Synthesis of functionalised aromatic oligamide rods†‡

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A current goal in synthetic chemistry is the design and synthesis of molecules that adopt well defined conformations—so called foldamers. In this manuscript we describe a modular approach for construction of rod shaped *para*-oligobenzamide molecules. Our approach permits regiospecific incorporation of side chains through a phenolic ether linkage on the scaffold; a feature that partly restricts the conformation of the rod through intramolecular hydrogen-bonding.

Introduction

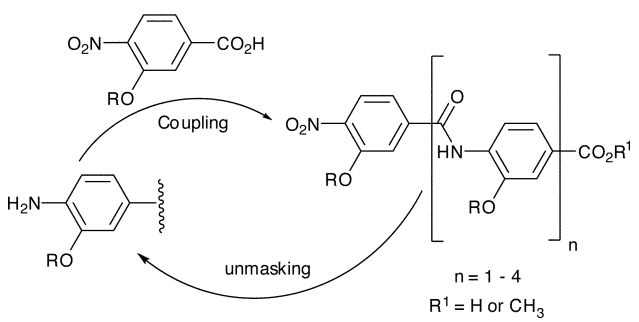
A current goal of biomolecular chemistry is to replicate the functions performed by nature's biomacromolecules with synthetic mimics. Nature uses polymers comprising well defined monodisperse sequences of monomers that adopt highly defined secondary and tertiary three dimensional architectures. Therefore, significant effort has been devoted to identifying model systems that give rise to well defined secondary structures termed '*foldamers*'.[1,2] More recently functional properties[3] have been illustrated as evidenced by reports on foldamers that inhibit protein–protein interactions,[4] act as bacteriocidal agents[5] and recognise small molecules.[6] Similarly, the knowledge derived from fundamental studies of secondary structural motifs has recently allowed some simple tertiary structures to be prepared.[7–9] For the most well studied class of foldamer, *i.e.* those derived from β-peptides,[10] a key feature that has permitted these studies is the availability of iterative syntheses that give rise to well defined sequences incorporating many different monomers.

We have become interested in the study of aromatic oligoamides[11–13] because their syntheses are in principle amenable to the methods used for conventional α-amino acid derived peptides. Most aromatic oligoamides adopt helical conformations pre-organised by intramolecular hydrogen-bonds, with extended or rod-like conformations less common.[14–18] Rod-like oligomers may find use in protein,[19] peptide[20] and oligonucleotide recognition.[21] We recently described a route to oligoamide macrocycle synthesis with regiospecific incorporation of functional groups.[22] The approach does not require hydrogen-bonding but instead exploits the helical conformation[23] adopted by linear *N*-alkylated aromatic oligoamides which preferentially adopt the *cis* conformer at the amide linkage.[24] Given that phenyl-benzamides prefer the *trans* conformation,[25] we hypothesized that it should be possible to construct short rod-like oliogoamides using a similar strategy. Indeed, a similar approach was used to assemble nanometre sized rods from 4′-amino-[1,1′-biphenyl]-4-carboxylic acid derivatives.[26] Herein we describe a robust modular synthesis of aromatic oligoamides and their structural characterisation. These *O*-alkylated oligomers were recently proposed to be potential α-helix mimetics.[27]

Results and discussion

Synthesis

Our design of rod-like oligomers necessitates placing the carboxylate and amine funtionalities that form the linking amide in a *para* relationship. We also required a robust method to incorporate side-chains into each monomer unit and were attracted by *O*-alkylation. This has the advantage of pre-organising the scaffold further through 5-membered intramolecular hydrogen-bonding between the oxygen of the alkoxy substituent and the amide NH. Iterative synthesis *via* sequential coupling of masked 4-nitro-3-alkoxybenzoic acid monomers (Scheme 1) as described for synthesis of β-sheet binding pyrazole oligoamides[20] was attractive to us. Such an approach is fully modular, so once a monomer has been synthesised it can be rapidly incorporated into any desired sequence. In previously described studies,[27] N to C terminal assembly was employed, but amide bond formation with alkylated monomers failed and a less modular amide formation then alkylation was necessary.



Scheme 1 Iterative synthetic strategy for construction of aromatic oligoamide rods.

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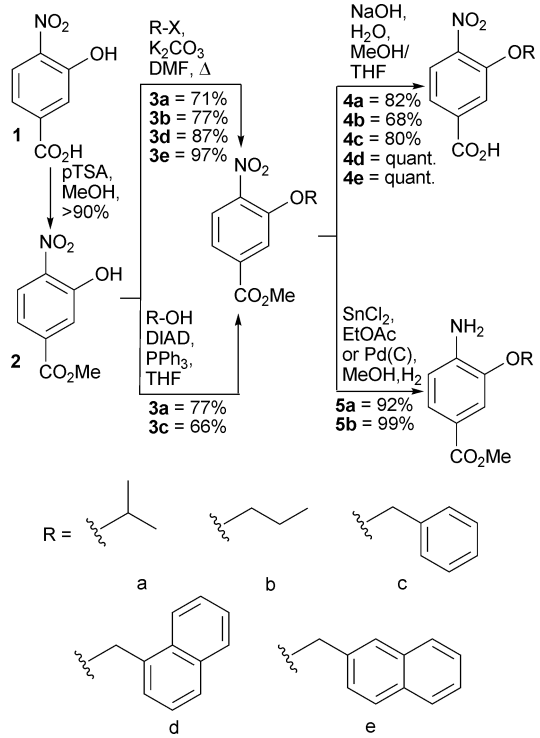
† Dedicated to Prof. Sir J. Fraser Stoddart on the occasion of his knighthood and 65th birthday.

‡ Electronic supplementary information (ESI) available: CIF files, full details of X-ray crystallographic structure determination and additional NMR spectra. See DOI: 10.1039/b712606a

For these solution phase studies we chose 4-nitro-3-hydroxybenzoic acid as the starting material due to the ease of monomer synthesis. Scheme 2 outlines our approach which furnishes both 4-nitro-3-alkoxybenzoic acids **4a–f** for chain elongation and unmasked amines **5a–b** that can be used as the starting monomer.

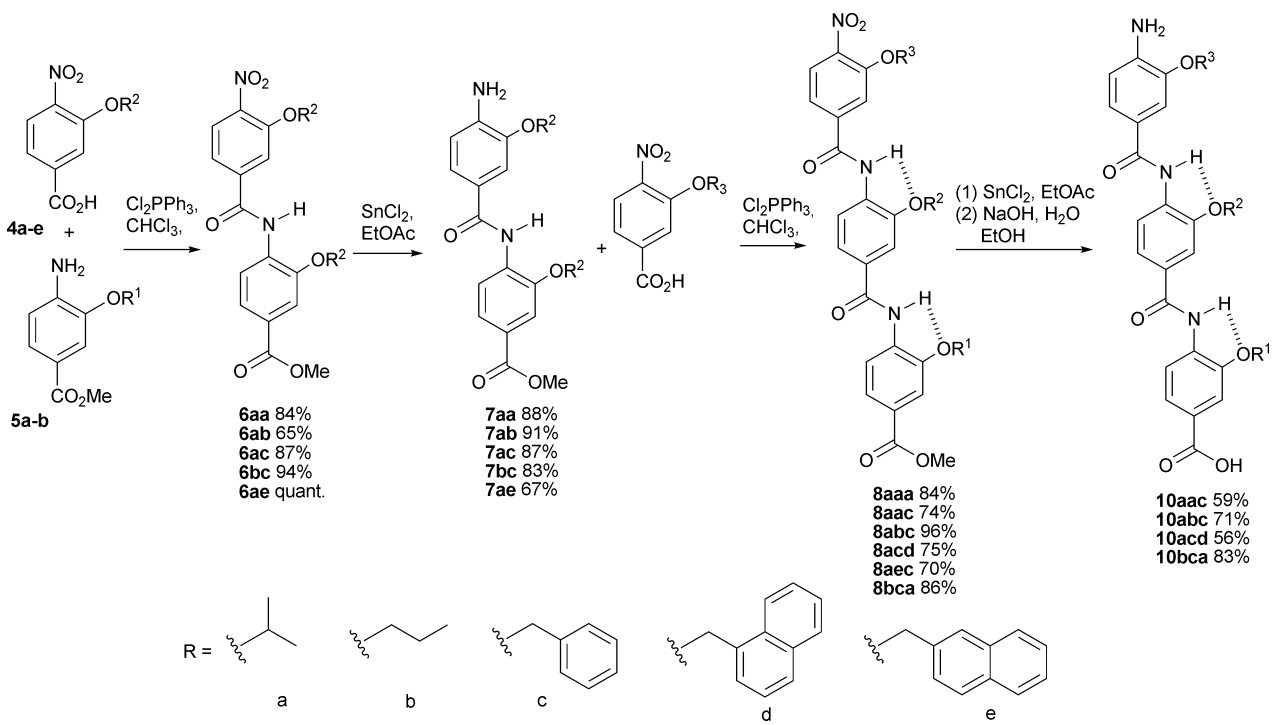


Scheme 2 Synthesis of monomers for iterative synthesis of aromatic oligoamide rods.

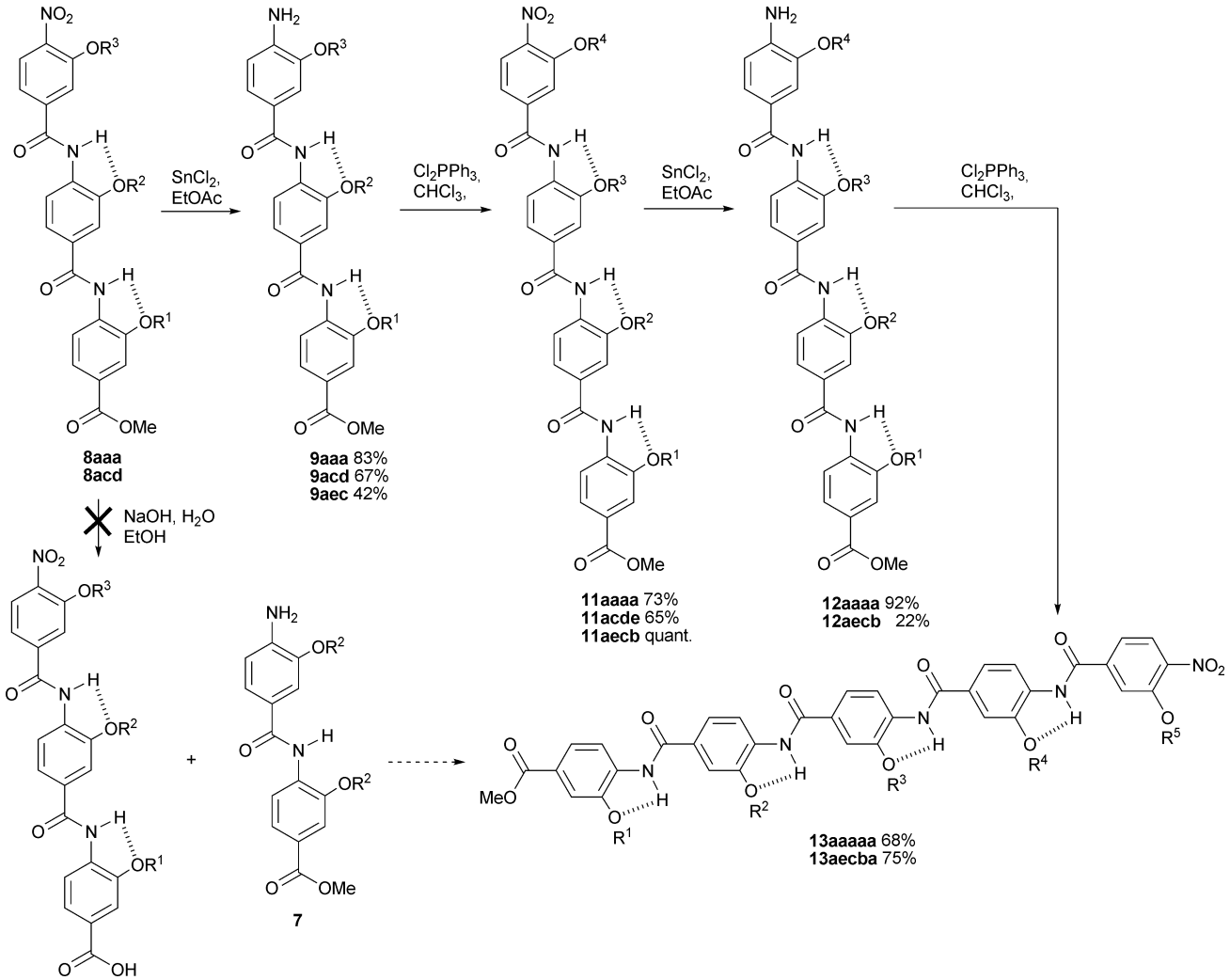
Alkylation of the phenolic oxygen is possible either by reaction with commercially available alkyl halides or *Mitsunobu* reaction with alcohols. The latter approach gives poorer yields and more difficult purification; however, the compatibility of both reactions coupled with the wide variety of commercially available alkyl halides and alcohols, augers well for future studies.

The synthesis of trimers is shown in Scheme 3. The key steps involve (i) amide bond formation, for which we selected dichlorotriphenyl phosphorane as activating agent and (ii) unmasking of an amino group, for which we selected tin (II) chloride. For amide bond formation, only coupling reagents that generate acid chlorides gave decent yields and then only when heated. For nitro group reduction, although hydrogenation over palladium on carbon proceeded smoothly, this is not compatible with benzylic *O*-alkyl substituents. We found reduction with tin (II) chloride to be a viable alternative. Yields were consistently above 90% for each of these steps. The final compounds **10** were fully deprotected to expose the terminal amine and carboxylate functionalities (hydrolysis followed hydrogenation—see below).

The synthesis of tetramers and pentamers was found to be more challenging. Initially we conceived a 2 + 3 fragment based strategy; however, our attempts to cleave the methyl ester of trimer **8aaa** resulted in hydrolysis of the amide group *para* to the terminal nitro group. This is perhaps unsurprising given the electron withdrawing nature of the nitro group. Thus, although we could have also explored a 3 + 2 strategy, this result suggested that clean hydrolysis of nitro masked dimers **6** was unlikely and we opted instead for a simple 3 + 1 then 4 + 1 chain elongation approach (Scheme 4). Only small reductions in yield were observed for the coupling steps, however, the tetramers and pentamers underwent sluggish nitro group reduction. The most likely reason for this is the poorer solubility of these compounds in the reaction media. Indeed,



Scheme 3 Synthesis of fully unmasked trimers **10** *via* an iterative chain elongation approach. Identity of side chains in oligomers is given from the C terminus *e.g.* for **10aac** $R^1 = a$, $R^2 = a$, and $R^3 = c$.



Scheme 4 Synthesis of oligoamide tetramers and pentamers (letters correspond to R groups as for Schemes 2 and 3).

we were unable to reduce tetramer **12acde** whilst **12aecb** gave a poor conversion resulting in only 22% of the reduced product although it should be noted that unreacted starting material was also recovered.

Structural studies

Single crystals were obtained by the slow evaporation of a solution of trimer **8abc** in ethyl acetate. The X-ray structure confirms the oligomer adopts an extended structure and the presence of an intramolecular hydrogen-bond between the amide NH and the alkoxy oxygen on the neighbouring phenyl ring (Fig. 1). NMR studies indicate that this behaviour is mirrored in solution. For example **8aaa**, in both DMSO-d_6 and chlorinated solvents, exhibits strong hydrogen bonds as evidenced by the downfield shift of the NH protons (H_f and H_l) (removed in the ^{1}H NMR spectra) (Fig. 2a and b). In both solvents, the NHs undergo no change upon dilution indicating these interactions are intramolecular (Fig. S1 and S2, ESI‡). This is further confirmed upon heating up to 100 °C (Fig. S3 and S4, ESI‡); in DMSO-d_6, H_f and H_l experience temperature induced shifts of 3.5 ppb K^{-1} and 4.3 ppb K^{-1} whilst in $C_2D_2Cl_4$ they exhibit shifts of 0.8 ppb K^{-1} and 0.6 ppb K^{-1}. The extended

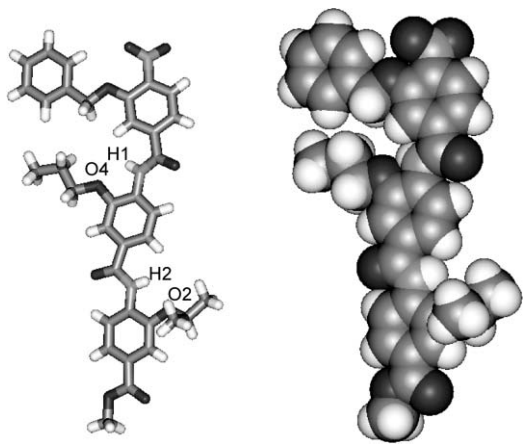


Fig. 1 X-Ray crystal structure of compound **8abc** shown in stick (left) and CPK (right) format. Key distances H1–O4 = 2.155 Å and H2–O2 = 2.132 Å.

rod-like structure is confirmed in solution by correlations in the ^{1}H–^{1}H NOESY spectrum between NH and ArCH on adjacent aromatic units (*i.e.* NH_l to H_k and H_j and NH_f to H_e and H_d)

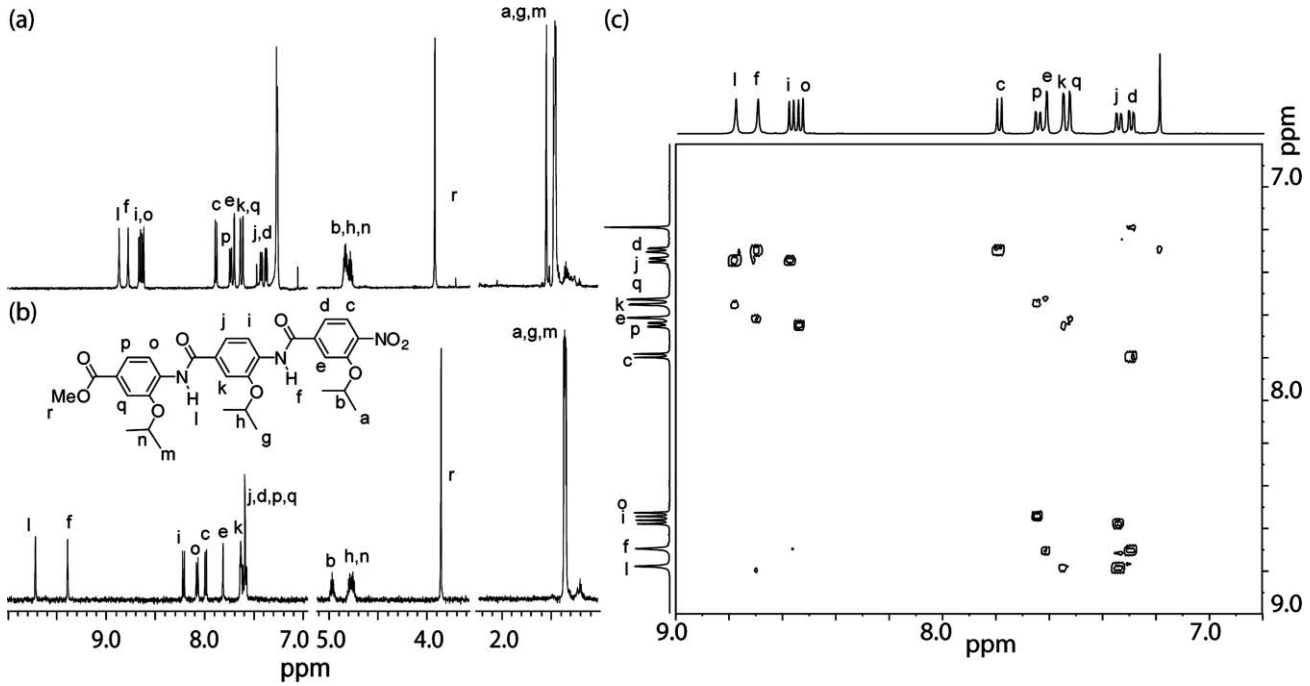


Fig. 2 ^{1}H NMR spectrum (500 MHz) of trimer **8aaa** (a) 3 mM in $CDCl_3$ and (b) 2 mM in DMSO-d_6 (c) ^{1}H–^{1}H NOESY spectrum of trimer **8aaa** in $CDCl_3$.

and the absence of cross-peaks between non-adjacent aromatic resonances (Fig. 2c). Furthermore, this observation confirms free rotation about the ArCO bonds, whilst the absence of cross-peaks between H_0 and NH_1 or H_i and NH_f suggests restricted rotation about the ArNH bonds.

The tetramers and pentamers also exhibit downfield shifted NH protons indicative of H-bonding, however signal overlap prevented a thorough conformational analysis as for the trimers. We therefore utilized molecular modelling by performing a full *Monte Carlo* search in Macromodel[28] using the MMFFs force field. This revealed the lowest energy conformation of pentamer **13aaaaa** in the gas phase was the extended structure (Fig. 3) and similar results were obtained when the dielectric was set to water. This clearly demonstrated the extended conformation is preferred in both solution phase and gas phase. Furthermore, we tentatively suggest that alternate alkoxy substituents prefer to reside on opposite faces of the rod—all but two of the 20 lowest energy conformers found in the search followed this trend.

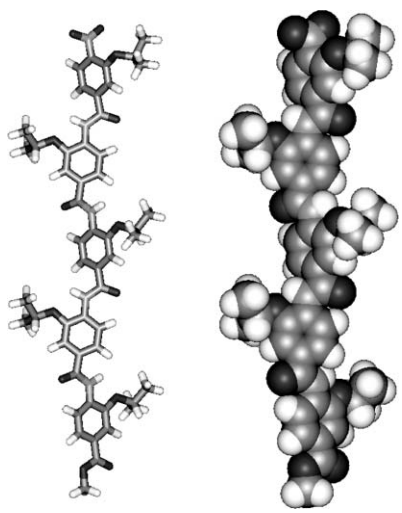


Fig. 3 Lowest energy conformer of pentamer **13aaaaa** identified by a *Monte Carlo* search in Macromodel using the MMFFs force field.

Taken together the X-ray, NMR and modelling studies clearly confirm an extended conformation is preferred in the solid state and solution, and that intermolecular hydrogen-bonding fixes rotation about the ArNH bond. However, like the nanometre sized rods described recently by Nowick and co-workers,[26] free rotation about the ArCO bond is possible. Our rationale is that the alkoxy substituents minimise steric hindrance by residing on opposing faces, although this conformation would also minimise dipole effects. The NOESY results suggest this preference is not overwhelming as both ArCO conformations are present in solution. Interestingly, in the solid state structure of **8abc** (Fig. 1) two of the alkoxy substituents reside on the same face suggesting that crystal packing effects and interactions between adjacent side chains can significantly influence the preferred conformation of these oligomers. This is significant for the following reason: where the molecular recognition properties of these foldamers depend on the alkoxy substituents being presented on one face and available for recognition (*e.g.* for protein[19] or crystal surface[29] recognition) an entropic price would need to be paid for fixing the ArCO bond rotation and/or breaking side-chain side-chain interactions. This can be advantageous in that it allows for induced-fit binding. These compounds therefore complement the fully rigidified crescent oligomers and rods described by the groups of Gong,[13] Hamilton[16] and Li.[17,18]

Conclusion

We have described the fully modular syntheses of a series of rod like aromatic oligoamides. These molecules can be made from

easily accessible monomers and adopt well defined conformations, whilst the building blocks and synthetic methods are compatible with the components of other aromatic oligoamides. Our own future studies will focus on making mixed structures containing building blocks from this pool, elaborating solid phase approaches for their synthesis and studying their molecular recognition properties.

Experimental

All chemicals and solvents were purchased from Aldrich and used without further purification. Melting points were determined using a Griffin D5 variable temperature apparatus and are uncorrected. ^{1}H Nuclear magnetic resonance spectra were recorded using a Bruker DRX 500 MHz or DPX 300 MHz machine. ^{1}H spectra are referenced to tetramethylsilane (TMS) and chemical shifts are given in parts per million downfield from TMS. Coupling constants are reported to the nearest 0.1 Hz. Microanalyses were obtained on a Carlo Erba Elemental Analyser MOD 1106 instrument. Infrared spectra were recorded on a Perkin-Elmer FTIR spectrometer and samples analysed in the solid phase. Mass spectra were obtained on a Bruker microTOF using electrospray ionisation. Representative characterisation is given here for all intermediates leading to a complete trimer **10abc** and a complete pentamer **13aecba**. The remaining data is available in the ESI.‡

Crystal structure determination for 8abc

Single crystals were grown by the slow evaporation of a solution of **8abc** in ethyl acetate. X-Ray diffraction data were collected at the University of Leeds. Crystal data. $C_{35}H_{35}N_3O_9$, $M = 641.66$, crystal size 0.3 × 0.1 × 0.1 mm, triclinic, $a = 8.0680(2)$, $b = 10.8740(2)$, $c = 19.1980(5)$ Å, $\alpha = 105.2700(10)$, $\beta = 8.0820(10)$, $\gamma = 8.0750(10)°$, $U = 1580.64(6)$ Å^3, $T = 150(2)$ K, $P\bar{1}$, $Z = 2$, $\mu = 0.098$ mm^{-1}, $\lambda = 0.71073$ Å [Mo–Kα], 13724 reflections measured, 7244 unique ($R_{int} = 0.035$), observed ($I > 2\sigma(I)$). The final R_1 was 0.0490 (observed reflections 0.0866) and $wR(F^2)$ was 0.1250 (all data 0.1638) for 436 parameters.§

Molecular modelling

Structures were minimized with Macromodel (MacroModel version 9.0, Schrodinger LLC, New York, NY, 2006) using the Monte Carlo method (5000 structures using the automatic setup) and minimized using the MMFF force field. The results were visualized with Maestro (version 7) and the lowest 20 energy structures were compared, and found to be similar.

General procedure A for the alkylation of phenol

Under an inert atmosphere, methyl-3-hydroxy-4-nitrobenzoate (1 equiv.) was dissolved in DMF (5 ml per g of phenol) and K_2CO_3 (5 equiv.) was added. The alkyl halide (1.4 equiv.) was then added and the solution stirred at 50 °C overnight. The resultant solution was poured into EtOAc (100 mL per g of phenol) and washed twice with H_2O (100 mL per g of phenol) and once with brine (100 mL per g of phenol). The organics were dried (Na_2SO_4) and removed under reduced pressure. The crude oil was subjected to column chromatography (SiO_2, CH_2Cl_2) to yield a pale yellow solid.

General procedure B for the saponification of esters

Oligoamide (1 equiv.) was dissolved in THF (25 mL per g of ester) and MeOH (25 mL per g of ester). NaOH (10% aqueous 5 mL per g of ester) was then added and the solution was sealed and stirred overnight. When the reaction was complete as observed by TLC, the organic solvent was removed under reduced pressure. The resulting viscous solution was diluted with water (40 mL per g of ester) and acidified to a pH of 1 using 10% aqueous HCl. The resulting suspension was then filtered and the solid dried overnight yielding a white solid. Alternatively the acid is dissolved in EtOAc and separated from the spurious water and dried (Na_2SO_4). Removal of the solvents under reduced pressure yielded the acid as a white solid.

General procedure C for the coupling reaction

Under an inert atmosphere, to a stirred solution of amine (1.0 equiv.) and acid (1.4 equiv.) in freshly distilled $CHCl_3$ (50 mL per g of amine), dichlorotriphenylphosphorane (4.5 equiv.) was added and the solution allowed to stir at reflux (80 °C) overnight. The solvents were removed under a reduced pressure and the resultant viscous oil subjected to column chromatography (SiO_2, CH_2Cl_2–Et_2O gradient) to yield the product.

General procedure D for reduction of a nitro group

To a solution of a nitro compound (1 equiv.) in EtOAc (5–10 mL) was added $SnCl_2{\cdot}2H_2O$ (5 equiv.) and the reaction mixture was heated to 50 °C under a drying tube. When TLC indicated complete reduction (typically 24 hours), the reaction mixture was cooled, then poured into NaOH solution (10% 100 mL) and the flask rinsed into ethyl acetate (×2). The combined organics were extracted twice with NaOH solution (10% 100 mL) before being washed once with brine (50 mL). The organics were then dried (Na_2SO_4) and the solvent removed under reduced pressure yielding oils that solidify upon standing. Alternatively, the oil was subjected to column chromatography (SiO_2, CH_2Cl_2–Et_2O gradient) to give a cream white to yellow crystalline product.

Methyl-3-hydroxy-4-nitrobenzoate 2

A stirred solution of 3-hydroxy-4-nitro benzoic acid **1** (2.50 g, 13.66 mmol) and *p*-toluene sulfonic acid (0.50 g, 2.63 mmol) in anhydrous methanol (50 mL) under an atmosphere of argon was heated at reflux (65 °C) for 60 h. The reaction mixture was concentrated to leave a bright yellow crystalline solid, which was partitioned between EtOAc and water (4 × 50 mL). The organic fraction was dried ($MgSO_4$), concentrated and dried under vacuum, isolating pure target material (2.38 g, >90%) as a bright yellow powdered solid; mp 90–91 °C (*90–91 °C Aldrich*); R_f 0.63 (10% EtOAc in CH_2Cl_2); δ_H (300 MHz, $CDCl_3$) 4.00 (s, 3H, CO_2Me), 7.65 (d, 1H, $J = 8.8$, ArCH), 7.87 (d, 1H, $J = 1.7$, ArCH), 8.21 (d, 1H, $J = 8.8$, ArCH).

§ CCDC reference number 661106. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b712606a

Methyl-3-isopropyloxy-4-nitrobenzoate 3a

To a stirred solution of methyl-3-hydroxy-4-nitrobenzoate **2** (1.00 g, 5.34 mmol), isopropanol (0.60 mL, 7.85 mmol, excess) and triphenylphosphine (1.33 g, 5.07 mmol) in anhydrous THF (15 mL), under an atmosphere of argon, at 0 °C, was added diisopropyl azodicarboxylate (DIAD) (1.00 mL, 4.82 mmol). The reaction mixture was allowed to warm to room temperature and stirred for a further 72 h. The reaction mixture was concentrated then dissolved in CH_2Cl_2 and washed with water (2 × 30 mL), saturated $NaHCO_3$ (3 × 30 mL) and brine (30 mL). The organic fraction was concentrated and purified by column chromatography (1 : 1; CH_2Cl_2–hexane) to yield the product (0.84 g, 77%) as a bright yellow crystalline solid; mp 39–41 °C (found: C, 55.30; H, 5.45; N, 5.75%. $C_{11}H_{13}NO_5$ requires: C, 55.23; H, 5.48; N, 5.86%); R_f 0.55 (CH_2Cl_2); δ_H (500 MHz, $CDCl_3$) 1.41 (6H, d, J = 6.0, 2-propyl CH_3), 3.96 (3H, s, CO_2Me), 4.77 (1H, hep, J = 6.0, CH), 7.65 (1H, d, J = 7.3, ArCH), 7.74 (1H, s, ArCH), 7.76 (1H, d, J = 8.5, Ar 6-CH); δ_C (75 MHz, $CDCl_3$) 21.8, 52.8, 73.0, 116.9, 121.1, 125.1, 134.4, 143.7, 150.8, 165.4; ν_{max}/cm^{-1} (solid state) = 3119, 3060, 2989, 1958 (aliph CH), 1725 (CO), 1528; ESI-MS m/z 262 $[M + Na]^+$; ESI-HRMS found m/z 262.0694 $[M + Na]^+$, $C_{11}H_{13}NNaO_5$ requires 262.0686.

Methyl-3-isopropyloxy-4-nitrobenzoate 3a

(Alternative preparation using procedure A) methyl-3-hydroxy-4-nitrobenzoate **2** (600 mg, 3.0 mmol), K_2CO_3 (510 mg, 3.7 mmol), anhydrous DMF (15 mL), 2-bromopropane (450 μL, 5.0 mmol). Purification by column chromatography (20% EtOAc–CH_2Cl_2) gave a bright yellow crystalline solid: yield: 520 mg, 71% (data as above).

3-Isopropyloxy-4-nitro benzoic acid 4a

(Using minor modifications to procedure B) a stirred solution of methyl-3-isopropoxy-4-nitrobenzoate (250 mg, 1.05 mmol) and 1 M NaOH solution (1.5 mL, 1.10 mmol) in methanol (10 mL) was heated at reflux temperature (65 °C) for 12 h until TLC indicated no remaining starting material. On cooling, the reaction mixture was acidified to pH ~1 (1 N HCl, ~2 mL) precipitating a solid which was collected by filtration and dried thoroughly under vacuum to give the target acid (194 mg, 82.1%) as a cream solid: mp 173–175 °C (found: C, 53.40; H, 4.90; N, 6.05%. $C_{10}H_{11}NO_5$ requires: C, 53.33; H, 4.92; N, 6.22%); R_f 0.31 (15% MeOH in CH_2Cl_2); δ_H (75 MHz, $CDCl_3$) 1.47 (d, 6H, J = 6.1, CH_3), 4.82 (q, 1H, J = 6.1, CH), 7.77 (d, 1H, J = 8.1, ArCH), 7.80 (d, 1H, J = 7.6, ArCH), 7.82 (d, 1H, J = 1.3 Hz, ArCH); δ_C (75 MHz, $CDCl_3$) 22.18, 73.52, 117.70, 122.18, 125.59, 133.70, 144.77, 151.19, 170.69; ν_{max}/cm^{-1} (solid state) = 2900 (broad, COOH), 1688 (CO), 1524, 1432; ESI-HRMS found m/z 224.0553 $[M - H]^-$, $C_{10}H_{10}NO_5$ requires 224.0553.

Methyl-4-amino-3-isopropyloxy benzoate 5a

To a stirred solution of methyl-3-isopropoxy-4-nitrobenzoate **3a** (340 mg, 1.42 mmol) in anhydrous methanol (10 mL), under an atmosphere of nitrogen, was added 10% palladium on charcoal (30 mg). The nitrogen atmosphere was evacuated under vacuum and hydrogen gas (1 L, excess) introduced *via* a balloon. The reaction mixture was stirred for 200 minutes until TLC indicated the reaction was complete. The mixture was passed through a celite pad and concentrated before drying under vacuum to yield the product (272 mg, 92%) as a runny pale brown oil; R_f 0.42 (5% EtOAc in CH_2Cl_2); δ_H (500 MHz, $CDCl_3$) 1.29 (d, 6H, J = 6.1, CH_3), 3.78 (s, 3H, CO_2Me), 4.10 (broad singlet, 2H, NH_2), 4.56 (septet, 1H, J = 6.1, CH), 6.59 (d, 1H, J = 8.1, ArCH), 7.39 (d, 1H, J = 1.5, ArCH), 7.45 (dd, 1H, J = 1.6 and 8.2, ArCH); δ_C (75 MHz, $CDCl_3$) 25.57, 52.05, 71.20, 113.80, 114.44, 119.81, 124.29, 142.62, 144.54, 167.75; ν_{max}/cm^{-1} (solid state) 3500, 3373 (NH_2), 2972, 2950 (CH), 1692, 1613 (CO); ESI-MS m/z 210 $[M + H]^+$; ESI-HRMS found m/z 210.1127 $[M + H]^+$, $C_{11}H_{15}NO_3$ requires 210.1125.

Methyl-3-isopropoxy-4-(3-propoxy-4-nitro-benzoylamido)-benzoate 6ab

(Procedure C) **5a** (166 mg, 0.8 mmol), **4b** (178 mg, 0.8 mmol), chloroform (20 mL), Cl_2PPh_3 (640 mg, 1.9 mmol). Purification by column chromatography (10% EtOAc in CH_2Cl_2) afforded the target material (215.7 mg, 65%), as a pale yellow solid; mp 132–133 °C (found C 60.00, H 5.80, N 6.60%. $C_{21}H_{24}N_2O_7$ requires: C 60.50, H 5.85, N 6.73%); δ_H (500 MHz, $CDCl_3$) 1.08 (3H, t, J = 7.4, CH_3), 1.44 (6H, d, J = 6.0, CH_3), 1.90 (2H, tq, J = 7.1 and 6.9, CH_2), 3.92 (3H, s, CO_2Me), 4.17 (2H, t, J = 6.4, CH_2), 4.78 (1H, hep, J = 6.1, CH), 7.37 (1H, d, J = 8.3, ArCH), 7.61 (1H, s, ArCH), 7.67 (1H, s, ArCH), 7.74 (1H, d, J = 8.4, ArCH), 7.92 (1H, d, J = 8.3, ArCH), 8.59 (1H, d, J = 8.5, ArCH), 8.79 (1H, s, NH); δ_C (75 MHz, $CDCl_3$) 10.8, 22.6, 22.7, 52.6, 71.8, 72.3, 113.4 (Ar C, CO), 114.5, 117.6, 119.3, 123.6, 126.2, 126.3, 132.6, 140.2, 142.2, 146.3, 153.1, 163.5, 167.0; ν_{max}/cm^{-1} (solid state) 3425 (NH), 3092, 2977, 2951, 2884, 2621, 1932, 1683 (CO), 1598 (C=C), 1516 (NO_2); ESI-MS m/z = 417 $[M + H]^+$.

Methyl-3-isopropoxy-4-(3-(2-naphthyloxy)-4-nitro-benzoylamido)-benzoate 6ae

(Procedure C) **5a** (914.3 mg, 4.4 mmol), **4e** (2.0 g, 6.43 mmol), Cl_2PPh_3 (6.4 g, 19.8 mmol), and chloroform (150 mL) afforded the product (2.2 g, 100%) as a yellow solid; mp 142–143 °C; δ_H (300 MHz, $CDCl_3$) 1.40 (6H, d, J = 6, iPrCH_3), 3.91 (3H, s, CO_2Me), 4.75 (1H, hep, J = 6, iPrCH), 5.47 (2H, s, benzylic CH_2), 7.37 (1H, d, J = 8.3, ArCH), 7.45–7.51 (2H, m, ArCH), 7.55 (1H, d, J = 8.4, ArCH), 7.59 (1H, s, ArCH), 7.72 (1H, d, J = 8.4, ArCH), 7.79–7.96 (6H, m, ArCH), 8.56 (1H, d, J = 8.5, ArCH), 8.76 (1H, s, NH); δ_C (75 MHz, $CDCl_3$) 22.6, 52.6, 72.0, 72.3, 113.5, 115.3, 118.1, 119.3, 123.6, 125.0, 126.3, 126.5, 126.7, 126.8, 126.9, 128.2, 128.5, 129.2, 132.5, 132.8, 133.6, 133.7, 140.3, 142.5, 146.3, 152.6, 163.3, 167.0; ν_{max}/cm^{-1} (solid state) 3423 (NH), 2982, 1713, 1691, 1597, 1522, 1481, 1348, 1273, 1114, 1003, 760; ESI-HRMS found m/z 515.1809 $[M + H]^+$, $C_{29}H_{27}N_2O_7$ requires 515.1813.

Methyl-3-isopropoxy-4-(3-propoxy-4-amino-benzoylamido)-benzoate 7ab

To a stirred solution of **6ab** (175 mg, 0.40 mmol) in anhydrous methanol (7 mL), under an atmosphere of nitrogen, was added palladium on charcoal catalyst (17.5 mg, 10% catalyst). The nitrogen atmosphere was evacuated under vacuum and hydrogen

gas (1 L, excess) introduced *via* a balloon. The reaction mixture was stirred until TLC indicated the reaction was complete and then passed through a celite pad, concentrated and dried under high vacuum to yield the product (141 mg, 91%); mp 103–104 °C; δ_H (500 MHz, $CDCl_3$) 1.07 (3H, t, J = 7.4, CH_3), 1.43 (6H, d, J = 6.0, CH_3), 1.88 (2H, tq, J = 6.9 and 6.8, CH_2), 3.91 (3H, s, CO_2Me), 4.06 (2H, t, J 6.4, CH_2), 4.22 (2H, s, NH_2), 4.75 (1H, hep, J = 6.1, CH), 6.73 (1H, d, J = 8.5, ArCH), 7.26 (1H, d, J = 8.3, ArCH), 7.44 (1H, s, ArCH), 7.58 (1H, s, ArCH), 7.71 (1H, d, J = 8.6, ArCH), 8.51 (1H, s, NH), 8.62 (1H, d, J = 7.8, ArCH); δ_C (75 MHz, $CDCl_3$) 22.3, 22.6, 30.9, 52.0, 70.0, 71.8, 91.1, 110.7, 113.2, 113.3, 118.5, 119.9, 123.5, 124.2, 124.5, 133.6, 140.5, 145.6, 146.2, 165.1, 166.9; ν_{max}/cm^{-1} (solid state) 3492, 3429, 3349, 2970, 2934, 2873, 1704 (CO), 1614; ESI-HRMS found m/z 387.1914 $[M + H]^+$, $C_{21}H_{28}N_2O_5$ requires 387.1842.

Methyl-3-isopropoxy-4-(3-(2-naphthyloxy)-4-amino-benzoylamido)-benzoate 7ae

(Procedure C) **6ae** (2.2 g, 4.4 mmol), $SnCl_2{\cdot}2H_2O$ (5.2 g, 23.1 mmol), ethyl acetate (150 mL) afforded the product (1.4 g, 67%) as a yellow oil that solidified upon standing; mp 70–72 °C; δ_H (300 MHz, $CDCl_3$) 1.40 (6H, d, J = 6, iPrCH_3), 3.89 (3H, s, CO_2Me), 4.33 (2H, br, NH_2), 4.71 (1H, hep, J = 6, iPrCH), 5.29 (2H, s, benzylic CH_2), 6.75 (1H, d, J = 8.1, ArCH), 7.29 (1H, d, J = 8.2, ArCH), 7.47–7.52 (2H, m, ArCH), 7.56 (1H, d, J = 8.2, ArCH), 7.58 (1H, s, ArCH), 7.61 (1H, s, ArCH), 7.71 (1H, d, J = 8.4, ArCH), 7.82–7.87 (4H, m, ArCH), 8.63 (1H, d, J = 8.5, ArCH), 8.74 (1H, s, NH); δ_C (75 MHz, $CDCl_3$) 22.6, 52.4, 71.1, 72.2, 111.8, 113.6, 113.9, 118.9, 120.7, 123.8, 124.5, 124.9, 125.9, 126.7, 126.8, 127.1, 128.2, 128.4, 128.9, 133.6, 133.7, 134.0, 134.4, 141.3, 146.1, 146.4, 165.4, 167.3; ν_{max}/cm^{-1} (solid state) 3482, 3429, 3364, 2978, 1714, 1668, 1596, 1515, 1481, 1347, 1256, 1203, 1124, 1003, 956, 872, 963, 604; ESI-HRMS found m/z 485.2041 $[M]^+$, $C_{29}H_{28}N_2O_5$ requires 485.2071.

Methyl-3-isopropoxy-4-(3-propoxy-4-(3-benzyloxy-4-nitro-benzoylamido)-benzoylamido)-benzoate 8abc

(Procedure C) **7ab** (125.0 mg, 0.3 mmol), **4c** (83.2 mg, 0.3 mmol), chloroform (20 mL), Cl_2PPh_3 (260.0 mg, 0.8 mmol) afforded the product (193.2 mg, 96%) as a yellow solid; mp 212–214 °C (found: C, 64.55; H, 5.1; N, 6.0%. $C_{35}H_{35}N_3O_9{\cdot}0.5H_2O$ requires: C, 64.61; H, 5.58; N, 6.46%); δ_H (500 MHz, $CDCl_3$) 1.11 (3H, t, J = 7.4, CH_3), 1.46 (6H, d, J = 6.0, CH_3), 1.94 (2H, tq, J = 7.1 and 6.9, CH_2), 3.92 (3H, s, CO_2Me), 4.18 (2H, t, J = 6.5, CH_2), 4.78 (1H, hep, J = 6.0, CH), 5.34 (2H, s, benzylic CH_2), 7.43–7.34 (5H, m, ArCH), 7.49 (2H, d, J = 7.3, ArCH), 7.62 (2H, d, J = 10.5, ArCH), 7.73 (1H, d, J = 8.5, ArCH), 7.80 (1H, s, ArCH), 7.97 (1H, d, J = 8.3, ArCH), 8.63 (2H, d, J = 9.1, ArCH), 8.75 (1H, s, NH), 8.87 (1H, s, NH); δ_C (75 MHz, $CDCl_3$) 10.57, 22.2, 22.5, 52.1, 70.5, 71.4, 71.8, 110.7, 113.1, 114.7, 117.7, 118.6, 118.9, 119.0, 123.3, 125.1, 126.1, 127.2, 128.5, 128.8, 130.6, 130.7, 132.9, 134.9, 139.7, 142.1, 145.8, 147.8, 152.2, 163.0, 164.3, 166.8; ν_{max}/cm^{-1} (solid state) 3427 (NH_2), 2968, 2934, 2879, 1721 (CO), 1596, 1516 (NO_2); ESI-HRMS found m/z 642.2445 $[M + H]^+$, $C_{35}H_{36}N_3O_9$ requires 642.2446.

Methyl-3-isopropoxy-4-(3-(2-napthyloxy)-4-(3-benzyloxy-4-nitro-benzoylamido)-benzoylamido)-benzoate 8aec

(Procedure D) **7ae** (1.1 g, 2.1 mmol), **4c** (753.7 mg, 2.7 mmol), Cl_2PPh_3 (3.2 g, 9.9 mmol), and chloroform (100 mL) afforded the product (1.1 g, 70%) as a yellow solid; mp 203–204 °C; δ_H (300 MHz, $CDCl_3$) 1.45 (6H, d J = 6 Hz, iPrCH_3), 3.92 (3H, s, CO_2Me), 4.77 (1H, hep, J = 6, CH), 5.13 (2H, s, benzylic CH_2), 5.43 (2H, s, benzylic CH_2), 7.28–7.53 (8H, m, ArCH), 7.60 (1H, s, ArCH), 7.65 (1H, s, ArCH), 7.71–7.76 (3H, m, ArCH), 7.80–7.88 (5H, m, ArCH), 7.90 (1H, s, ArCH), 8.62 (1H, d J 8.5 Hz, ArCH), 8.67 (1H, d J 8.4 Hz, ArCH), 8.76 (1H, s, NH), 8.87 (1H, br, NH); δ_C (75 MHz, $CDCl_3$) 22.2, 42.5, 52.1, 71.3, 71.9, 72.1, 111.9, 113.2, 114.4, 116.9, 118.1, 118.7, 119.3, 119.5, 122.3, 123.3, 125.1, 125.2, 125.9, 126.8, 126.9, 127.2, 127.9, 128.5, 128.8, 129.0, 130.8, 131.1, 132.9, 133.0, 134.8, 139.3, 145.8, 147.9, 163.0, 164.0, 166.9; ν_{max}/cm^{-1} (solid state) 3426, 2978, 1717, 1599, 1492, 1235, 1125, 1013, 957, 849, 746; ESI-HRMS found m/z 740.2565 $[M + H]^+$, $C_{43}H_{38}N_3O_9$ requires 740.2603.

Methyl-3-isopropoxy-4-(3-propoxy-4-(3-benzyloxy-4-amino-benzoylamido)-benzoylamido)-benzoate 9abc

(Procedure D) **8abc** (110.0 mg, 0.2 mmol), $SnCl_2{\cdot}2H_2O$ (200.0 mg, 1 mmol) ethyl acetate (40 mL) afforded the product (87.4 mg, 84%) as a pale yellow solid; mp 185 °C (found C 66.2, H 6.10, N 6.40%. $C_{35}H_{37}N_3O_7{\cdot}H_2O$ requires C 66.67, H 6.24, N 6.67%); δ_H (500 MHz, $CDCl_3$) 1.12 (3H, t, J = 7.2, CH_3), 1.45 (6H, d, J 6.0, CH_3), 1.94 (2H, tq, J = 7.0 and 6.9, CH_2), 3.91 (3H, s, CO_2Me), 4.16 (2H, t, J = 6.4, CH_2), 4.77 (1H, hep, J = 5.9, CH), 4.23 (2H, s, NH_2), 5.18 (2H, s, benzylic CH_2), 6.41 (1H, d, J = 8.8, ArCH), 7.63–7.31 (10H, m, Ar CH), 7.73 (1H, d, J = 8.6, ArCH), 8.62 (1H, d, J = 8.6, ArCH), 8.68 (1H, d, J = 8.7, ArCH), 8.72 (1H, s, NH), 8.87 (1H, s, NH); δ_C (75 MHz, $CDCl_3$) 9.6, 21.2, 21.5, 51.0, 69.4, 69.6, 70.9, 109.5, 110.3, 112.2, 112.5, 117.6, 118.0, 119.3, 122.4, 123.0, 123.9, 126.8, 127.3, 127.7, 128.3, 131.0, 132.2, 135.5, 139.8, 144.8, 145.0, 146.6, 163.6, 164.1, 165.82; ν_{max}/cm^{-1} (solid state) 3439, 3368 (NH), 2966, 2873, 1693 (CO), 1601, 1516, 1253; ESI-MS m/z 612 $[M + H]^+$, 650 $[M + K]^+$.

Methyl-3-isopropoxy-4-(3-(2-napthyloxy)-4-(3-benzyloxy-4-amino-benzoylamido)-benzoylamido)-benzoate 9aec

(Procedure C) **8aec** (1.3 g, 1.8 mmol), $SnCl_2$ (2.5 g, 11.1 mmol) and ethyl acetate (150 mL) afforded the product (530.1 mg, 42%) as a yellow solid; mp 92–93 °C; δ_H (300 MHz, $CDCl_3$) 1.48 (6H, d, J = 6, iPrCH_3), 3.95 (3H, s, CO_2Me), 4.27 (2H, br, NH_2), 4.77 (1H, hep, J = 6, CH), 4.98 (2H, s, benzylic CH_2), 5.42 (2H, s, benzylic CH_2), 6.65 (1H, d, J = 8.1, ArCH), 7.28 (1H, d, J = 8.2, ArCH), 7.33–7.41 (6H, m, ArCH), 7.47 (1H, s, ArCH), 7.49–7.60 (3H, m, ArCH), 7.62 (1H, d, J = 8.2, ArCH), 7.64 (1H, s, ArCH), 7.76 (1H, d, J = 8.4, ArCH), 7.78–7.82 (2H, m, ArCH), 7.88–7.91 (2H, m, ArCH), 7.96 (1H, s, ArCH), 8.67 (1H, d, J = 8.5, ArCH), 8.77 (1H, d, J = 8.4, ArCH), 8.80 (1H, s, NH), 8.91 (1H, br, NH); δ_C (75 MHz, $CDCl_3$) 22.6, 52.5, 70.8, 71.8, 72.3, 111.2, 111.6, 113.6, 113.9, 119.0, 119.1, 119.9, 121.2, 123.7, 123.9, 125.3, 125.5, 126.9, 127.0, 127.2, 127.3, 127.9, 128.3, 128.4, 128.6, 128.9, 129.0, 129.2, 129.6, 132.7, 133.5, 133.6, 133.7, 133.8, 136.8, 141.3, 143.2, 143.3, 147.9, 164.8, 165.4, 167.2; ν_{max}/cm^{-1} (solid state) 3432, 3344, 2974, 1707, 1682, 1594, 1514, 1487, 1347, 1262, 1144, 1124, 1020, 871,

749, 593; ESI-HRMS found m/z 710.2869 $[M + H]^+$, $C_{43}H_{40}N_3O_7$ requires 710.2861.

3-Isopropoxy-4-(3-propoxy-4-(3-benzyloxy-4-amino-benzoylamido)-benzoylamido)-benzoic acid 10abc

(Procedure B) **9abc** (70 mg, 0.1 mmol) afforded product (58 mg, 85%) isolated by precipitation; mp >246 °C (dec); δ_H NMR (500 MHz, DMSO-d_6) 1.04 (3H, t, $J = 7.2$, CH_2CH_3), 1.36 (6H, d, $J = 6.0$, $CH(CH_3)_2$), 1.86 (2H, m, $CH_2CH_2CH_3$), 4.15 (2H, t, $J = 7.2$, OCH_2), 4.72 (1H, m, OCH), 5.20 (2H, s, OCH_2Ar), 5.56 (2H, brs, NH_2), 6.74 (1H, d, $J = 7.7$, ArCH), 7.38 (4H, m, ArCH), 7.48 (3H, m, ArCH), 7.52 (4H, m, ArCH), 8.17 (1H, m, ArCH), 8.24 (1H, m, ArCH), 9.03 (1H, s, NH), 9.32 (1H, m, ArCH); ν_{max}/cm^{-1} (solid state) 3429, 3364 (NH), 2971, 1681 (CO), 1594, 1488, 1259; ESI-HRMS found m/z 596.2397 $[M - H]^-$, $C_{34}H_{34}N_3O_7$ requires 596.2475.

Tetramer 11aecb

(Procedure C), **9aec** (118.4 mg, 0.17 mmol), **4b** (104.5 mg, 0.46 mmol), Cl_2PPh_3 (641.3 mg, 1.98 mmol), and chloroform (50 mL) afforded the product (147.9 mg, 100%) as a yellow solid; mp 252–253 °C; δ_H (300 MHz, $CDCl_3$) 1.05 (3H, t, $J = 7.2$, $PrCH_3$), 1.44 (6H, d, $J = 6$, $iPrCH_3$), 1.85 (2H, sex, $J = 6.3$, $-OCH_2CH_2CH_3$), 3.91 (3H, s, CO_2Me), 4.01 (2H, t, $J = 6.3$, $PrCH_2$), 4.76 (1H, hep, $J = 6$, iPrCH), 5.05 (2H, s, benzylic CH_2), 5.43 (2H, s, benzylic CH_2), 7.23 (1H, d, $J = 8.3$, ArCH), 7.32–7.38 (2H, m, ArCH), 7.39–7.52 (8H, m, ArCH), 7.58–7.61 (3H, m, ArCH), 7.71 (1H, d, $J = 8.4$, ArCH), 7.76–7.81 (3H, m, ArCH), 7.82–7.93 (3H, m, ArCH), 8.55 (1H, d, $J = 8.5$, ArCH), 8.61 (1H, d, $J = 8.5$, ArCH), 8.68 (1H, s, NH), 8.72 (1H, d, $J = 8.4$, ArCH), 8.84 (1H, br, NH), 8.86 (1H, br, NH); δ_C (75 MHz, $CDCl_3$) 10.4, 22.2, 52.1, 71.3, 71.5, 71.7, 71.9, 110.8, 111.4, 113.7, 117.3, 117.6, 118.6, 119.0, 119.2, 119.5, 120.1, 123.3, 124.1, 125.7, 126.6, 126.7, 127.1, 127.8, 127.9, 128.9, 130.0, 130.2, 131.1, 131.7, 133.0, 133.1, 133.3, 135.5, 139.3, 141.8, 145.8, 147.6, 147.7, 152.6, 163.0, 164.2, 164.3, 166.8; ν_{max}/cm^{-1} (solid state) 3433, 3068, 2972, 1708, 1668, 1596, 1519, 1348, 1268, 1125, 1011, 958, 872, 745; ESI-HRMS found 917.3410 m/z $[M + H]^+$, $C_{53}H_{49}N_4O_{11}$ requires 917.3392.

Tetramer 12aecb

(Procedure D) **11aecb** (151.2 mg, 0.17 mmol), $SnCl_2 \cdot H_20$ (284.6 mg, 1.26 mmol) ethyl acetate (200 mL) and THF (50 mL) afforded the product (33.4 mg, 22%) as a yellow solid; mp 208–210 °C; δ_H (300 MHz, $CDCl_3$) 1.04 (3H, t, $J = 7.3$, $PrCH_3$), 1.44 (6H, d, $J = 6$, $iPrCH_3$), 1.83 (2H, sex, $J = 6.5$, $OCH_2CH_2CH_3$), 3.91 (3H, s, CO_2Me), 3.92 (2H, t, $J = 6.3$, $PrCH_2$), 4.22 (2H, br, NH_2), 4.76 (1H, hep, $J = 6$, iPrCH), 5.06 (2H, s, benzylic CH_2), 5.43 (2H, s, benzylic CH_2), 6.63 (1H, d, $J = 8.1$, ArCH), 7.18 (1H, d, $J = 8.3$, ArCH), 7.29 (1H, s, ArCH), 7.37–7.51 (9H, m, ArCH), 7.57–7.60 (3H, m, ArCH), 7.72 (1H, d, $J = 8.4$, ArCH), 7.76–7.92 (5H, m, ArCH), 8.61 (1H, d, $J = 8.5$, ArCH), 8.62 (1H, d, $J = 8.5$, ArCH), 8.66 (1H, s, NH), 8.73 (1H, d $J = 8.4$, ArCH), 8.84 (1H, br, NH), 8.87 (1H, br, NH); δ_C (75 MHz, $CDCl_3$) 10.6, 22.2, 30.3, 52.1, 69.8, 71.2, 71.6, 71.9, 110.3, 110.6, 111.4, 113.2, 113.3, 118.7, 119.0, 119.5, 120.1, 120.3, 123.3, 123.8, 125.0, 126.6, 126.7, 127.0, 127.9, 128.0, 128.6, 128.8, 128.9, 129.8, 131.9, 132.4, 133.1, 133.3, 135.9, 140.6, 145.8, 146.1, 147.3, 147.7, 164.4, 164.6, 165.1, 166.8; ν_{max}/cm^{-1} (solid state) 3490, 3429, 3356, 2926, 1708, 1665, 1596, 1519, 1348, 1269, 1128, 996, 871, 750; ESI-HRMS found 887.3644 m/z $[M + H]^+$, $C_{53}H_{51}N_4O_9$ requires 887.3651.

Pentamer 13aecba

(Procedure C) **12aecb** (17.6 mg, 0.02 mmol), **4a** (14.3 mg, 0.06 mmol), Cl_2PPh_3 (143.2 mg, 0.44 mmol), and chloroform (30 mL) afforded the product (16.2 mg, 75%) as a yellow solid; mp 255–257 °C; δ_H (300 MHz, $CDCl_3$) 1.09 (3H, t, $J = 7.2$ Hz, $PrCH_3$), 1.43 (12H, apparent d, $J = 6$, $iPrCH_3$), 1.89 (2H, sex, $J = 6.3$, $-OCH_2CH_2CH_3$), 3.91 (3H, s, CO_2Me), 4.05 (2H, t, $J = 6.3$, $PrCH_2$), 4.71–4.89 (2H, m overlapping hep, iPrCH), 5.08 (2H, s, benzylic CH_2), 5.44 (2H, s, benzylic CH_2), 7.30–7.52 (13H, m, ArCH), 7.56–7.61 (3H, m, ArCH), 7.69 (1H, s, ArCH), 7.73 (1H, d J 8.4 Hz, ArCH), 7.79–7.93 (6H, m, ArCH), 8.55 (1H, d J 8.5 Hz, ArCH), 8.61 (1H, d J 8.5 Hz, ArCH), 8.63 (1H, d J 8.4 Hz, ArCH), 8.73 (1H, s, NH), 8.74 (1H, d, $J = 8.4$, ArCH), 8.78 (1H, br, NH), 8.86 (1H, br, NH), 8.88 (1H, br, NH); ν_{max}/cm^{-1} (solid state) 3431, 2927, 1671, 1597, 1514, 1424, 1349, 1267, 1123, 1017, 851, 745; ESI-HRMS found 1094.4221 m/z $[M + H]^+$, $C_{63}H_{60}N_5O_{13}$ requires 1094.4182.

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