert*-butyl group may eventually serve in selective postsynthesis removal and modification as we have previously demonstrated in both peptoids and arylopeptoids.[12c,19] Three series were studied, originating from the use of three different simple aliphatic amines in the substitution steps: series **a** carrying the least bulky ethyl side chains, series **b** decorated with the moderately bulky isopropyl side chains, and series **c**, carrying the highly bulky *tert*-butyl side chains (Scheme 1 and Table 1). We chose not to synthesize oligomers longer than trimers **4a**–**c**.



Scheme 1. Iterative submonomer solution-phase synthesis of *ortho*-arylopeptoids. *Reagents and conditions:* (a) R-NH_2, Et_3N, THF, 0 °C to room temp., overnight; (b) $BrCH_2ArCOBr$, Et_3N, THF, 0 °C, 1 h; see Table 1 for yields.

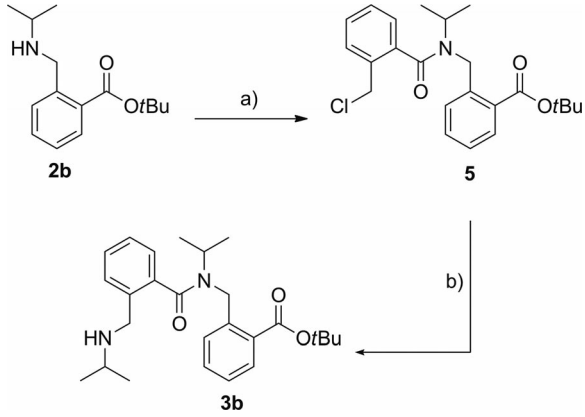
Table 1. Isolated yields (HPLC purity ≥ 97%) after column chromatography for iterative solution-phase synthesis of *ortho*-arylopeptoids (see Scheme 1).

Entry	*n*	Et [%][a]	*i*Pr [%][a]	*t*Bu [%][b]
1	1	**2a**: 62[c]	**2b**: 88	**2c**: 89
2	2	**3a**: 81	**3b**: 86	**3c**: 85
3	3	**4a**: 85	**4b**: 84	**4c**: 78

[a] 1.05 equiv. of acylating reagent was used and the synthesis of each residue was performed as a one-pot procedure. [b] 2.0 equiv. of acylating reagent was used and the acylated intermediates were purified by column chromatography. [c] 2-Ethyl-2,3-dihydro-1*H*-isoindol-1-one (26%), formed by cyclization of **2a**, was also isolated.

We have previously developed a convenient one-pot procedure for solution-phase synthesis of *meta*- and *para*-arylopeptoid residues using 3- and 4-(bromomethyl)benzoyl

bromide (1.05 equiv.) and Et_3N (1.05 equiv.) in tetrahydrofuran (THF) at 0 °C in the coupling steps, followed directly by substitution with the required primary amine (10.0 equiv.) in the presence of further Et_3N (2.0 equiv.) at 0 °C to room temp. overnight.[12c] We were satisfied to find that this method could be adapted directly to the synthesis of *ortho*-arylopeptoids **2a**–**4a** and **2b**–**4b** simply by using 2-(bromomethyl)benzoyl bromide instead. The residues were synthesized and isolated in comparably high yields (81–85%), except for monomer **2a**, which was isolated in a lower yield (62%) due to formation of the corresponding isoindolinone. In the case of *ortho*-arylopeptoids **2c**–**4c**, with the highly bulky *tert*-butyl side chains, each acylated intermediate had to be purified because a greatly increased excess of acylation reagent (2.0 equiv.) was needed for the reactions to proceed to completion. This was also necessary for the corresponding *meta*- and *para*-arylopeptoids,[12c] and with this modification each residue was formed in comparably high yield (78–89%). Solution-phase synthesis is useful for accessing products on gram-scale and, overall, the methods previously developed by us for solution-phase synthesis of *meta*- and *para*-arylopeptoids could be adapted directly to the synthesis of *ortho*-arylopeptoids.



Scheme 2. Solution-phase model studies. *Reagents and conditions:* (a) $ClCH_2ArCOOH$ (1 M), coupling reagent, DIPEA, NMP, room temp. *or* $ClCH_2ArCOCl$ (0.5 M), DIPEA, CH_2Cl_2, room temp., further conditions in Table 2. (b) *i*$PrNH_2$ (20 equiv., 2 M), DMSO, 50 °C, 7.5 min *or* room temp., 30 min.

Solid-Phase Synthesis – A Model Study

A small solution-phase study of the substitution and coupling conditions was carried out prior to the development of a solid-phase methodology. The study was carried out with monomer **2b**, chloromethyl intermediate **5**, and dimer **3b**, carrying the moderately bulky isopropyl side chain, as a model system (Scheme 2, Table 2, and the Supporting Information for details).[12b]

The potential use of the corresponding bromomethyl intermediate was quickly discarded; although we found that 2-(chloromethyl)benzoic acid and 2-(bromomethyl)benzoic acid were transformed into the derived phthalide in under 2 min in *N*-methyl-2-pyrrolidinone (NMP) and CH_2Cl_2 when DIPEA was added, transformation into an active species by use of a coupling reagent was only fast enough to compete with phthalide formation in the case of 2-(chloromethyl)benzoic acid.

We first tested the use of a selection of peptide type coupling reagents in combination with 2-(chloromethyl)benzoic acid (3.0 equiv. activated species) as 1.0 M solutions in NMP in the presence of DIPEA (Table 2, entries 1–5). We have previously tested these coupling conditions on the analogous *para*-substituted model system,[12b] and in both studies we found COMU (entry 1) to be the best coupling reagent. However, compared with a reaction time of 5 min found in the *para*-arylopeptoid study, the reaction on the *ortho*-arylopeptoid backbone required no less than one hour to reach completion, presumably as a result of increased steric hindrance. Furthermore, the extended reaction time caused the formation of minor amounts of unidentified impurities. Using our most recently developed conditions,[12a] we then found that monomer **2b** could be converted cleanly into intermediate **5** in less than 2 min by reaction with 2-(chloromethyl)benzoyl chloride (3.0 equiv.) as a 0.5 M solution in CH_2Cl_2 in the presence of DIPEA (Table 2, entry 6). Although it may therefore be possible to synthesize *ortho*-arylopeptoids using 2-(chloromethyl)benzoic acid in combination with a peptide coupling reagent, the use of the corresponding acid chloride is much more efficient.

In the analogous *para*-arylopeptoid study, we found reaction with isopropylamine (20 equiv.) as a 2 M solution in dimethyl sulfoxide (DMSO) at 50 °C to be the optimal conditions for the substitution step.[12b] When adapted directly to the conversion of intermediate **5** into *ortho*-arylopeptoid dimer **3b**, we found that the reaction proceeded four times faster than in the *para*-arylopeptoid study; the reaction was complete within 30 min at room temp. or 7.5 min at 50 °C. We suggest that this is brought about by a neighboring group effect from the adjacent amide.

Table 2. Optimization of coupling step from **2b** to give **5**.

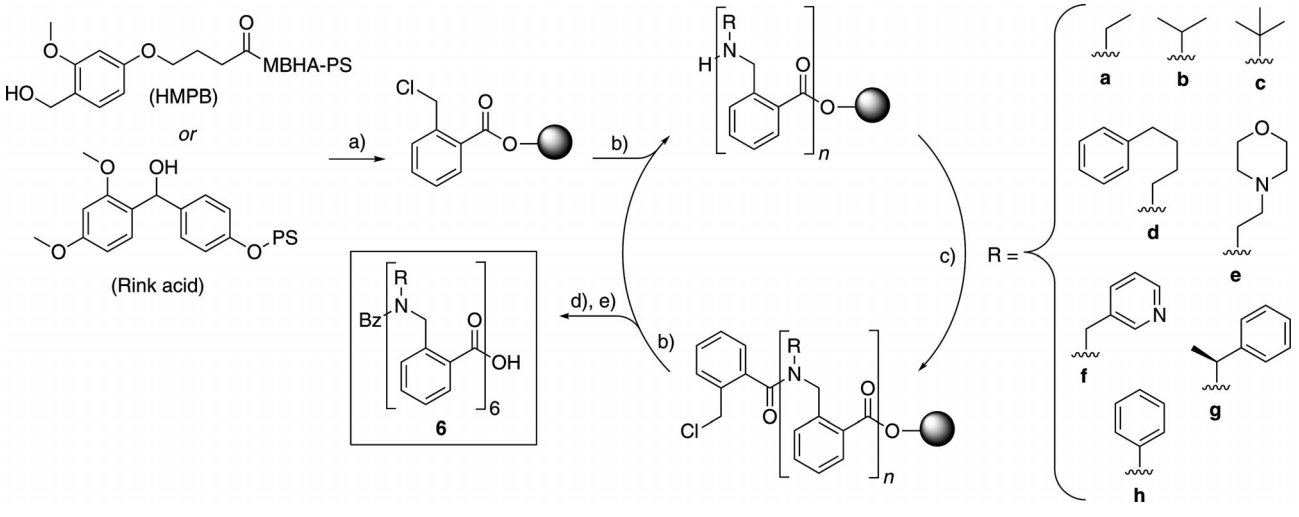
Entry	Coupling method (equiv.)	Reaction time [min][a]	Comments
1	$ClCH_2ArCOOH$ (3.0)/COMU (3.5)/DIPEA (7.0)	60	slightly impure reaction to **5**
2	$ClCH_2ArCOOH$ (6.0)/DIC (3.0)/DIPEA (7.0)	> 60	93% conv. after 60 min
3	$ClCH_2ArCOOH$ (3.0)/HATU (3.5)/DIPEA (7.0)	> 60	59% conv. after 60 min
4	$ClCH_2ArCOOH$ (3.0)/PyBOP (3.5)/DIPEA (7.0)	> 60	53% conv. after 60 min
5	$ClCH_2ArCOOH$ (3.0)/HBTU (3.5)/DIPEA (7.0)	> 60	36% conv. after 60 min
6	$ClCH_2ArCOCl$ (3.0)/DIPEA (6.0)	< 2	clean reaction to **5**

[a] Reactions monitored by analytical HPLC.

Solid-Phase Synthesis – A Free Acid at the *C*-Terminus

The promising results obtained in the above model study thus indicated that we could adapt our previously developed methods for solid-phase synthesis of *meta*- and *para*-arylopeptoids based on the use of chloromethylbenzoyl chlorides in the coupling steps directly to the synthesis of *ortho*-arylopeptoids. These methods are derived from the optimal conditions found in the model studies, albeit with extended reaction times in both the acylation steps (20 min) and the substitution steps (1 h at 50 °C) because this proved advantageous.[12a,12b] Using these methods as a starting point, we then investigated the solid-phase synthesis of a selection of model *ortho*-arylopeptoid hexamers **6a**–**h** with free acids at the *C*-terminus (Scheme 3 and Table 3). We have previously used the highly acid labile 2-chlorotrityl chloride polystyrene resin (cleavage in HFIP/CH_2Cl_2, 1:4) for solid-phase synthesis of the analogous *meta*- and *para*-arylopeptoids.[12a,12b] However, we found that the rapid conversion of 2-(chloromethyl)benzoic acid into the derived phthalide under basic conditions excluded the use of the 2-chlorotrityl chloride linker. Instead, we tested the use of the likewise highly acid labile Rink acid linker (cleavage in HFIP/CH_2Cl_2, 1:4) and the moderately acid labile HMPB linker (cleavage in TFA/water, 95:5). After some experimentation, we found that the loading of these linkers was best carried out by reaction with 2-(chloromethyl)benzoyl chloride (3.0 equiv.) as a 0.5 M solution in CH_2Cl_2 in the presence of DIPEA (3.0 equiv.) and 4-(dimethylamino)pyridine (DMAP) (3.0 equiv.); loading did not proceed efficiently in the absence of DMAP, whereas the use of 6.0 equiv. DMAP caused the formation of trace amounts of impurities. The efficiencies of the Rink acid and HMPB linkers were first studied using hexamer **6b**, carrying the moderately bulky isopropyl side chain, as the model target (Table 3, entries 1–4). When using the Rink acid linker and performing the substitution steps at room temp., hexamer **6b** was isolated in excellent crude purity (93%) and the purified product was likewise obtained in excellent yield after preparative HPLC (97%, >99% purity, entry 1). Performing the substitution reactions at 50 °C resulted in a slight increase in crude purity (99%) but concomitantly also resulted in a dramatic decrease in yield of crude material and, thus, purified **6b** (29%, >99% purity, entry 2). This dramatic loss of product during synthesis can most likely be explained by an increase in aminolysis of the growing arylopeptoid chain from the Rink acid linker when raising the temperature during the substitution steps.

For comparison, aminolysis of arylopeptoids from the more bulky 2-chlorotrityl chloride linker only appeared to be a problem when using extended reaction times (3 h) or DMSO/water mixtures in the substitution steps.[12a,12b] Isoindolinone formation after the first substitution step could represent an additional or alternative explanation. However, a test reaction showed that the previously synthesized monomer **2b** (also of the isopropyl series, see Scheme 1) remained completely stable when subjected to the solid-phase substitution conditions (monitored by analytical HPLC). As would then be expected, we found that the use of the less hindered HMPB linker resulted in substantial decreases in purified yields of hexamer **6b** compared with the Rink acid linker (67 vs. 97% and 16 vs. 29%, >99% purity, entries 3–4). We therefore chose to concentrate our efforts on the use of the Rink acid polystyrene resin. For the synthesis of hexamer **6a**, decorated with ethyl side chains (Table 3, entry 5), we unfortunately only isolated trace amounts of



Scheme 3. Solid-phase submonomer synthesis of *ortho*-arylopeptoid hexamers with free acids at the *C*-terminus. *Reagents and conditions:* (a) $ClCH_2ArCOCl$ (3.0 equiv., 0.5 M), DMAP (3.0 equiv.), DIPEA (3.0 equiv.), CH_2Cl_2, room temp., 20 min. (b) **6a**–**g**: R-NH_2 (20 equiv., 2.0 M), DMSO, room temp. or 50 °C, 1 h; **6h**: R-NH_2 (20 equiv., 4.0 M), DMSO, 50 °C, 3 h. (c) **6a**–**b** and **6d**–**h**: $ClCH_2ArCOCl$ (3.0 equiv., 0.5 M), DIPEA (6.0 equiv.), CH_2Cl_2, room temp., 20 min; **6c**: $ClCH_2ArCOCl$ (6.0 equiv., 1.0 M), DIPEA (12.0 equiv.), CH_2Cl_2, room temp., 180 min. (d) **6a**–**b** and **6d**–**h**: BzCl (3.0 equiv., 0.5 M), DIPEA (6.0 equiv.), CH_2Cl_2, room temp., 20 min; **6c**: BzCl (6.0 equiv., 1.0 M), DIPEA (12.0 equiv.), CH_2Cl_2, room temp., 180 min. (e) Rink acid polystyrene resin: HFIP/CH_2Cl_2, 1:4, room temp., 1 h. HMPB-MBHA polystyrene resin: TFA/water, 95:5, room temp., 1 h. See Table 3 for further details, yields and purities.

Table 3. Results for solid-phase submonomer synthesis of *ortho*-arylopeptoid hexamers with free acids at the *C*-terminus.

Entry	Hexamer	Linker	Substitution conditions			Acylation conditions			Crude yield	Crude purity	Pure yield
			Conc. [M]	Temp. [°C]	*t* [h]	ArCOCl [equiv.]	Conc. [M]	*t* [min]	[%]	[%][a]	[%][b]
1	**6b**	Rink acid	2	r.t.	1	3	0.5	20	101	93	97
2	**6b**	Rink acid	2	50	1	3	0.5	20	35	99	29
3	**6b**	HMPB	2	r.t.	1	3	0.5	20	96	92	67
4	**6b**	HMPB	2	50	1	3	0.5	20	35	86	16
5	**6a**	Rink acid	2	r.t.	1	3	0.5	20	trace	–	–
6	**6c**	Rink acid	2	r.t.	1	6	1.0	40	33	trace[c]	–
7	**6c**	Rink acid	2	50	1	6	1.0	180	54	23[d]	7
8	**6d**	Rink acid	2	r.t.	1	3	0.5	20	trace	–	–
9	**6e**	Rink acid	2	r.t.	1	3	0.5	20	16	76	10
10	**6f**	Rink acid	2	r.t.	1	3	0.5	20	86	36	23
11	**6f**	Rink acid	2	50	1	3	0.5	20	11	32	2
12	**6g**	Rink acid	2	r.t.	1	3	0.5	20	97	50	–[e]
13	**6g**	Rink acid	2	50	1	3	0.5	20	92	98	94[f]
14	**6h**	Rink acid	4	r.t.	3	3	0.5	20	48	trace[g]	–
15	**6h**	Rink acid	4	50	3	3	0.5	20	7	91	5

[a] Determined by analytical HPLC. [b] Yield of product isolated in >99% purity after preparative HPLC. [c] LC-MS revealed only trace amounts of oligomers longer than trimer length. [d] Major impurities: pentamer and tetramer (LC-MS). [e] HPLC purification hindered due to poor solubility. [f] Purified by aqueous extraction due to poor solubility in HPLC solvents. [g] Complex HPLC; LC-MS showed the presence of all oligomer lengths.

crude product, presumably as a result of even more favorable aminolysis and/or isoindolinone formation when installing this small side chain. To accommodate the expected difficult acylations in the synthesis of hexamer **6c**, with the highly bulky *tert*-butyl side chains, we first doubled the concentrations and number of equivalents of reagents as well as the reaction time of these steps,[12a] whereas the substitution steps were performed at room temp. (entry 6). This proved not to suffice, however, because the crude product contained only trace amounts of oligomers longer than trimers. The reaction time of the acylation steps was therefore extended to 3 h and the substitution steps were performed at 50 °C, which allowed for isolation of hexamer **6c** in 7% yield (>99% purity, entry 7). The next hexamers studied, **6d**–**g**, followed the same trend as above; the lower the encumbrance of the primary amine used in the substitution steps, the lower the yield, presumably due to more facile aminolysis and/or isoindolinone formation.

Thus, attempts at the synthesis of hexamer **6d**, with phenylbutyl side chains, produced only trace amounts of crude products even though the substitution steps were performed at room temp. (Table 3, entry 8). More success was achieved in the syntheses of the water soluble oligomers **6e** and **6f**, with 2-morpholinoethyl and pyridinylmethyl side chains, respectively (entries 9–10). These oligomers were obtained in 10 and 23% yield (>99% purity) when performing the substitution reactions at room temp. Attempts to improve on the crude purity of **6f** by performing the substitution reactions at 50 °C proved futile and, as expected, caused a dramatic decrease in yield to 2% (entry 11). When performing the substitution reactions at room temp., hexamer **6g**, with the bulky (*S*)-*N*-(1-phenylethyl) (*spe*) side chains, was first isolated in 92% crude yield and 50% crude purity (entry 12). Due to poor solubility, this product could not be purified by preparative reverse-phase HPLC. However, we found that hexamer **6g** could be obtained in 94% yield and 98% purity by performing the substitution steps at 50 °C and purifying the crude product by aqueous extraction (entry 13). The final *ortho*-arylopeptoid of this model study, hexamer **6h**, decorated with phenyl side chains, was obtained through the use of unreactive aniline in the substitution steps. Compensating for this low reactivity by using 4 M solutions of aniline in DMSO at room temp., in combination with reaction times extended to 3 h in the substitution steps,[12a] first afforded a crude product containing a complex mixture of all oligomer lengths between monomer and hexamer (48% crude yield, entry 14). Performing the substitution steps at 50 °C caused a dramatic decrease in crude yield (7%) but allowed for isolation of 5% of the desired hexamer **6h** (entry 15).

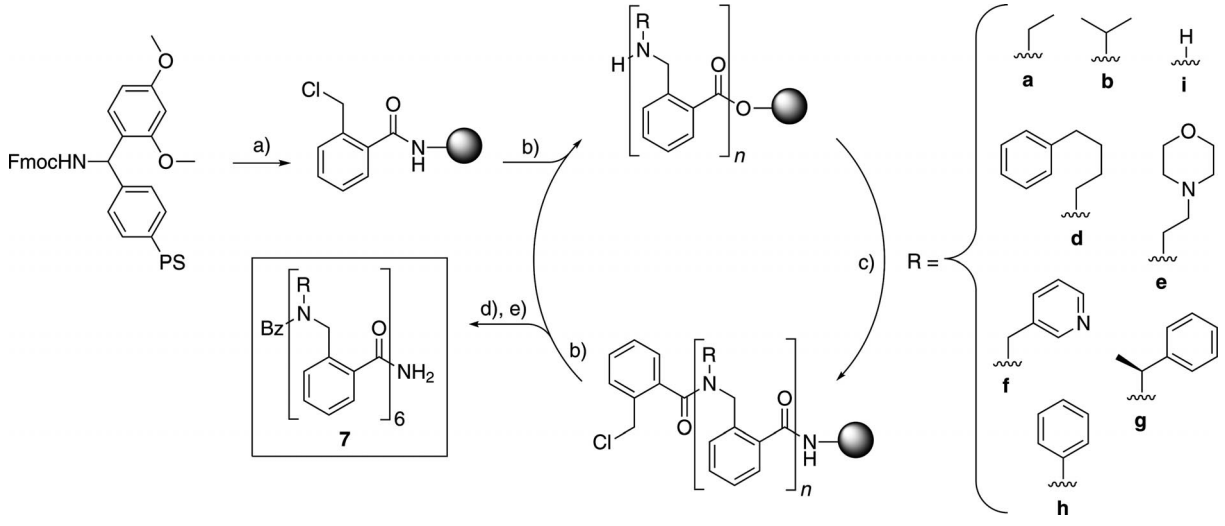
Solid-Phase Synthesis; Primary Amide at the *C*-Terminus

Although selected oligomers of *ortho*-arylopeptoids with free acids at the *C*-terminus may be synthesized using the Rink acid linker, the limited stability of this linker prevented comparison of the efficiency of the chain elongation process in *ortho*-arylopeptoids with that of the corresponding *meta*- and *para*-arylopeptoids. To enable this comparison, we therefore synthesized *ortho*-hexamers **7a**–**h**, which carry a primary amide at the *C*-terminus (Scheme 4 and Table 4). As in our previous syntheses of the *meta*- and *para*-counterparts,[12a] these *ortho*-arylopeptoids were synthesized on the highly stable Rink amide polystyrene resin (cleavage in TFA/water, 95:5), for which the risk of aminolysis and/or isoindolinone formation is minimal. The only modification to the submonomer chain growth procedures compared with synthesis on the Rink acid linker was that all substitution reactions were carried out at 50 °C. The first two *ortho*-hexamers, **7b** of the isopropyl series and **7a** of the ethyl series, were isolated in 96 and 81% yields, respectively (>99% purity, Table 4, entries 1 and 2). For comparison, the yield of hexamer **7b** was approximately 25% higher than what was previously achieved in the synthesis of the analogous *para*-hexamer using identical conditions.[12a] The harsh cleavage conditions (TFA/water, 95:5, 2 h) was anticipated to cause concomitant removal of any *tert*-butyl side chains installed on the backbone amides. Indeed, when using *tert*-butylamine in the substitution steps we isolated the derived hexamer **7i** with free backbone amide protons in 101% crude yield and 48% crude purity (entry 3). Although poor solubility hindered purification by preparative HPLC, the crude product was soluble enough to allow analysis by HPLC and HRMS. This is the first time we have been able to establish that the *tert*-butyl group can be used as a masked free amide proton in arylopeptoid synthesis; the nature of the crude products obtained in the analogous syntheses of the corresponding *meta*- and *para*-hexamers could not be established due to complete insolubility in any useful organic solvent.[12a] Hexamer **7d**, with phenylbutyl side chains, and the water soluble hexamer **7e**, with 2-morpholinoethyl side chains, were isolated in crude purities and purified yields (76 and 63%, entries 4 and 5) similar to those previously obtained in the synthesis of the analogous *meta*- and *para*-hexamers.[12a] Although hexamer **7g**, with *spe* side chains, was also obtained in a crude purity reminiscent of what was obtained for the corresponding *meta*- and *para*-hexamers,[12a] the desired product was only isolated in 23% yield (>99% purity, entry 7), presumably due to loss of product during preparative HPLC purification caused by low solubility. It should be noted that the cleavage time was

Table 4. Results for solid-phase submonomer synthesis of *ortho*-arylopeptoid hexamers with primary amides at the *C*-terminus.

Entry	Hexamer	Crude yield [%]	Crude purity [%][a]	Purified yield [%][b]
1	**7b**	141	99	96
2	**7a**	132	91	81
3	**7i**[c]	101	48	–[d]
4	**7d**	117	92	76
5	**7e**	107	84	63
6	**7f**	106	28	20
7	**7g**	104	80	23[e]
8	**7h**	106	50[f]	35

[a] Determined by analytical HPLC. [b] Yield of product isolated in >99% purity after preparative HPLC. [c] *tert*-Butylamine used in the substitution steps. [d] HPLC purification hindered due to poor solubility. [e] Low purified yield presumably due to low solubility of crude and pure product. [f] Major byproducts: pentamer and tetramer.



Scheme 4. Solid-phase submonomer synthesis of *ortho*-arylopeptoid hexamers with primary amides at the *C*-terminus. *Reagents and conditions:* (a) piperidine/NMP, 1:4, room temp., 2 and 15 min; then $ClCH_2ArCOCl$ (3.0 equiv., 0.5 M), DIPEA (6.0 equiv.), CH_2Cl_2, room temp., 20 min. (b) **7a**–**g** and **7i**: R-NH_2 (20 equiv., 2.0 M), DMSO, 50 °C, 1 h; **7h**: R-NH_2 (20 equiv., 4.0 M), DMSO, 50 °C, 3 h. (c) **7a**–**h**: $ClCH_2ArCOCl$ (3.0 equiv., 0.5 M), DIPEA (6.0 equiv.), CH_2Cl_2, room temp., 20 min; **7i**: $ClCH_2ArCOCl$ (6.0 equiv., 1.0 M), DIPEA (12.0 equiv.), CH_2Cl_2, room temp., 180 min. (d) **7a**–**h**: BzCl (3.0 equiv., 0.5 M), DIPEA (6.0 equiv.), CH_2Cl_2, room temp., 20 min; **7i**: BzCl (6.0 equiv., 1.0 M), DIPEA (12.0 equiv.), CH_2Cl_2, room temp., 180 min. (e) TFA/water, 95:5, room temp., 2 h (2× 10 min for **7g**). See Table 4 for yields and purities.

reduced to 2× 10 min in the case of hexamer **7g** to minimize degradation of the crude product.[12a] The last two hexamers, **7f** of the water soluble pyridinylmethyl series and **7h** of the phenyl series, were isolated in lower crude purities compared with the corresponding *meta*- and *para*-hexamers,[12a] however, the purified products were still isolated in comparable yields (20 and 35%, respectively, >99% purity, entries 6 and 8). These results using the Rink amide linker demonstrate that when adapting the methods we previously developed for solid-phase synthesis of *meta*- and *para*-arylopeptoids[12a] to the synthesis of the corresponding *ortho*-arylopeptoids, similar levels of efficiencies may be obtained. The most prominent exception is when installing the *tert*-butyl side chain in *ortho*-arylopeptoids, in which case much extended reaction times were needed in the acylation steps.

Conformational Studies

We have previously undertaken the first conformational studies of *meta*- and *para*-arylopeptoids by means of NMR spectroscopy.[12a,12c] Intriguingly, we found that the *tert*-butyl and phenyl side chains represented particularly interesting cases because only single, sharp sets of signals were observed in the spectra of *meta*- and *para*-arylopeptoids carrying these side chains. NOESY experiments revealed that the highly bulky *tert*-butyl side chain invoked a 100% *cis* conformation about the amide bond, presumably as a result of steric effects, whereas the phenyl side chain resulted in a 100% *trans* conformation.[12a,12c] The latter observation was in agreement with results reported on closely related *N*-alkylated benzanilide monomers[3d] and *N*-methyl-*N*-phenyl acetamides.[20] For the *N*-methyl-*N*-phenylacetamides, ab initio molecular orbital calculations indicated that this preference may be due to a combination of the *N*-phenyl side chain being less bulky than the *N*-methylbenzyl group and electronic repulsions between the carbonyl lone pair and the phenyl π-electrons.[20b] The *tert*-butyl and phenyl side chains thus enabled a rarely seen complete control over the amide conformations in *meta*- and *para*-arylopeptoids. For *meta*- and *para*-arylopeptoids with any other type of side chain we observed NMR spectra with very broad signals, indicating that these oligomers underwent conformational changes in the intermediate time regime on the NMR time scale. Furthermore, due to the presence of *cis*/*trans* amide mixtures, the NMR spectra of these *meta*- and *para*-arylopeptoids contained partly overlapping sets of signals for carbons and/or protons in close proximity to the amide nitrogen atom(s).[12a,12c] In general, no distinct length-dependent changes to the spectra of *meta*- and *para*-arylopeptoids were observed.

Interestingly, the NMR spectra of the *ortho*-arylopeptoids synthesized herein (see the Supporting Information) showed very different characteristics to those of the corresponding *meta*- and *para*-arylopeptoids. Thus, although dimer **3c** and trimer **4c**, with *tert*-butyl side chains, as expected, showed the presence of only a single set of signals, very broad signals were observed for the benzylic protons adjacent to the amide moieties (CONCH_2Ar). We propose that this is a result of the environment around these protons undergoing conformational changes in the intermediate time regime on the NMR time scale. In the case of dimer **3c**, the broad signal was furthermore split into two broad signals of equal size. We suggest this signal splitting is a result of the highly encumbered environment, which may cause these benzylic protons to have different dihedral angles to the surrounding substituents. This effect is then most clearly observed in dimer **4c**, which only contains a single amide moiety. Furthermore, dimers with ethyl side chains (**3a**) or isopropyl side chains (**3b**) produced NMR spectra with sharp signals even though *cis*/*trans*-amide mixtures were present. At trimer length (**4a**–**b**), the complexity increased and the hexamers (**6** and **7**), in general, all produced spectra that were considerably more complex than their *meta*- and *para*-counterparts. These observations indicate that the rotation about each amide bond in *ortho*-arylopeptoids is, as expected, more restricted than for their *meta*- and *para*-counterparts. The combination of the restricted rotation and the more "congested" backbone structure resulting from the *ortho*-connectivity pattern in *ortho*-arylopeptoids then offers a plausible explanation for the highly complex NMR spectra observed for the longer oligomers.

To enable more detailed NMR studies of *ortho*-arylopeptoids, we therefore synthesized model monomers **8b** (isopropyl side chain), **8c** (*tert*-butyl side chain), **8g** (*spe* side chain), **8h** (phenyl side chain), and **8i** (free backbone amide proton) as illustrated in Figure 2. These model monomers all consisted of an arylopeptoid residue with a free acid at the *C*-terminus and a 2-methylbenzoyl capping group at the *N*-terminus that served as a simple model for a continuing *ortho*-arylopeptoid backbone. The model monomers were synthesized as described above using the Rink acid linker, in all cases performing the substitution reaction at 50 °C.

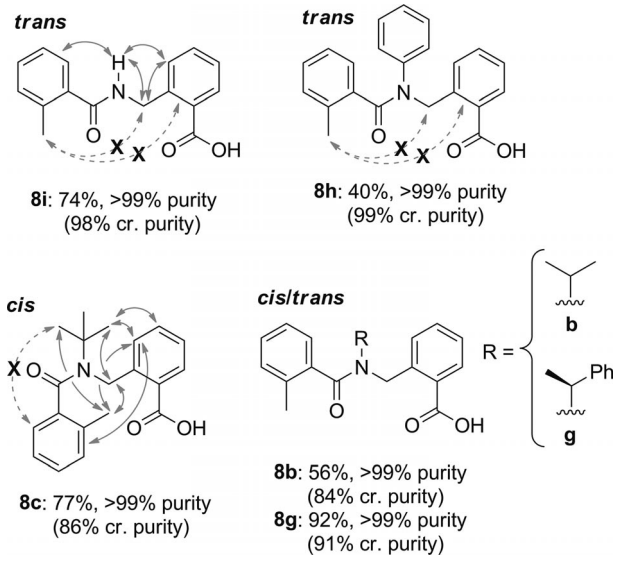


Figure 2. Model monomer arylopeptoids and observed NOESY correlations if applicable.

The correlations observed in the NOESY spectrum of **8c** (*tert*-butyl side chain) in $CDCl_3$ at room temp. were, as expected, indicative of a 100% *cis* conformation (see Figure 2 and the Supporting Information); the methyl substituent on the *N*-capping group correlated with both the benzylic protons and the aromatic protons of the arylopeptoid residue, whereas the *tert*-butyl side chain showed no correlations with the aromatic part of the capping group. As a result of the congested backbone structure of the *cis*-amide conformation, a correlation between the *tert*-butyl side chain and the methyl substituent of the *N*-capping group was also observed. Previous attempts to study the *meta*- and *para*-arylopeptoids with free backbone amide proton(s) were hindered because of insolubility.[12a] We were therefore satisfied to find that model monomer **8i**, with a free backbone amide proton, was sufficiently soluble to allow for NMR analysis in $[D_6]$DMSO as well as in MeOD. Only one conformer was observed in both solvents, and the NOESY spectrum was indicative of a 100% *trans* amide conformation. Correlations between the backbone amide proton and the aromatic protons of the *N*-capping group were observed, whereas no correlations were observed between the methyl group of the *N*-capping group and the benzylic or aromatic protons of the arylopeptoid residue (see Figure 2 and the Supporting Information). Interestingly, overall, this means that the *tert*-butyl side chain can be used both for invoking a 100% *cis* conformation in arylopeptoids and serve as a protecting group during synthesis, which can later be removed to allow the amide group(s) to adopt a 100% *trans* amide conformation instead. Model monomer **8h**, which carries a phenyl side chain, was likewise expected to adopt a 100% *trans* amide conformation and, indeed, only a single conformer was observed in the NMR spectrum of **8h** in $CDCl_3$ at room temp., but overlap in the aromatic region of the NOESY spectra unfortunately did not allow as many correlations to be identified as in the case of **8i** (see Figure 2 and the Supporting Information). The absence of correlations between the methyl group of the *N*-capping group and the benzylic or aromatic protons of the arylopeptoid residue did, however, still indicate the presence of the expected 100% *trans* amide conformation. NMR spectra of model monomer **8b** of the isopropyl series revealed the presence of two conformers in ca. 80:20 ratio in $CDCl_3$ at room temp. (see the Supporting Information). Overlap in the aromatic region of the NOESY spectra unfortunately hindered the extraction of any additional information. However, in general, we observed the following: (1) the highly bulky *tert*-butyl side chain was shown to invoke a 100% *cis* conformation; (2) dimer **3b**, with the least hindered ethyl side chain, existed as a ca. 50:50 mixture of *cis* and *trans* amides (see the Supporting Information); (3) in the NMR spectra of model monomer **8b** as well as dimer **3b**, which both carry the moderately bulky isopropyl side chain, we observed the existence of mixtures of two conformers in ca. 80:20 ratio (see the Supporting Information). In cases with simple alkyl side chains, these observations suggest that increasing bulk of the side chain resulted in an increasing proportion of *cis*-amide conformation, and the major conformer in model monomer **8b** (as well as in dimer **3b**) therefore most likely corresponded to the *cis*-conformer. It is worth noting that these ratios are similar to those previously observed for the analogous *meta*- and *para*-dimers.[12c]

The *spe* side chain is interesting because it has been used extensively in conformational studies of peptoids.[15,19,21] Model monomer **8g** existed as a 75:25 mixture of two conformers in $CDCl_3$ at room temp. (see the Supporting Information), which is similar to what was observed in the analogous *meta*- and *para*-arylopeptoids with *spe* side chains,[12a] but extensive overlap in the NOESY spectrum hindered further analysis. For the corresponding *meta*- and *para*-arylopeptoids, we have, however, previously deduced that the major conformer may correspond to the *trans* conformer.[12a] To investigate the presence of any length-dependent behavior in *ortho*-arylopeptoids carrying the *spe* side chain, we synthesized monomer **9g** and trimer **10g** (Figure 3) and compared the NMR spectra ($CDCl_3$ at room temp.) to those obtained for hexamer **6g**. The corresponding nonamer was also synthesized but the crude product was discarded due to insolubility.

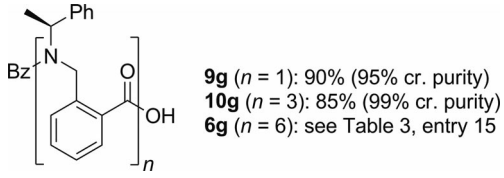


Figure 3. The *spe* series *ortho*-arylopeptoids; the yields are of products isolated in more than 99% purity after preparative HPLC.

The *spe*-series of *ortho*-arylopeptoids was found to follow the same pattern as the rest of the *ortho*-arylopeptoid family; monomer **9g** produced simple NMR spectra with sharp signals, whereas increased complexity was observed for trimer **10g** and highly complex spectra were obtained in the case of hexamer **6g** (see the Supporting Information). We are currently studying these *spe*-series *ortho*-arylopeptoids by means of circular dichroism spectroscopy.

Conclusions

Examples of "one-way sequence" aromatic oligoamides constructed of aromatic amino acids that are connected through *ortho*-linked aromatics are very rare. Herein, we have presented the first synthesis and studies of *ortho*-arylopeptoids as an entirely new type of aromatic oligoamides with an *ortho*-connection pattern in the backbone. These oligoamides may be synthesized both in solution and on solid-phase by using unique and highly efficient submonomer methods wherein the residues are created directly on the growing chain in an iterative manner. Only commercially available reagents are needed and our methods allow the synthesis of target arylopeptoids on a gram scale as well as synthesis of highly diversified libraries. The methods we have used are reminiscent of those we have previously developed for *meta*- and *para*-arylopeptoids, although the *ortho*-

arylopeptoids show a slightly different reaction pattern. Exceptions include longer reaction times in the acylations of *ortho*-arylopeptoids carrying the highly bulky *tert*-butyl side chain as well as a necessitated change from the 2-chlorotrityl chloride linker to the Rink acid linker in the solid-phase synthesis of *ortho*-arylopeptoids with a free acid at the *C*-terminus. The latter change reduced the synthetic scope in some cases, in particular when synthesizing *ortho*-arylopeptoids with small side chains. In general, however, it was shown that the efficiency of the chain growth process in *ortho*-arylopeptoids was similar to that of the corresponding *meta*- and *para*-arylopeptoids. The *ortho*-arylopeptoids were studied by NMR spectroscopy and were shown to display different length-dependent trends to those of their *meta*- and *para*-counterparts; whereas the NMR spectra of shorter oligomers showed sharp signals, longer oligomers produced highly complex NMR spectra. These observations indicate that there is more restricted rotation about the amide bonds in *ortho*-arylopeptoids, presumably due to a more congested backbone structure resulting from the *ortho*-connectivity pattern. Model studies showed that the *tert*-butyl and phenyl side chains offer a rarely seen complete control over the amide conformations; (short) *ortho*-arylopeptoids with *tert*-butyl side chains adopt a 100% *cis* conformation, whereas the presence of a phenyl side chain resulted in the complete opposite 100% *trans* amide conformation. We furthermore found that the *tert*-butyl side chain can be used both for invoking a 100% *cis* conformation in arylopeptoids and to serve as a protecting group during synthesis, which can later be removed to allow the amide(s) to adopt a 100% *trans* amide conformation instead.

The development of *ortho*-arylopeptoids presented herein greatly increases the possible scope for design and diversity in the field of arylopeptoids. We will continue to study and explore all aspects of this intriguing family of aromatic oligoamides and will report our findings in due course.

Experimental Section

General Methods: CH_2Cl_2, Et_3N and THF used in reactions were dried with 4 Å molecular sieves. Technical grade 2-(bromomethyl)-benzoyl bromide obtained from Matrix Scientific was distilled under reduced pressure before use. All other chemicals obtained from commercial sources (Alfa Aesar, Fluka, Merck and Sigma–Aldrich) were used as received. Rink amide copoly(styrene-1% DVB) resin (100–200 mesh) with a listed loading of 0.74 mmol/g, Rink acid copoly(styrene-1% DVB) resin (100–200 mesh) with a listed loading of 0.55 mmol/g, and HMPB-MBHA copoly(styrene-1% DVB) resin (100–200 mesh) with a listed loading of 0.71 mmol/g were purchased from Merck. Primary amines (2.0 or 4.0 M in DMSO) used in the substitution steps during solid-phase synthesis were prepared from the neat, free amines, except in the case of ethylamine for which a saturated aqueous solution was used as a source of the amine. Melting points were determined with a Mettler Toledo MP70 melting point system and are referenced to the melting points of benzophenone and benzoic acid. NMR spectra were recorded with a Bruker Avance 300 MHz spectrometer. Chemical shifts are referenced to the residual solvent peak and *J* values are given in Hz. The following multiplicity abbreviations are used: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), and broad (br). Where applicable, assignments were based on COSY, HMBC, HSQC and *J*-mod experiments. TLC analyses were performed on Merck TLC aluminum sheets (silica gel 60, F_{254}). Progress of reactions was, when applicable, followed by HPLC, NMR and/or TLC. Visualizing spots on TLC was effected with UV-light and/or ninhydrin in EtOH/AcOH. Flash chromatography was performed with silica gel 60 (35–75 μm), purchased from Fluka. Unless otherwise stated, flash chromatography was performed in the eluent system for which the R_f values are given. HRMS were recorded with a Micromass LCT apparatus equipped with an AP-ESI probe calibrated with Leu-Enkephalin.

Solution-Phase Synthesis

Method A. General Procedure for Synthesis of the First Arylopeptoid Residue: To a solution of **1**[18] (1.0 equiv., 0.2 M in THF) at 0 °C under N_2 was added Et_3N (2.0 equiv.) and then the chosen primary amine (10.0 equiv., either neat or as a 2 M solution in THF). After stirring overnight at room temp., the resulting mixture was concentrated under reduced pressure. The residue was taken up in EtOAc and washed with satd. aq. $NaHCO_3$ (1×) and brine (1×). The combined aqueous layers were extracted with EtOAc (1×) and the combined organic layers were dried with Na_2SO_4, filtered, and concentrated under reduced pressure. Flash chromatography of the residue yielded the desired product.

Method B. General Procedure for Synthesis of Arylopeptoid Residues (except for *tert*-butyl side chain): To a solution of the secondary amine (1.0 equiv., 0.2 M in THF) at 0 °C under N_2 was added Et_3N (1.05 equiv.) and then 2-(bromomethyl)benzoyl bromide (1.05 equiv.). After stirring for 1 h at 0 °C, Et_3N (2.0 equiv.) and then the chosen primary amine (10.0 equiv., either neat or as a 2 M solution in THF) were added. After stirring overnight at room temp., the resulting mixture was concentrated under reduced pressure. The residue was taken up in EtOAc (dimers) or CH_2Cl_2 (trimers) and washed with satd. aq. $NaHCO_3$ (1×) and brine (1×). The combined aqueous layers were extracted with EtOAc (dimers, 1×) or CH_2Cl_2 (trimers, 1×) and the combined organic layers were dried with Na_2SO_4, filtered, and concentrated under reduced pressure. Flash chromatography of the residue gave the desired product.

Method C. General Procedure for Synthesis of Arylopeptoid Residues with *tert*-Butyl Side Chain: To a solution of the secondary amine (1.0 equiv., 0.2 M in THF) at 0 °C under N_2 was added Et_3N (2.0 equiv.) and then 2-(bromomethyl)benzoyl bromide (2.0 equiv.). After stirring for 1 h at 0 °C, the resulting mixture was concentrated under reduced pressure. The residue was taken up in CH_2Cl_2 and washed with satd. aq. $NaHCO_3$/brine, 1:1 (1×). The aqueous layer was extracted with CH_2Cl_2 (1×) and the combined organic layers were dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was passed through a short silica gel column to give the sufficiently pure acylated intermediate. To a solution of the acylated intermediate (1.0 equiv., 0.2 M in THF) at 0 °C under N_2 was added Et_3N (2.0 equiv.) and then *tert*-butylamine (10.0 equiv.). After stirring overnight at room temp., the resulting mixture was concentrated under reduced pressure. The residue was taken up in CH_2Cl_2 and washed with satd. aq. $NaHCO_3$ (1×) and brine (1×). The combined aqueous layers were extracted with CH_2Cl_2 (1×) and the combined organic layers were dried with Na_2SO_4, filtered, and concentrated under reduced pressure. Flash chromatography of the residue gave the desired product.

***tert*-Butyl 2-[(Ethylamino)methyl]benzoate (2a):** Treatment of **1**[18] (543 mg, 2.00 mmol) by Method A with ethylamine (2 M) in THF

yielded **2a** (290 mg, 62%, >99% purity) as a pale-yellowish oil. R_f (EtOAc/MeOH, 95:5) = 0.08. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.82–7.77 (m, 1 H, *o*-C_6H_4COO), 7.46–7.37 (m, 2 H, *p*-C_6H_4COO and *m*′-C_6H_4COO), 7.31–7.25 (m, 1 H, *m*-C_6H_4COO), 3.97 (s, 2 H, HNCH_2Ar), 2.66 (q, *J* = 7.1 Hz, 2 H, HNCH_2CH$_3$), 1.89–1.82 (br. s, 1 H, N*H*), 1.60 (s, 9 H, O*t*Bu), 1.12 (t, *J* = 7.1 Hz, 3 H, HNCH$_2$CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.2 (C_q, *C*OO), 141.0 (C_q, *o*′-C_6H_4COO), 131.9 (C_q, *ipso*-C_6H_4COO), 131.3 (CH, *p*-C_6H_4COO), 130.6 (CH, *m*′-C_6H_4COO), 130.4 (CH, *o*-C_6H_4COO), 126.8 (CH, *m*-C_6H_4COO), 81.4 (C_q, O*t*Bu), 52.5 (CH_2, HN*C*H$_2$Ar), 43.5 (CH_2, HN*C*H$_2$CH$_3$), 28.2 (3× CH_3, O*t*Bu), 15.3 (CH_3, HNCH$_2$*C*H$_3$) ppm. HRMS (TOF MS, ES$^+$): *m*/*z* calcd. for $C_{13}H_{20}NO_2$ [M + H]$^+$ 236.1645; found 236.1647.

Also isolated was 2-ethyl-2,3-dihydro-1*H*-isoindol-1-one (84 mg, 26%) as a pale-yellowish solid; m.p. 40–43 °C. R_f (EtOAc/MeOH, 95:5) = 0.58. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.83–7.79 (m, 1 H), 7.53–7.38 (m, 3 H), 4.35 (s, 2 H), 3.65 (q, *J* = 7.3 Hz, 2 H), 1.25 (t, *J* = 7.3 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.1 (C_q), 141.0 (C_q), 133.0 (C_q), 131.0 (CH), 127.9 (CH), 123.5 (CH), 122.6 (CH), 49.2 (CH_2), 36.9 (CH_2), 13.5 (CH_3) ppm. HRMS (TOF MS, ES$^+$): *m*/*z* calcd. for $C_{10}H_{12}NO$ [M + H]$^+$ 162.0913; found 162.0910.

Arylopeptoid Dimer 3a: Treatment of **2a** (236 mg, 1.00 mmol) by Method B with ethylamine (2 M) in THF yielded **3a** (323 mg, 81%, >99% purity) as a pale-yellowish oil. R_f (EtOAc/MeOH, 80:20) = 0.21. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.86 (m, *J* = 7.8, 1.2 Hz, 0.49 H, *o*-C_6H_4COO, minor isomer), 7.83 (dd, *J* = 7.8, 1.3 Hz, 0.51 H, *o*-C_6H_4COO, major isomer), 7.57–7.19 (m, 6 H), 7.09–7.04 (m, 1 H), 5.19 (s, 1.02 H, CONCH_2Ar, major isomer), 4.74 (s, 0.98 H, CONCH_2Ar, minor isomer), 3.80–3.10 (br., 0.98 H, CONCH_2CH$_3$, minor isomer), 3.78, 3.76 (2× s, 2 H, HNCH_2Ar), 3.15 (q, *J* = 7.1 Hz, 1.02 H, CONCH_2CH$_3$, major isomer), 2.70–2.60 (m, 2 H, HNCH_2CH$_3$), 2.11–2.04 (br. s, 1 H, N*H*), 1.59 (s, 4.59 H, O*t*Bu, major isomer), 1.48 (s, 4.41 H, O*t*Bu, minor isomer), 1.25 (t, *J* = 7.1 Hz, 1.47 H, CONCH$_2$CH_3, minor isomer), 1.11, 1.08 (2× t, *J* = 7.1 and 7.1 Hz, 3 H, HNCH$_2$CH_3), 1.02 (t, *J* = 7.1 Hz, 1.53 H, CONCH$_2$CH_3, major isomer) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.7, 171.6 (C_q, *C*ON), 166.6, 165.9 (C_q, *C*OO), 138.6, 138.6 (C_q, *o*′-C_6H_4COO), 137.0, 136.9, 136.5, 136.0 (2× C_q, *ipso*-C_6H_4CON and *o*′-C_6H_4CON), 131.9, 131.7 (CH), 131.1, 130.4 (C_q, *ipso*-C_6H_4COO), 130.9, 130.5, 129.9, 129.8, 128.8, 128.8, 127.7, 126.8, 126.8, 126.7, 126.6, 126.6, 125.7, 125.1 (7CH), 81.5, 81.4 (C_q, O*t*Bu), 51.7, 51.5 (CH_2, HN*C*H$_2$Ar), 50.0 (0.49× CH_2, CON-*C*H$_2$Ar, minor isomer), 44.6 (0.51×CH_2, CON*C*H$_2$Ar, major isomer), 43.7, 43.6, 43.4 (1.51× CH_2, HN*C*H$_2$CH$_3$ and CON*C*H$_2$CH$_3$, major isomer), 40.0 (0.49× CH_2, CON*C*H$_2$CH$_3$, minor isomer), 28.1, 28.0 (3× CH_3, O*t*Bu), 15.1 (2× CH_3, HNCH$_2$*C*H$_3$), 13.6 (0.51× 2CH_3, CONCH$_2$*C*H$_3$), 12.0 (0.49× 2CH_3, CONCH$_2$*C*H$_3$) ppm. HRMS (TOF MS, ES$^+$): *m*/*z* calcd. for $C_{24}H_{33}N_2O_3$ [M + H]$^+$ 397.2486; found 397.2479.

Arylopeptoid Dimer 4a: Treatment of **3a** (238 mg, 0.60 mmol) by Method B with ethylamine (2 M) in THF yielded **4a** (285 mg, 85%, >99% purity) as a pale-yellowish oil. R_f (EtOAc/MeOH, 70:30) = 0.24. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.91–7.78 (m, 1 H), 7.63–6.98 (m, 11 H), 5.28–4.20 (m, 4 H, 2×CONCH_2Ar), 4.05–3.02 (m, 6 H, HNCH_2Ar and CONCH_2CH$_3$), 2.70–2.58 (m, 2 H, HNCH_2CH$_3$), 1.90–1.70 (br. s, 1 H, N*H*), 1.60, 1.58, 1.50 (3× s, 9 H), 1.32–0.92 (m, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.7, 171.6, 171.6, 171.5, 171.1, 171.0, 170.4, 170.3 (2C_q), 166.6, 166.5, 165.9, 165.7 (C_q), 138.5, 138.4, 138.3, 138.3, 137.1, 137.0, 136.9, 136.3, 136.3, 136.2, 136.1, 136.0, 135.1, 134.9, 134.5, 134.2, 133.8 (5C_q), 131.9, 131.9, 131.8, 131.6, 131.0, 130.7, 130.6, 129.8, 129.7, 129.7, 129.2, 129.2, 128.9, 128.8, 128.8, 128.2, 127.8, 127.6, 127.2, 127.1, 127.0, 127.0, 126.9, 126.8, 126.7, 126.6, 126.3, 126.2, 126.0, 125.7, 125.7, 125.4, 125.3, 125.2, 125.2 (12CH), 131.3, 131.2, 130.3 (C_q), 81.6, 81.5, 81.5, 81.4 (C_q), 51.7, 51.6, 51.5, 51.5 (CH_2, HN*C*H$_2$Ar), 49.8, 49.7, 48.8, 48.8, 44.9, 44.1 (2× CH_2, 2× CON-*C*H$_2$Ar), 43.7, 43.0, 42.8, 40.2, 40.1, 40.0, 39.7 (3× CH_2, HN*C*H$_2$CH$_3$ and 2× CON*C*H$_2$CH$_3$), 28.2, 28.1 (3× CH_3), 15.2, 13.7, 13.5, 13.4, 12.4, 12.2, 12.0, 12.0 (3CH_3) ppm. HRMS (TOF MS, ES$^+$): *m*/*z* calcd. for $C_{34}H_{44}N_3O_4$ [M + H]$^+$ 558.3326; found 558.3327.

***tert*-Butyl 2-[(Propan-2-ylamino)methyl]benzoate (2b):** Treatment of **1**[18] (543 mg, 2.00 mmol) by Method A with isopropylamine yielded **2b** (441 mg, 88%, >99% purity) as a pale-yellowish oil. R_f (EtOAc/MeOH, 95:5) = 0.19. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.78 (d, *J* = 7.78 Hz, 1 H, *o*-C_6H_4COO), 7.46–7.36 (m, 2 H, *p*-C_6H_4COO and *m*′-C_6H_4COO), 7.32–7.23 (m, 1 H, *m*-C_6H_4COO), 3.97 (s, 2 H, HNCH_2Ar), 2.88–2.74 [m, 1 H, HNC*H*(CH$_3$)$_2$], 1.97–1.86 (br. s, 1 H, N*H*), 1.60 (s, 9 H, O*t*Bu), 1.09 [d, *J* = 6.2 Hz, 6 H, HNCH(CH_3)$_2$] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.2 (C_q, *C*OO), 141.2 (C_q, *o*′-C_6H_4COO), 132.0 (C_q, *ipso*-C_6H_4COO), 131.4 (CH, *p*-C_6H_4COO), 130.6 (CH, *m*′-C_6H_4COO), 130.3 (CH, *o*-C_6H_4COO), 126.7 (CH, *m*-C_6H_4COO), 81.3 (C_q, O*t*Bu), 50.0 (CH_2, HN*C*H$_2$Ar), 47.7 [CH, HN*C*H(CH$_3$)$_2$], 28.2 (3× CH_3, O*t*Bu), 22.9 [2× CH_3, HNCH(*C*H$_3$)$_2$] ppm. HRMS (TOF MS, ES$^+$): *m*/*z* calcd. for $C_{15}H_{24}NO_2$ [M + H]$^+$ 250.1802; found 250.1797.

Arylopeptoid Dimer 3b: Treatment of **2b** (374 mg, 1.50 mmol) by Method B with isopropylamine yielded **3b** (550 mg, 86%, >99% purity) as a pale-yellowish oil. R_f (EtOAc/MeOH, 90:10) = 0.19. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.89 (dd, *J* = 7.8, 1.2 Hz, 0.78 H, *o*-C_6H_4COO, major isomer), 7.75 (dd, *J* = 7.8, 1.2 Hz, 0.22 H, *o*-C_6H_4COO, minor isomer), 7.60–7.15, 7.06–6.95 (2× m, 7 H), 5.18 (d, *J* = 17.2 Hz, 0.78 H, CONC*H*HAr, major isomer), 5.04 (d, *J* = 17.2 Hz, 0.78 H, CONCH*H*Ar, major isomer), 4.80–4.57 [m, 0.66 H, CONC*H*(CH$_3$)$_2$, minor isomer and CONCH_2Ar, minor isomer], 4.05–3.90 [m, 0.78 H, CONC*H*(CH$_3$)$_2$, major isomer], 3.81 (s, 1.56 H, HNCH_2Ar, major isomer), 3.71 (s, 0.44 H, HNCH_2Ar, minor isomer), 2.92–2.77 [m, 1 H, HNC*H*(CH$_3$)$_2$], 1.61 (s, 7.02 H, O*t*Bu, major isomer), 1.49 (s, 1.98 H, O*t*Bu, minor isomer), 1.33–1.22, 1.13–1.01 [2× m, 12 H, HNCH(*C*H$_3$)$_2$, CONCH-(*C*H$_3$)$_2$] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.5 (0.22× C_q, *C*ON, minor isomer), 171.6 (0.78× C_q, *C*ON, major isomer), 166.7 (0.78× C_q, *C*OO, major isomer), 166.0 (0.22× C_q, *C*OO, minor isomer), 140.2 (C_q, *o*′-C_6H_4COO), 137.4, 136.9, 136.8, 136.7 (2× C_q, *ipso*-C_6H_4CON, *o*′-C_6H_4CON), 131.5, 131.3, 130.0, 129.5, 128.8, 128.6, 127.4, 126.9, 126.8, 126.6, 126.5, 126.2, 125.4, 125.1 (7× CH), 130.6 (0.22× CH, *o*-C_6H_4COO, minor isomer), 130.6 (0.78× CH, *o*-C_6H_4COO, major isomer), 129.9 (0.78× C_q, *ipso*-C_6H_4COO, major isomer), 129.8 (0.22× C_q, *ipso*-C_6H_4COO, minor isomer), 81.4 (0.22× C_q, O*t*Bu, minor isomer), 81.3 (0.78× C_q, O*t*Bu, major isomer), 50.6 [0.78× CH, CON*C*H(CH$_3$)$_2$, major isomer], 49.6 (0.78× CH_2, HN*C*H$_2$Ar, major isomer), 49.1 (0.22× CH_2, HN*C*H$_2$Ar, minor isomer), 48.5 [0.78× CH, HN*C*H(CH$_3$)$_2$, major isomer], 48.1 [0.22× CH, HN*C*H(CH$_3$)$_2$, minor isomer], 47.4 [0.22× CH, CON*C*H(CH$_3$)$_2$, minor isomer], 47.3 (0.22× CH_2, CON*C*H$_2$Ar, minor isomer), 41.6 (0.78× CH_2, CON*C*H$_2$Ar, major isomer), 28.2 (0.78× 3CH_3, O*t*Bu, major isomer), 28.1 (0.22× 3CH_3, O*t*Bu, minor isomer), 22.9 [0.22× 2CH_3, HNCH(*C*H$_3$)$_2$, minor isomer], 22.8 [0.78× 2CH_3, HNCH(*C*H$_3$)$_2$, major isomer], 21.4, 20.9, 20.1 [2× CH_3, CONCH(*C*H$_3$)$_2$] ppm. HRMS (TOF MS, ES$^+$): *m*/*z* calcd. for $C_{26}H_{37}N_2O_3$ [M + H]$^+$ 425.2799; found 425.2799.

Arylopeptoid Trimer 4b: Treatment of **3b** (446 mg, 1.05 mmol) by Method B with isopropylamine yielded **4b** (530 mg, 84%, 97% purity) as a colorless solid. R_f (EtOAc/MeOH, 80:20) = 0.23; m.p. 52–55 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.94–7.74 (m, 1 H), 7.68–6.98 (br. m, 11 H), 5.30–3.64 [m, 8 H, 2× CONCH_2Ar, 2× CONCH(CH$_3$)$_2$, HNCH_2Ar], 3.00–2.72 [m, 1 H, HNCH(CH$_3$)$_2$], 2.20–1.94 (br. s, 1 H, NH), 1.62, 1.61, 1.59, 1.50 (4× s, 9 H), 1.38–0.90 (br. m, 18 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.5, 172.2, 171.8, 171.8, 171.5, 170.6 (2× C_q), 166.8, 166.6, 166.1 (C_q), 140.4, 140.3, 140.1, 140.0, 137.6, 137.0, 136.9, 136.8, 136.2, 135.8, 135.5, 135.3, 135.2, 134.8 (5× C_q), 131.6, 131.6, 131.4, 130.8, 130.7, 130.4, 130.3, 129.9, 129.8, 129.0, 128.9, 128.8, 128.7, 127.7, 127.4, 127.2, 127.0, 126.8, 126.7, 126.6, 126.5, 126.4, 126.3, 125.6, 125.6, 125.5, 125.4, 125.2, 125.1 (12× CH), 130.1, 130.0 (C_q), 81.7, 81.4 (C_q), 51.1, 50.8, 50.6, 48.9, 48.6, 48.3, 48.0, 47.8, 47.7 [3× CH, 2× CONCH(CH$_3$)$_2$ and HNCH(CH$_3$)$_2$], 49.6, 49.5, 49.2, 47.3, 47.2, 41.8, 41.7, 41.4, 41.1, 40.6 (3× CH_2, HNCH$_2$Ar and 2× CON-CH$_2$Ar), 28.3, 28.2 (3× CH_3), 22.8, 22.7, 21.8, 21.3, 21.1, 20.9, 20.7, 20.3, 20.3 (6× CH_3) ppm. HRMS (TOF MS, ES$^+$): *m*/*z* calcd. for $C_{37}H_{50}N_3O_4$ [M + H]$^+$ 600.3796; found 600.3805.

***tert*-Butyl 2-[(*tert*-Butylamino)methyl]benzoate (2c):** Treatment of **1**[18] (488 mg, 1.80 mmol) by Method A with *tert*-butylamine yielded **2c** (420 mg, 89%, >99% purity) as a pale-yellowish oil. R_f (EtOAc/MeOH, 95:5) = 0.15. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.73 (dd, J = 7.7, 1.4 Hz, 1 H, *o*-C$_6H_4$COO), 7.47 (dd, J = 7.7, 1.4 Hz, 1 H, *m*′-C$_6H_4$COO), 7.41 (ddd, J = 7.7, 7.7, 1.4 Hz, 1 H, *p*-C$_6H_4$COO), 7.25 (ddd, J = 7.7, 7.7, 1.4 Hz, 1 H, *m*-C$_6H_4$COO), 3.91 (s, 2 H, HNCH_2Ar), 1.69–1.62 (br. s, 1 H, NH), 1.60 (s, 9 H, O*t*Bu), 1.18 [s, 9 H, HNC(CH_3)$_3$] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.3 (C_q, *C*OO), 142.1 (C_q, *o*′-C_6H$_4$COO), 132.1 (C_q, *ipso*-C_6H$_4$COO), 131.5 (CH, *p*-C_6H$_4$COO), 130.4 (CH, *m*′-C_6H$_4$COO), 129.9 (CH, *o*-C_6H$_4$COO), 126.5 (CH, *m*-C_6H$_4$COO), 81.1 (C_q, O*t*Bu), 50.7 [C_q, HN*C*(CH$_3$)$_3$], 45.6 (CH_2, HN*C*H$_2$Ar), 29.1 [3× CH_3, HNC(*C*H$_3$)$_3$], 28.2 (3× CH_3, O*t*Bu) ppm. HRMS (TOF MS, ES$^+$): *m*/*z* calcd. for $C_{16}H_{26}NO_2$ [M + H]$^+$ 264.1958; found 264.1959.

Arylopeptoid Dimer 3c: Treatment of **2c** (369 mg, 1.40 mmol) by Method C with *tert*-butylamine yielded **3c** (541 mg, 85%, >99% purity) as a pale-yellowish oil. Acylated intermediate: R_f (heptane/EtOAc, 75:25) = 0.41. Data for **3c**: R_f (EtOAc/MeOH, 90:10) = 0.21. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.77 (dd, J = 7.7, 1.4 Hz, 1 H, *o*-C$_6H_4$COO), 7.68 (d, J = 7.7 Hz, 1 H, *m*′-C$_6H_4$COO), 7.53 (ddd, J = 7.7, 7.7, 1.4 Hz, 1 H, *p*-C$_6H_4$COO), 7.40 (d, J = 7.7 Hz, 1 H, *m*′-C$_6H_4$CON), 7.26 (ddd, J = 7.7, 7.7, 1.4 Hz, 1 H, *m*-C$_6H_4$COO), 7.16 (ddd, J = 7.7, 7.7, 1.4 Hz, 1 H, *p*-C$_6H_4$CON), 7.01 (dd, J = 7.7, 1.4 Hz, 1 H, *o*-C$_6H_4$CON), 6.94 (ddd, J = 7.7, 7.7, 1.4 Hz, 1 H, *m*-C$_6H_4$CON), 5.22–4.88 (br. s, 1 H, CONCH*H*Ar), 4.88–4.48 (br. s, 1 H, CONC*H*HAr), 3.82–3.52 (br. s, 2 H, HNCH_2Ar), 1.54 [s, 9 H, CONC(CH_3)$_3$], 1.49 (s, 9 H, O*t*Bu), 1.18 [s, 9 H, HNC(CH_3)$_3$] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.4 (C_q, *C*ON), 166.0 (C_q, *C*OO), 141.6 (C_q, *o*′-C_6H$_4$COO), 138.4 (C_q, *ipso*-C_6H$_4$CON), 137.1 (C_q, *o*′-C_6H$_4$CON), 131.3 (CH, *p*-C_6H$_4$COO), 130.7 (CH, *o*-C_6H$_4$COO), 129.8 (CH, *m*′-C_6H$_4$CON), 129.2 (C_q, *ipso*-C_6H$_4$COO), 128.4 (CH, *p*-C_6H$_4$CON), 127.2 (CH, *m*′-C_6H$_4$COO), 126.4 (CH, *m*-C_6H$_4$COO), 126.2 (CH, *m*-C_6H$_4$CON), 124.2 (CH, *o*-C_6H$_4$CON), 81.3 (C_q, O*t*Bu), 58.1 [C_q, CON*C*(CH$_3$)$_3$], 50.7 [C_q, HN*C*(CH$_3$)$_3$], 49.5 (CH_2, CON*C*H$_2$Ar), 44.7 (CH_2, HN*C*H$_2$Ar), 29.1 [3× CH_3, HNC-(*C*H$_3$)$_3$], 28.5 [3× CH_3, CONC(*C*H$_3$)$_3$], 28.1 (3× CH_3, O*t*Bu) ppm. HRMS (TOF MS, ES$^+$): *m*/*z* calcd. for $C_{28}H_{41}N_2O_3$ [M + H]$^+$ 453.3112; found 453.3107.

Arylopeptoid Trimer 4c: Treatment of **3c** (408 mg, 0.90 mmol) by Method C with *tert*-butylamine yielded **4c** (449 mg, 78%, >99% purity) as a colorless solid. Acylated intermediate: R_f (heptane/EtOAc, 75:25) = 0.28. Data for **4c**: R_f (EtOAc/MeOH, 90:10) = 0.15; m.p. 70–73 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.78 (d, J = 7.5 Hz, 1 H), 7.59–7.42 (m, 4 H), 7.35–7.19 (m, 3 H), 7.10–6.95 (m, 4 H), 5.10–4.00 (br. s, 4 H, 2× CONCH_2Ar), 3.71 (s, 2 H, HNCH_2Ar), 1.56 (s, 9 H), 1.51 (s, 9 H), 1.41 (s, 9 H), 1.18 (s, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.5 (C_q), 172.0 (C_q), 165.7 (C_q), 141.5 (C_q), 138.2 (C_q), 136.8 (C_q), 136.2 (C_q), 135.7 (C_q), 131.4 (CH), 130.9 (CH), 129.9 (CH), 129.1 (C_q), 128.8 (CH), 128.2 (CH), 127.0 (CH), 126.7 (CH), 126.6 (CH), 126.5 (CH), 126.3 (CH), 124.4 (CH), 124.1 (CH), 81.2 (C_q), 58.3 (C_q), 58.2 (C_q), 50.8 (C_q), 48.9 (CH_2, CON*C*H$_2$Ar), 48.6 (CH_2, CON*C*H$_2$Ar), 44.6 (CH_2, HN*C*H$_2$Ar), 29.1 [3× CH_3, HNC(*C*H$_3$)$_3$], 28.7 [3× CH_3, CONC(*C*H$_3$)$_3$], 28.5 [3× CH_3, CONC(*C*H$_3$)$_3$], 28.1 (3× CH_3) ppm. HRMS (TOF MS, ES$^+$): *m*/*z* calcd. for $C_{40}H_{56}N_3O_4$ [M + H]$^+$ 642.4265; found 642.4265.

Chloromethyl Intermediate 5: To a solution of **2b** (100 mg, 0.42 mmol) in THF (2.0 mL) at 0 °C under N_2 was added Et_3N (0.059 mL, 0.42 mmol) and then 2-(chloromethyl)benzoyl chloride (79 mg, 0.42 mmol). After stirring for 1 h at 0 °C, the resulting mixture was concentrated under reduced pressure at room temp. The residue was taken up in EtOAc (10 mL) and the mixture was washed with satd. aq. $NaHCO_3$ (5 mL) and brine (5 mL). The combined aqueous layers were extracted with EtOAc (5 mL) and the combined organic layers were dried with Na_2SO_4, filtered and concentrated under reduced pressure. Flash chromatography of the residue gave **5** (150 mg, 93%, >99% purity) as a colorless oil. R_f (heptane/EtOAc, 75:25) = 0.30. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.91 (dd, J = 7.8, 1.3 Hz, 0.79 H, *o*-C$_6H_4$COO, major isomer), 7.78 (dd, J = 7.8, 1.2 Hz, 0.21 H, *o*-C$_6H_4$COO, minor isomer), 7.64–7.20 (m, 6.58 H), 7.09–7.01 (m, 0.42 H), 5.13 (s, 1.58 H, CON-CH_2Ar, major isomer), 4.93 (d, J = 11.2 Hz, 0.79 H, ClC*H*HAr, major isomer), 4.80–4.52 [m, 1.84 H, ClCH_2Ar, minor isomer, CONCH_2Ar, minor isomer and CONCH(CH$_3$)$_2$, minor isomer and ClCH*H*Ar, major isomer], 4.10–3.94 [m, 0.79 H, CONCH(CH$_3$)$_2$, major isomer], 1.63 (s, 7.11 H, O*t*Bu, major isomer), 1.49 (s, 1.89 H, O*t*Bu, minor isomer), 1.38–1.26 [m, 1.26 H, CONCH(*C*H$_3$)$_2$, minor isomer], 1.20–1.05 [m, 4.74 H, CONCH(*C*H$_3$)$_2$, major isomer] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.4 (0.21× C_q, *C*ON, minor isomer), 170.4 (0.79× C_q, *C*ON, major isomer), 166.7 (0.79× C_q, *C*OO, major isomer), 166.3 (0.21× C_q, *C*OO, minor isomer), 140.0 (0.21× C_q, *o*′-C_6H$_4$COO, major isomer), 139.6 (0.79× C_q, *o*′-C_6H$_4$COO, minor isomer), 137.2, 134.7, 133.8 (2× C_q, *ipso*-C_6H$_4$CON and *o*′-C_6H$_4$CON), 131.6, 131.2, 130.9, 130.3, 129.3, 129.1, 128.3, 128.1, 127.3, 126.9, 126.7, 126.2, 125.8, 125.0 (7× CH), 130.7 (CH, *o*-C_6H$_4$COO), 130.4 (0.21× C_q, *ipso*-C_6H$_4$COO, minor isomer), 129.9 (0.79× C_q, *ipso*-C_6H$_4$COO, major isomer), 81.7 (0.21× C_q, O*t*Bu, minor isomer), 81.3 (0.79× C_q, O*t*Bu, major isomer), 50.7 [0.79× CH, CON*C*H(CH$_3$)$_2$, major isomer], 48.2 (0.21× CH_2, CON*C*H$_2$Ar, minor isomer), 48.1 [0.21× CH, CON*C*H(CH$_3$)$_2$, minor isomer], 43.4 (0.21× CH_2, Cl*C*H$_2$Ar, minor isomer), 43.3 (0.79× CH_2, Cl*C*H$_2$Ar, major isomer), 42.0 (0.79× CH_2, CON*C*H$_2$Ar, major isomer), 28.3 (0.79× 3CH$_3$, O*t*Bu, major isomer), 28.1 (0.21× 3CH$_3$, O*t*Bu, minor isomer), 21.2, 20.9 [0.79× 2CH$_3$, CONCH(*C*H$_3$)$_2$, major isomer], 20.1 [0.21× 2CH$_3$, CONCH(*C*H$_3$)$_2$, minor isomer] ppm. HRMS (TOF MS, ES$^+$): *m*/*z* calcd. for $C_{23}H_{29}ClNO_3$ [M + H]$^+$ 402.1830; found 402.1829.

Solid-phase Synthesis

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 2-(chloromethyl) benzoyl chloride (71 mg, 0.38 mmol) in CH_2Cl_2 (0.76 mL) at room temp. 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 room temp. The resin was drained and washed with CH_2Cl_2 (3× 2 mL) and DMSO (3× 2 mL).

General Procedure for Attachment to Rink Acid Resin: Rink acid resin (218 mg, 0.55 mmol g^{-1}; thus 0.120 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 solution of DMAP (45.6 mg, 0.38 mmol) in CH_2Cl_2 (0.76 mL) at room temp. was added 2-(chloromethyl)-benzoyl chloride (71 mg, 0.38 mmol) and then DIPEA (0.132 mL, 0.76 mmol). The mixture was added to the resin and the resulting mixture was agitated for 20 min at room temp. The resin was drained and washed with CH_2Cl_2 (3× 2 mL) and DMSO (3× 2 mL).

Methods D and E. General Procedure for Acylation Step (except for *tert*-butyl side chain): To a solution of 2-(chloromethyl)benzoyl chloride (71 mg, 0.38 mmol) in CH_2Cl_2 (0.76 mL) at room temp., 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 room temp. The resin was drained and washed with CH_2Cl_2 (3× 2 mL) and DMSO (3× 2 mL).

Method F. General Procedure for Acylation Step (only for *tert*-butyl side chain): To a solution of 2-(chloromethyl)benzoyl chloride (143 mg, 0.76 mmol) in CH_2Cl_2 (0.76 mL) at room temp., was added DIPEA (0.264 mL, 1.52 mmol). The mixture was added to the resin and the resulting mixture was agitated for 180 min at room temp. The resin was drained and washed with CH_2Cl_2 (3× 2 mL) and DMSO (3× 2 mL).

Methods D and F. General Procedure for Substitution Step (except for phenyl side chain): 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).

Method E. General Procedure for Substitution Step (only for phenyl side chain): 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).

Methods D and E; General Procedure for Capping Step (except for *tert*-butyl side chain): To a solution of benzoyl chloride or 2-methylbenzoyl chloride (0.38 mmol) in CH_2Cl_2 (0.76 mL) at room temp., 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 room temp. 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, only Rink amide), and CH_2Cl_2 (3× 2 mL).

Method F. General Procedure for Capping Step (only for *tert*-butyl side chain): To a solution of benzoyl chloride or 2-methylbenzoyl chloride (0.76 mmol) in CH_2Cl_2 (0.76 mL) at room temp., was added DIPEA (0.264 mL, 1.52 mmol). The solution was added to the resin and the resulting mixture was agitated for 180 min at room temp. 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, only Rink amide), and CH_2Cl_2 (3× 2 mL).

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 **7g**). 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) giving the crude product, which was purified by preparative HPLC (see the Supporting Information for details).

General Procedure for Cleavage from Rink Acid Resin: The resin was cleaved in HFIP/CH_2Cl_2, 1:4 (2 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), giving the crude product, which was purified by preparative HPLC (see the Supporting Information for details).

Arylopeptoid Hexamer 6b: Synthesized on Rink acid resin using Method D, performing the substitution steps at room temp. (142 mg crude, 101%, 93% crude purity). Data for **6b**: Colorless foam (136 mg, 97%, >99% purity); m.p. 165–168 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.98–9.52 (br. s, 1 H, COO*H*), 7.94–7.00 (m, 29 H), 5.24–4.30 (br. m, 12 H, 6× CONCH_2Ar), 4.30–4.00 [br. m, 6 H, 6× CONCH(CH$_3$)$_2$], 1.48–0.65 (m, 36 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.0, 171.8, 171.6 (7× C_q), 136.5, 136.3, 135.8, 134.8, 134.6, 134.3 (13× C_q), 131.9, 131.0, 129.6, 129.3, 128.6, 127.3, 127.0, 126.7, 126.1, 125.3 (29× CH), 51.4, 51.2 [6× CH, 6×CONCH(CH$_3$)$_2$], 42.2, 41.6, 41.2, 40.7 (6× CH_2, 6× CONCH_2Ar), 21.6, 21.2, 20.9 (12× CH_3) ppm. HRMS (TOF MS, ES$^+$): *m*/*z* calcd. for $C_{73}H_{85}N_6O_8$ [M + 2 H]$^{2+}$ 587.3248; found 587.3246.

Arylopeptoid Hexamer 6c: Synthesized on Rink acid resin using Method F (81 mg crude, 54%, 23% crude purity). Data for **6c**: Colorless foam (9 mg, 7%, >99% purity); m.p. 154–157 °C (dec.). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.02–6.88 (m, 30 H), 4.94–4.20 (m, 12 H, 6× CONCH_2Ar), 1.80–1.10 (s, 54 H, 6× CON*t*Bu) ppm. Insufficient amounts of material to obtain satisfactory ^{13}C NMR spectra. HRMS (TOF MS, ES$^+$): *m*/*z* calcd. for $C_{79}H_{98}N_6O_8$ [M + 2H]$^{2+}$ 629.3718; found 629.3713.

Arylopeptoid Hexamer 6e: Synthesized on Rink acid resin using Method D, performing the substitution steps at room temp. (31 mg crude, 20%, 76% crude purity). Data for **6e**: Colorless foam isolated as the corresponding TFA-salt (28 mg, 10%, >99% purity); m.p. 98–101 °C. ^{1}H NMR (300 MHz, [D$_3$]MeCN): δ = 8.04–7.86 (m, 1 H), 7.82–6.74 (m, 28 H), 5.50–2.50 (m, 91 H) ppm. Insufficient amounts of material to obtain satisfactory ^{13}C NMR spectra. HRMS (TOF MS, ES$^+$): *m*/*z* calcd. for $C_{91}H_{118}N_{12}O_{14}$ [M + 4H]$^{4+}$ 400.7217; found 400.7221.

Arylopeptoid Hexamer 6f: Synthesized on Rink acid resin using Method D, performing the substitution steps at room temp. (150 mg crude, 86%, 36% crude purity). Data for **6f**: Pale-yellowish foam isolated as the corresponding TFA-salt (58 mg, 23%, >99% purity); m.p. 63–66 °C. ^{1}H NMR (300 MHz, [D$_3$]MeCN): δ = 8.92–6.60 (m, 60 H), 5.18–3.88 (m, 24 H) ppm. ^{13}C NMR (75 MHz, [D$_3$]MeCN): δ = 172.2, 171.9 (6× C_q), 168.5 (C_q), 161.1 (q, *J* = 36.5 Hz, 6× C_q, 6× CF_3*C*OOH), 146.7, 146.5, 146.1, 142.6 (18× CH), 139.1, 138.9, 138.1, 137.6, 136.4, 135.4, 135.2, 134.2 (19× C_q), 131.9, 131.0, 129.6, 129.2, 129.0, 128.6, 127.6 (35× CH), 117.2 (q, *J* = 289.2 Hz, 6× C_q, 6× *C*F_3COOH), 53.1, 52.8, 52.1, 51.6, 47.2, 46.6 (2× 6CH_2, 6× CONCH_2Ar and 6× CONCH_2Pyr) ppm. HRMS (TOF MS, ES$^+$): *m*/*z* calcd. for $C_{91}H_{81}N_{12}O_8$ [M + 3H]$^{3+}$ 489.8761; found 489.8761.

Arylopeptoid Hexamer 6g: Synthesized on Rink acid resin using Method D (170 mg crude, 92%, 98% crude purity). Due to poor

solubility, the crude product was purified as follows: The crude product was taken up in CH_2Cl_2 (10 mL) and the mixture was washed with 1 M HCl (10 mL). The aqueous layer was extracted with CH_2Cl_2 (10 mL) and the combined organic layers were concentrated and dried in vacuo, giving **6g** (174 mg, 94%, 98% purity) as a colorless foam; m.p. > 250 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.80–6.70 (m, 60 H), 5.50–3.90 (m, 18 H, 6× CONC*H*CH_3 and 6× $CONCH_2$Ar), 1.85–1.10 (m, 18 H, 6× CONCHC*H*$_3$) ppm. Not sufficiently soluble to obtain satisfactory ^{13}C NMR spectra. HRMS (TOF MS, ES$^+$): *m*/*z* calcd. for $C_{103}H_{98}N_6O_8$ $[M + 2H]^{2+}$ 773.3718; found 773.3724.

Arylopeptoid Hexamer 6h: Synthesized on Rink acid resin using Method E (11 mg crude, 7%, 91% crude purity). Data for **6h**: Colorless solid (9 mg, 5%, >99% purity); m.p. 168–171 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.79–6.72 (m, 60 H), 5.62–5.10 (m, 12 H, 6× CONC*H*$_2$Ar) ppm. Insufficient amounts of material to obtain satisfactory ^{13}C NMR spectra. HRMS (TOF MS, ES$^+$): *m*/*z* calcd. for $C_{91}H_{74}N_6O_8$ $[M + 2H]^{2+}$ 689.2779; found 689.2779.

Arylopeptoid Hexamer 7a: Synthesized on Rink amide resin using Method D (172 mg crude, 132%, 91% crude purity). Data for **7a**: Colorless foam (106 mg, 81%, >99% purity); m.p. 95–98 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.80–7.00 (m, 29 H), 6.62–6.08 (m, 2 H, CON*H*$_2$), 5.42–2.54 (m, 24 H, 6× CONC*H*$_2$Ar and 6× CONC*H*$_2$CH$_3$), 1.32–0.52 (m, 18 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.4, 172.3, 171.4, 171.3, 171.1, 171.0, 170.6, 170.5, 170.4 (7× C_q), 136.0, 135.8, 135.7, 135.6, 134.7, 134.2, 134.1, 133.9, 133.4, 133.3 (13× C_q), 130.9, 130.7, 130.7, 129.6, 129.5, 128.5, 128.1, 127.9, 127.7, 127.5, 127.3, 126.3, 126.0, 125.8, 125.7 (29× CH), 48.9, 45.8, 45.4, 44.3, 44.0, 43.7, 43.6, 40.3 (12× CH_2, 6× CON*C*H$_2$Ar and 6× CON*C*H$_2$CH$_3$), 14.0, 13.7, 13.4, 12.5, 12.4, 12.2 (6× CH_3) ppm. HRMS (TOF MS, ES$^+$): *m*/*z* calcd. for $C_{67}H_{75}N_7O_7$ $[M + 2H]^{2+}$ 544.7859; found 544.7851.

Arylopeptoid Hexamer 7b: Synthesized on Rink amide resin using Method D (135 mg crude, 141%, 99% crude purity). Data for **7b**: Colorless foam (135 mg, 96%, >99% purity); m.p. 140–143 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.20–8.00 (br. s, 1 H, CON*H*H), 7.72–7.00 (m, 29 H), 6.80–6.62 (br. s, 1 H, CONH*H*), 5.24–3.96 [m, 18 H, 6× CONC*H*$_2$Ar and 6× CONC*H*(CH$_3$)$_2$], 1.42–0.90 (m, 36 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.0, 172.5, 172.2, 171.7 (7× C_q), 136.5, 136.2, 135.6, 134.7, 134.4 (13× C_q), 130.5, 130.4, 129.5, 129.2, 129.0, 128.6, 128.2, 127.3, 127.1, 126.7, 126.1, 125.4 (29× CH), 51.3, 51.1 [6× CH, 6× CON*C*H(CH$_3$)$_2$], 41.7, 41.2, 40.8 (6× CH_2, 6× CON*C*H$_2$Ar), 21.7, 21.6, 21.5, 21.3, 20.9, 20.9 (12× CH_3) ppm. HRMS (TOF MS, ES$^+$): *m*/*z* calcd. for $C_{73}H_{86}N_7O_7$ $[M + 2H]^{2+}$ 586.8328; found 586.8331.

Arylopeptoid Hexamer 7d: Synthesized on Rink amide resin using Method D (241 mg crude, 117%, 92% crude purity). Data for **7d**: Colorless foam (157 mg, 76%, >99% purity); m.p. 60–63 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.78–6.86 (m, 59 H), 6.45–5.74 (m, 2 H, CON*H*$_2$), 5.40–2.14 (m, 36 H), 1.82–0.94 (m, 24 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.4, 172.4, 171.3, 171.2, 171.0, 170.9, 170.6, 170.5 (7× C_q), 142.2, 142.1, 142.1, 142.0, 141.9, 141.6, 141.5, 141.4, 136.1, 136.0, 135.7, 135.6, 135.6, 134.9, 134.7, 134.5, 134.1, 133.8, 133.4 (19× C_q), 130.7, 130.6, 130.5, 129.5, 128.4, 128.3, 128.2, 127.5, 127.4, 127.3, 126.5, 126.2, 125.9, 125.8, 125.7 (59× CH), 50.8, 50.7, 49.8, 49.7, 49.4, 46.5, 45.4, 45.3, 45.0, 44.9, 44.8, 44.3 (12× CH_2, 6× CON*C*H$_2$Ar and 6× CON*C*H$_2$CH$_2$), 35.5, 35.0, 34.9, 34.8 (6× CH_2), 29.0, 28.9, 28.8, 28.2, 28.1, 28.0, 27.8, 27.5, 27.1, 27.0 (12× CH_2) ppm. HRMS (TOF MS, ES$^+$): *m*/*z* calcd. for $C_{115}H_{123}N_7O_7$ $[M + 2H]^{2+}$ 856.9737; found 856.9736.

Arylopeptoid Hexamer 7e: Synthesized on Rink amide resin using Method D (294 mg crude, 107%, 84% crude purity). Data for **7e**: Colorless foam isolated as the corresponding TFA-salt (173 mg, 63%, >99% purity); m.p. 78–81 °C. ^{1}H NMR (300 MHz, [D$_3$]-MeCN): δ = 7.74–6.15 (m, 37 H), 5.40–5.52 (m, 84 H) ppm. ^{13}C NMR (75 MHz, [D$_3$]MeCN): δ = 172.9, 172.7, 172.3 (7× C_q), 160.9 (q, *J* = 36.1 Hz, 6× C_q, 6× CF_3*C*OOH), 136.0, 135.9, 135.6, 135.2, 134.5, 134.4, 133.9, 133.3, 133.1 (13× C_q), 131.8, 131.6, 131.4, 130.0, 129.6, 129.3, 129.1, 128.7, 128.1, 127.9, 127.3, 127.2 (29× CH), 117.2 (q, *J* = 290.7 Hz, 6× C_q, 6× *C*F_3COOH), 64.5, 64.3 (12× CH_2), 56.2, 56.1, 55.9, 55.8, 55.3, 55.1, 54.3, 54.3, 53.1, 52.6, 52.4, 52.1, 51.7, 51.3 (24× CH_2), 40.7, 40.5, 40.4, 40.0 (6× CH_2) ppm. HRMS (TOF MS, ES$^+$): *m*/*z* calcd. for $C_{91}H_{119}N_{13}O_{13}$ $[M + 4H]^{4+}$ 400.4763; found 400.4771.

Arylopeptoid Hexamer 7f: Synthesized on Rink amide resin using Method D (273 mg crude, 106%, 28% crude purity). Data for **7f**: Pale-yellowish foam isolated as the corresponding TFA-salt (52 mg, 20%, >99% purity); m.p. 72–75 °C. ^{1}H NMR (300 MHz, [D$_3$]-MeCN): δ = 8.98–8.02 (m, 18 H), 7.94–7.62 (m, 8 H), 7.60–7.03 (m, 27 H), 6.02–6.40 (m, 8 H, 6× CF_3COO*H* and CON*H*$_2$), 5.10–3.90 (m, 24 H, 6× CONC*H*$_2$Ar and 6× CONC*H*$_2$Pyr) ppm. ^{13}C NMR (75 MHz, [D$_3$]MeCN): δ = 172.1, 172.0, 171.7 (7× C_q), 161.1 (q, *J* = 36.2 Hz, 6× C_q, 6× CF_3*C*OOH), 146.7, 146.5, 146.1, 142.5, 141.2, 141.0 (18× CH), 139.1, 136.4, 135.9, 135.4, 135.1, 134.9 (19× C_q), 131.5, 131.4, 131.0, 130.7, 130.4, 130.1, 129.6, 129.4, 129.1, 128.9, 128.6, 128.1, 127.9, 127.6, 127.5, 127.0 (35× CH), 117.2 (q, *J* = 290.0 Hz, 6× C_q, 6× *C*F_3COOH), 52.2, 52.0, 46.9, 46.7, 46.6 (2× 6CH_2, 6× CON*C*H$_2$Ar and 6× CON*C*H$_2$Pyr) ppm. HRMS (TOF MS, ES$^+$): *m*/*z* calcd. for $C_{91}H_{82}N_{13}O_7$ $[M + 3H]^{3+}$ 489.5481; found 489.5485.

Arylopeptoid Hexamer 7g: Synthesized on Rink amide resin using Method D (192 mg crude, 104%, 80% crude purity), performing the final cleavage in 2× 10 min. Data for **7g**: Colorless foam (43 mg, 23%, >99% purity); m.p. > 250 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.98–6.70 (m, 59 H), 6.45–5.90 (br. m, 3.14 H, CON*H*$_2$ and 1.14× CONC*H*CH_3), 5.42–3.88 (br. m, 16.86 H, 4.86× CONC*H*CH_3 and 6× $CONCH_2$Ar), 1.74–1.20 (m, 18 H, 6× CONCHC*H*$_3$) ppm. Not sufficiently soluble to obtain satisfactory ^{13}C NMR spectra. HRMS (TOF MS, ES$^+$): *m*/*z* calcd. for $C_{103}H_{99}N_7O_7$ $[M + 2H]^{2+}$ 772.8803; found 772.8801.

Arylopeptoid Hexamer 7h: Synthesized on Rink amide resin using Method E (175 mg crude, 106%, 50% crude purity). Data for **7h**: Colorless solid (57 mg, 35%, >99% purity); m.p. 156–159 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.48–6.76 (m, 59 H), 6.36–6.10 (br. m, 2 H, CON*H*$_2$), 5.47–5.12 (m, 12 H, 6× CONC*H*$_2$Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.3, 170.9, 170.1 (7× C_q), 143.5, 142.7, 142.4, 142.1, 135.8, 135.5, 135.4, 135.3, 135.1, 134.9 (19× C_q), 130.5, 129.7, 129.1, 129.0, 128.9, 128.9, 128.8, 128.8, 128.7, 128.3, 128.0, 127.8, 127.7, 127.6, 127.5, 126.8, 126.5, 126.3 (59× CH), 51.9, 50.9, 50.8 (6× CH_2, 6× CON*C*H$_2$Ar) ppm. HRMS (TOF MS, ES$^+$): *m*/*z* calcd. for $C_{91}H_{75}N_7O_7$ $[M + 2H]^{2+}$ 688.7859; found 688.7850.

Arylopeptoid Hexamer 7i: Synthesized on Rink amide resin using Method F. Purification of the crude product (111 mg crude, 101%, 48% crude purity) was hindered due to poor solubility in HPLC solvents and other useful organic and inorganic solvents. Major peak in analytical HPLC of the crude product corresponded to the desired product as established by LC-MS and HRMS: HRMS (TOF MS, ES$^+$): *m*/*z* calcd. for $C_{55}H_{50}N_7O_7$ $[M + H]^+$ 920.3766; found 920.3769.

Arylopeptoid Model Monomer 8b: Synthesized on Rink acid resin using Method D (52 mg crude, 70%, 84% crude purity) at twice the scale described in the general methods. Data for **8b**: Colorless foam (42 mg, 56%, >99% purity); m.p. 178–181 °C. ^{1}H NMR

(300 MHz, $CDCl_3$): δ = 11.25–10.85 (br. s, 1 H, COO*H*), 8.01 (dd, *J* = 7.6, 1.0 Hz, 0.80 H, *o*-C_6H_4COO, major), 7.97 (d, 0.20 H, *o*-C_6H_4COO, minor), 7.62–7.49 (m, 2 H, *p*/*m*′-C_6H_4COO), 7.40–7.21 (m, 4.20 H, *m*-C_6H_4COO and C_6H_4CON, major), 7.20–7.09 (m, 0.40 H, C_6H_4CON, minor), 7.09–7.02 (m, 0.20 H, C_6H_4CON, minor), 6.99–6.90 (m, 0.20 H, C_6H_4CON, minor), 5.09 (d, *J* = 16.7 Hz, 0.80 H, CONC*H*HAr, major), 4.99 (d, *J* = 16.7 Hz, 0.80 H, CONCH*H*Ar, major), 4.92–4.67 [m, 0.60 H, CONC*H*$(CH_3)_2$, minor and CONCH_2Ar, minor], 4.06–3.90 [m, 0.80 H, CONC*H*$(CH_3)_2$, major], 2.40 (s, 2.40 H, CH_3Ar, major), 2.33 (s, 0.60 H, CH_3Ar, minor), 1.34–1.22 [m, 1.20 H, CONCH(CH_3)$_2$, minor], 1.21–1.10 [m, 4.80 H, CONCH(CH_3)$_2$, major] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.8 (0.20× C_q, *C*ON, minor), 173.2 (0.80× C_q, *C*ON, major), 171.7 (0.80× C_q, *C*OO, major), 171.0 (0.20× C_q, *C*OO, minor), 141.3 (0.20× C_q, *o*′-C_6H_4COO, minor), 139.5 (0.80× C_q, *o*′-C_6H_4COO, major), 135.9 (0.20× C_q, C_6H_4CON, minor), 135.7 (0.80× C_q, C_6H_4CON, major), 134.2 (0.80× C_q, C_6H_4CON, major), 133.6 (0.20× C_q, C_6H_4CON, minor), 132.8 (0.20× CH, *p*-C_6H_4COO, minor), 132.6 (0.80× CH, *p*-C_6H_4COO, major), 131.9 (0.20× CH, *o*-C_6H_4COO, minor), 131.4 (0.20× CH, *o*-C_6H_4COO, minor), 130.7 (0.80× CH, C_6H_4CON, major), 130.3 (0.20× CH, C_6H_4CON, minor), 129.2 (0.80× CH, C_6H_4CON, major), 128.9 (0.20× CH, C_6H_4CON, minor), 128.8 (0.80× C_q, *ipso*-C_6H_4COO, major), 127.6 (0.20× CH, *m*′-C_6H_4COO, minor), 127.2 (0.80× CH, *m*′-C_6H_4COO, major), 127.0 (CH, *m*-C_6H_4COO), 126.7 (0.20× C_q, *ipso*-C_6H_4COO, minor), 125.9 (0.80× CH, C_6H_4CON, major), 125.5 (0.20× CH, C_6H_4CON, minor), 125.3 (0.80× CH, C_6H_4CON, major), 125.1 (0.20× CH, C_6H_4CON, minor), 51.2 [0.80× CH, CONCH$(CH_3)_2$, major], 47.6 [0.20× CH, CONCH$(CH_3)_2$, minor], 46.7 (0.20× CH_2, CONCH_2Ar, minor), 42.2 (0.80× CH_2, CONCH_2Ar, major), 21.5, 21.1 [0.80× CH_3, CONCH(CH_3)$_2$, major], 20.2 [0.20× CH_3, CONCH(CH_3)$_2$, minor], 19.3 (0.80× CH_3, CH_3Ar, major), 18.9 (0.20× CH_3, CH_3Ar, minor) ppm. HRMS (TOF MS, ES$^+$): *m*/*z* calcd. for $C_{19}H_{22}NO_3$ [M + H]$^+$ 312.1600; found 312.1600.

Arylopeptoid Model Monomer 8c: Synthesized on Rink acid resin using Method F (91 mg crude, 117%, 86% crude purity) at twice the scale described in the general methods. Data for **8c**: Colorless foam (60 mg, 77%, >99% purity); m.p. 205–208 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 11.00–10.40 (br. s, 1 H, COO*H*), 7.96 (dd, *J* = 7.8, 1.3 Hz, 1 H, *o*-C_6H_4COO), 7.71 (d, *J* = 7.5 Hz, 1 H, *m*′-C_6H_4COO), 7.62 (ddd, *J* = 7.9, 7.5, 1.3 Hz, 1 H, *p*-C_6H_4COO), 7.32 (ddd, *J* = 7.9, 7.7, 1.3 Hz, 1 H, *m*-C_6H_4COO), 7.14–7.03 (m, 3 H, *o*/*p*/*m*′-C_6H_4CON), 6.96–6.87 (m, 1 H, *m*-C_6H_4CON), 5.50–4.91 (br. s, 1 H, CONC*H*HAr), 4.91–4.30 (br. s, 1 H, CONCH*H*Ar), 2.34 (s, 3 H, CH_3Ar), 1.55 (s, 9 H, CON*t*Bu) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.0 (C_q, *C*ON), 170.9 (C_q, *C*OO), 142.6 (C_q, *o*′-C_6H_4COO), 138.2 (C_q, *ipso*-C_6H_4CON), 133.2 (C_q, *o*′-C_6H_4CON), 132.7 (CH, *p*-C_6H_4COO), 132.0 (CH, *o*-C_6H_4COO), 130.2 (CH, *m*′-C_6H_4CON), 128.3 (CH), 127.4 (CH, *m*′-C_6H_4COO), 126.7 (CH, *m*-C_6H_4COO), 126.3 (C_q, *ipso*-C_6H_4COO), 125.5 (CH, *m*-C_6H_4CON), 124.4 (CH), 58.6 (C_q, CON*t*Bu), 49.0 (CH_2, CONCH_2Ar), 28.6 (3× CH_3, CON*t*Bu), 18.9 (CH_3, CH_3Ar) ppm. HRMS (TOF MS, ES$^+$): *m*/*z* calcd. for $C_{20}H_{24}NO_3$ [M + H]$^+$ 326.1751; found 326.1751.

Arylopeptoid Model Monomer 8g: Synthesized on Rink acid resin using Method D (100 mg crude, 112%, 91% crude purity) at twice the scale described in the general methods. Data for **8g**: Colorless foam (82 mg, 92%, >99% purity); m.p. 61–64 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 11.20–10.75 (br. s, 1 H, COO*H*), 7.87 (dd, *J* = 7.8, 0.8 Hz, 1 H, *o*-C_6H_4COO, major), 7.84 (d, 1 H, *o*-C_6H_4COO, minor), 7.48–7.03 (m, 12.75 H), 6.99–6.90 (m, 0.25 H), 6.19 (q, *J* = 6.8 Hz, 0.25 H, CONC*H*CH_3, minor), 5.16–4.98 (m, 1.50 H, CONC*H*CH_3, minor and CONC*H*HAr, major), 4.98–4.62 (m, 1.25 H, CONCH*H*Ar, major and CONCH_2Ar, minor), 2.47, 2.38, 2.24 (3× s, 3 H, CH_3Ar), 1.66–1.52 (m, 3 H, CONCHCH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.3 (0.75× C_q, *C*ON, major), 173.3 (0.25× C_q, *C*ON, minor), 171.5 (0.75× C_q, *C*OO, major), 171.0 (0.25× C_q, *C*OO, minor), 141.0, 140.2, 139.3, 138.6, 136.0, 135.6, 135.3, 134.3, 133.8, 129.6 (5× C_q), 132.3, 132.1, 131.5, 131.2, 130.9, 130.3, 129.4, 129.4, 129.3, 128.8, 128.7, 128.4, 128.1, 128.1, 127.9, 127.8, 127.6, 127.3, 127.2, 127.0, 126.9, 126.6, 126.2, 125.9, 125.7, 125.5 (13× CH), 58.1, 57.8 (0.75× CH, CON*C*HCH$_3$, major), 53.2 (0.25× CH, CON*C*HCH$_3$, minor), 46.3, 43.5 (CH_2, CON*C*H_2Ar), 19.5, 19.0 (CH_3, *C*H_3Ar), 18.3, 17.6 (CH_3, CONCH*C*H_3) ppm. HRMS (TOF MS ES$^+$): *m*/*z* calcd. for $C_{24}H_{24}NO_3$ [M + H]$^+$ 374.1751; found 374.1754.

Arylopeptoid Model Monomer 8h: Synthesized on Rink acid resin using Method E (40 mg crude, 48%, 99% crude purity) at twice the scale described in the general methods. Data for **8h**: Colorless foam (33 mg, 40%, >99% purity); m.p. 175–178 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.40–9.90 (br. s, 1 H, COO*H*), 7.99 (dd, *J* = 7.8, 1.3 Hz, 1 H, *o*-C_6H_4COO), 7.66 (dd, *J* = 7.7, 1.2 Hz, 1 H, *m*′-C_6H_4COO), 7.57 (ddd, *J* = 7.8, 7.7, 1.3 Hz, 1 H, *p*-C_6H_4COO), 7.36 (ddd, *J* = 7.8, 7.8, 1.2 Hz, 1 H, *m*-C_6H_4COO), 7.15–6.90 (m, 9 H, C_6H_4CON and CONC$_6H_5$), 5.61 (s, 2 H, CONCH_2Ar), 2.39 (s, 3 H, CH_3Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.8 (C_q, *C*ON), 171.7 (C_q, *C*OO), 142.4 (C_q), 138.9 (C_q, *o*′-C_6H_4COO), 135.8 (C_q, *o*′-C_6H_4CON), 135.0 (C_q), 132.9 (CH, *p*-C_6H_4COO), 131.5 (CH, *o*-C_6H_4COO), 130.3 (CH), 128.9 (3× CH), 128.6 (CH, *m*′-C_6H_4COO), 127.5 (CH and C_q), 127.3 (CH), 127.2 (2× CH), 127.0 (CH), 125.0 (CH), 51.4 (CH_2, CONCH_2Ar), 19.7 (CH_3, CH_3Ar) ppm. HRMS (TOF MS, ES$^+$): *m*/*z* calcd. for $C_{22}H_{20}NO_3$ [M + H]$^+$ 346.1438; found 346.1444.

Arylopeptoid Model Monomer 8i: Synthesized on Rink acid resin using Method F at twice the scale described in the general methods with *tert*-butylamine. The crude product (94 mg) carrying the *tert*-butyl side chain was agitated in TFA/water, 95:5 (2 mL) for 2 h at room temp. The solvents were evaporated under reduced pressure and the residue was evaporated with CH_2Cl_2 (3× 5 mL), yielding the crude product (85 mg crude, 132%, 98% crude purity), which was purified by preparative HPLC. Data for **8i**: Colorless foam (48 mg, 74%, >99% purity); m.p. 168–171 °C. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 8.68 (t, *J* = 6.0 Hz, CON*H*), 7.89 (dd, *J* = 7.8, 1.3 Hz, 1 H, *o*-C_6H_4COO), 7.58 (m, 1 H, *p*-C_6H_4COO), 7.49 (dd, *J* = 7.7, 0.8 Hz, 1 H, *m*′-C_6H_4COO), 7.46–7.31 (m, 3 H, C_6H_4CON and *m*-C_6H_4COO), 7.29–7.22 (m, 2 H, C_6H_4CON), 4.78 (d, *J* = 6.0 Hz, 2 H, CONCH_2Ar), 2.35 (s, 3 H, CH_3Ar) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 169.1 (C_q, *C*ON), 168.3 (C_q, *C*OO), 140.4 (C_q, *o*′-C_6H_4COO), 136.8 (C_q), 135.2 (C_q), 131.9 (CH, *p*-C_6H_4COO), 130.4 (CH), 130.3 (CH, *o*-C_6H_4COO), 129.3 (C_q, *ipso*-C_6H_4COO), 129.3 (CH), 127.3 (CH, *m*-C_6H_4COO), 127.0 (CH), 126.6 (CH, *m*′-C_6H_4COO), 125.4 (CH), 41.0 (CH_2, CONCH_2Ar), 19.4 (CH_3, CH_3Ar) ppm. Similar NMR spectra were obtained in [D$_4$]MeOH except for the disappearance of the amide proton. HRMS (TOF MS, ES$^+$): *m*/*z* calcd. for $C_{16}H_{16}NO_3$ [M + H]$^+$ 270.1130; found 270.1138.

Arylopeptoid Monomer 9g: Synthesized on Rink acid resin using Method D (97 mg crude, 113%, 95% crude purity) at twice the scale described in the general methods. Data for **9g**: Colorless foam (78 mg, 90%, >99% purity); m.p. 51–54 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 11.15–10.95 (br s, 1 H, COO*H*), 7.89 (dd, *J* = 7.6, 0.9 Hz, 1 H), 7.65–7.15 (m, 13 H), 6.24–5.88 (br. m, 0.23 H, 0.23× CONC*H*CH_3), 5.43–5.18 (br. m, 0.77 H, 0.77× CONC*H*CH_3),

5.14–4.54 (m, 2 H, $CONCH_2Ar$), 1.60 (d, J = 7.0 Hz, 3 H, $CONCHCH_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.6 (C_q), 171.3 (C_q), 139.4 (C_q), 138.9 (C_q), 136.0 (C_q), 132.4 (CH), 131.1 (CH), 130.0, 128.7, 127.9, 127.3, 126.8, 126.4 (12× CH), 57.9 (br., CH, $CONCHCH_3$), 43.7 (br., CH_2, $CONCH_2Ar$), 18.0 (br., CH_3, $CONCHCH_3$) ppm. HRMS (TOF MS, ES^+): *m/z* calcd. for $C_{23}H_{22}NO_3$ $[M + H]^+$ 360.1594; found 360.1591.

Arylopeptoid Trimer 10g: Synthesized on Rink acid resin using Method D (100 mg crude, 100%, 99% crude purity). Data for **10g**: Colorless foam (85 mg, 85%, >99% purity); m.p. 131–134 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 10.55–10.05 (br. s, 1 H, $COOH$), 7.87–6.58 (m, 32 H), 6.06–3.90 (m, 9 H, 3× $CONCHCH_3$ and 3× $CONCH_2Ar$), 1.75–1.20 (m, 9 H, 3× $CONCHCH_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.0, 172.6, 172.4, 172.1, 170.6, 169.5 (4× C_q), 140.4, 140.0, 138.5, 136.4, 136.1, 135.5, 135.0, 134.5, 134.1, 133.7 (10× C_q), 132.0, 131.7, 131.3, 130.9, 129.9, 129.4, 128.7, 128.4, 128.3, 127.9, 127.7, 127.5, 127.5, 127.3, 126.8, 126.6, 126.4, 126.1, 125.8 (32× CH), 58.0, 57.7, 57.6 (3× CH, 3× $CONCHCH_3$), 44.1, 44.0, 43.8, 42.9 (3× CH_2, 3× $CONCH_2Ar$), 20.0, 19.7, 17.7, 17.2 (3× CH_3, 3× $CONCHCH_3$) ppm. HRMS (TOF MS, ES^+): *m/z* calcd. for $C_{55}H_{52}N_3O_5$ $[M + H]^+$ 834.3907; found 834.3815.

Supporting Information (see footnote on the first page of this article): Methods used for analytical and preparative HPLC; details concerning optimization of acylation and substitution steps using HPLC; HPLC profiles and NMR spectra (proton and *j*-mod) of synthesized *ortho*-arylopeptoids; NOESY spectra of model monomers **8c**, **8h**, and **8i**.

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