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Towards a biomimetic poly-aminoketone foldamer: synthesis of a triply protected monomer and its coupling to a dimer, trimer and tetramer

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Abstract—The design of a new biomimetic foldamer, relying on the weak amine–carbonyl interaction for secondary structure formation, is presented. The efficient synthesis of a triply protected monomer starting from glycidol was developed. This monomer contains a dioxolane-protected keto group that will allow liberation of the ketone functionality in the backbone once construction of the oligomeric backbone is complete. This monomer contains two additional orthogonal protecting groups at its two termini, the Fmoc and the TBDMS groups. The Fmoc group in particular permits oligomerisation towards the N terminus as seen in Fmoc solid phase peptide synthesis. Construction and full characterisation of a ketone-protected dimer, trimer and tetramer are reported.

1. Introduction

The field of bio-inspired polymeric materials has yielded an astonishing variety of backbone constitutions,[1] largely starting from a modification of the peptide backbone. In most of these studies, the underlying interest is the creation of soluble oligomers that adopt a defined secondary structure in a given medium, thus showing a particular *folding* pattern, which led to the proposal of the term *foldamer.* Since its inception, this field has yielded many new insights into the way that the backbone architecture is determining the three-dimensional structure in solution and in the solid state.

Foldamers can be subdivided into two distinct classes: those that exploit high pre-organisation on the level of their monomeric units, and those that rely on *weak donor–acceptor interactions* between one repetitive unit and another being distant on the backbone, or on another strand as observed in peptides or peptidomimetics. Of course, foldamers incorporating both strategies have also surfaced. However, while the structural diversity of the monomers has been enormous in all of these endeavours, this is not true for the number of underlying *weak bonds*. In effect, the choice has been largely limited to the all-important hydrogen bond. Metal-to-ligand coordinative bonds, though considered weak and kinetically labile to a certain extent, cannot principally serve as a replacement for H bonds; in their case, the resulting secondary structure is not determined solely by the properties of the monomers, but necessitates the presence of a sufficient concentration of the metal ion. Even so, in an exceptional case nature has relied on this phenomenon, namely the structurally reinforcing zinc finger motif.[2]

Other weak contacts may not have been looked at for reasons of stability of interacting functional groups or simply because of their non-existence under desired environmental conditions, i.e., aqueous media. The latter constitutes also a recurrant problem in the field of peptidomimetic oligomers or even small to medium-sized natural peptides; in fact, the secondary structure of these compounds is often studied in chlorinated solvents such as chloroform or in methanol.[3] In most of the cases, structural integrity is lost when passing on to pure aqueous media.[4]

We propose here to create a new type of oligomer that does not rely on the cooperative effect of hydrogen bonding for folding.[5] Rather, for secondary structure formation, our oligomer will make use of a rarely observed natural weak bond: the tertiary amine–carbonyl interaction. The $^{\delta+}N\rightarrow C{=}O^{\delta-}$ interaction has been described as a through-space homoconjugation of the n and π molecular orbitals of the nitrogen and C=O double bond, respectively, where electron density is shifted from the n orbital to the π^* orbital, giving rise to an enhanced dipole moment and a hypsochromic shift of the carbonyl UV absorption.[6,7] What makes this weak bond particularly attractive for the purpose of rivalling hydrogen bonds, and consequently for practical applications, is its *favoured* formation in water.[8] As a direct consequence the envisaged oligomers may actively adopt their intrinsic energy-minimised secondary structure upon water solvation rather than loosing it.[9]

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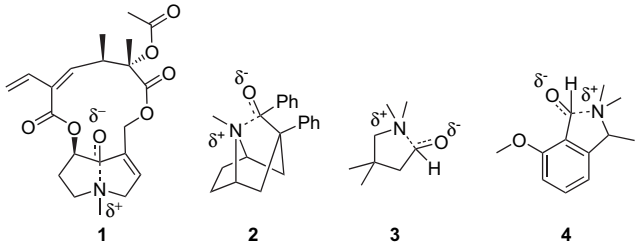


Figure 1. Examples of compounds displaying the tertiary amine–carbonyl interaction.

The $^{\delta+}N\rightarrow C{=}O^{\delta-}$ interaction has been observed for nearly 80 years in a class of alkaloids[10] (Fig. 1, **1**) and in artificially made derivatives thereof. Researchers in the 1950s have performed solution-phase studies on these interactions in tropane derivatives (Fig. 1, **2**),[11] before they served as objects for the estimation of collision trajectories in nucleophilic attack on carbonyl groups by way of X-ray structure analysis in the 1970s.[12] Later, sporadic occurrences in the synthetic literature (Fig. 1, **3** and **4**)[13] proved that these interactions were by no means limited to alkaloid systems. More recently we demonstrated that the $^{\delta+}N\rightarrow C{=}O^{\delta-}$ interaction can be incorporated into a peptidomimetic aimed to inhibit a particular protease.[6]

2. Results and discussion

In line with the theory of cooperativity as applied to folding in biopolymers, it is now assumed that the repetition of a motive composed of a ketone functionality and a tertiary amine group in a polymer backbone will lead to interactions either between sites that are distant on the backbone (analogous to beta-sheet formation in proteins) or in the vicinity of the backbone (alpha helix). In analogy to the peptide bond where the amide nitrogen functions as a hydrogen donor and the amide carbonyl as acceptor, our monomer was chosen so as to possess at the same time a tertiary amine moiety as donor and a ketone functionality as acceptor. The structure of our monomer was also conceived so as to allow for the formation of chair-like six-membered ring elements to form upon folding in accord with the (pseudo)tetrahedral geometries that the carbonyl carbon and the nitrogen centre will adopt (Fig. 2, **5**).

In loose analogy to peptide coupling, we then decided to exploit reductive amination as the principal coupling reaction to build up the oligomer. We were guided by the well-known efficacy of this reaction, its applicability to the synthesis on solid support and the mild conditions it requires so that protecting groups are not endangered.[14] In order to avoid the risk of precipitation of the oligomer by aggregation we envisaged grafting two oligomeric chains onto a suitable moiety acting as beta-turn, thus forcing the backbone to fold back upon itself (Fig. 2, **6**).

In view of the unknown properties of a highly functionalised monomer in its fully protected or partially protected form, we anticipated a major challenge in synthetic optimisation of the underlying chemistry and opted for a convergent synthetic scheme (Fig. 2). A *convergent* solution-phase synthesis as proposed in Figure 2 is the starting point of choice to

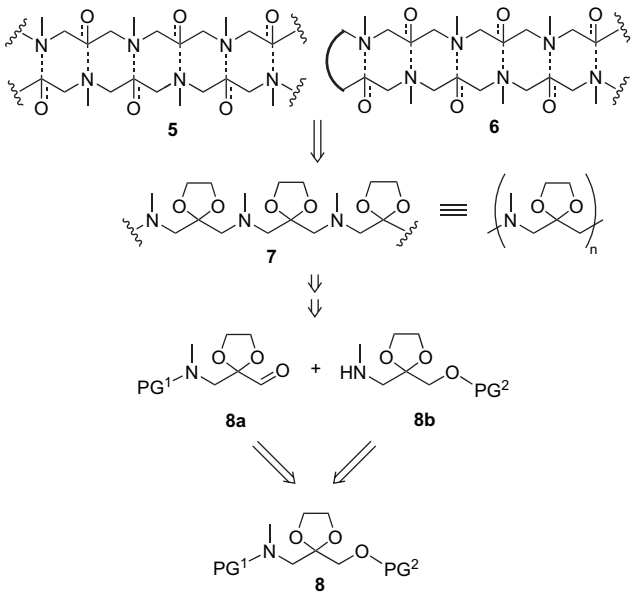


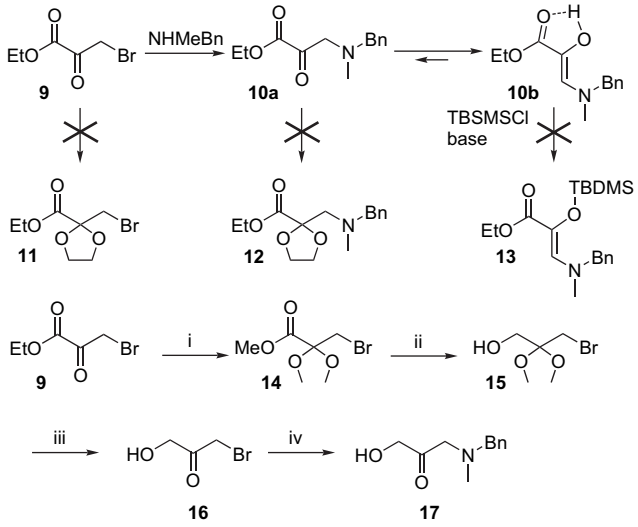
Figure 2. Design of retrosynthesis of a new biomimetic poly-aminoketone foldamer.

obtain as quickly as possible a first molecule for structural studies. Alternatively and in analogy to the Merrifield peptide synthesis, a polymer-supported monomer-wise built-up of an oligomer chain may be envisaged. Such an approach should be particularly fruitful when employing the superior and already optimised Fmoc methodology[15] in peptide synthesis. This approach then allows for the very flexible incorporation of a range of *different monomers* to expand the technology. During our synthesis development down below, we thus eventually decided to focus on the application of the Fmoc group to our synthetic targets. We present here the efficient synthesis of a triply protected monomer, and its coupling to a dimer, trimer and tetramer.

2.1. Monomer synthesis

To obtain the target monomer **8** (Fig. 2), we first explored the use of ethyl bromopyruvate, which is available in large quantities (technical grade), and is triply functionalised (Scheme 1). These advantages appeared ideal for a rapid construction of the monomer. However, direct protection of the ketone moiety by a dioxolane moiety turned out to be impossible. Introduction of the protected secondary nitrogen found in **8** required the use of *N*-benzyl-*N*-methylamine, despite the inherent disadvantages of the benzyl group as a protecting group on nitrogen. Reaction of **9** with this reactant led to **10a** that was found to be sensitive to moisture leading to the formation of *N*-benzyl-*N*-methylformamide. Optimisation of the conditions (under argon) gave a yield of 63%. According to NMR data, this compound existed in a tautomeric equilibrium, with the major isomer being the enolic form **10b**. Any attempt for its protection, either on the level of its carbonyl form (leading to **12**) or its enol form (leading to **13**), only led to decomposition, so that nucleophilic substitution as the first step could be ruled out.

Ketalisation of **9** according to the literature-described procedure[16] using methanol instead of ethylene glycol was found to be a surprisingly effective reaction with a 76% yield,



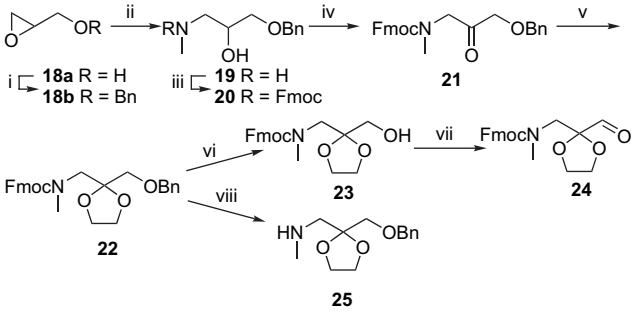
Scheme 1. Synthesis of amino alcohol **17**. *Reagents and conditions*: (i) MeOH, $HC(OMe)_3$, H_2SO_4, 76%; (ii) $LiAlH_4$, Et_2O, 88%; (iii) acetone, Amberlyst-15®, H_2O (0.3 equiv); (iv) HNMeBn, K_2CO_3 (3 equiv), 43% (two steps).

and the subsequent reduction of **14** by $LiAlH_4$ gave the bromoalcohol **15** in 88% yield. However, either flash column chromatography or distillation led to significant decomposition of **14** or **15**, and the latter had to be introduced into the nucleophilic substitution as is. As feared, compound **15** was inert to *N*-benzyl-*N*-methylamine, likely because of steric reasons, and a deprotection prior to nucleophilic substitution was explored. All classic conditions of ketal cleavage led to decomposition of **15**, but the use of thoroughly washed sulfonic acid-based resin Amberlyst-15® in acetone was found to be an exceptionally mild procedure. Ketone **16**, being too delicate for purification, was introduced directly into the reaction with *N*-benzyl-*N*-methylamine and gave **17** in 43% over two steps. Once again, the obtained compound showed a pronounced instability during silica gel chromatography, and numerous attempts to ketalize it in order to reach the target synthon **8** were in vain. These results illustrate the synthetic challenge associated with a densely functionalized low-molecular weight compound.

We thus turned to an entirely independent synthetic strategy starting from glycidol (**18a**), another tri-functionalised and easily affordable synthon (Scheme 2). Our initial scheme included the use of silyl-protected glycidol, but its subsequent reaction with *N*-benzyl-*N*-methylamine led to poor regioselectivity during epoxide opening (repartition 68/32). However, benzyl-protected glycidol (**18b**) could be reacted with methylamine in quantitative yields, and subsequent protection with the largely preferred protecting group Fmoc gave alcohol **20** in 91% yield. Swern oxidation and protection of the resulting keto functionality by dioxolane formation furnished the desired triply protected monomer **22** (a manifestation of **8**) in an overall six-step synthesis with excellent yields throughout.

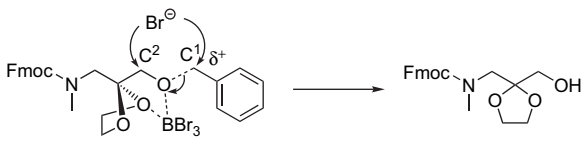
2.2. Preparation for monomer coupling

In order to prepare the protected monomer **22** for coupling via reductive amination, it had to be selectively deprotected on both termini, namely the O-terminal end by



Scheme 2. Synthesis of compounds **24** and **25**. *Reagents and conditions*: (i) BnBr, NaH, DMF, 91%; (ii) NH_2Me (40 wt % solution in water), 100%; (iii) Fmoc Cl, $NaHCO_3$, dioxane/water, 91%; (iv) oxalyl chloride, DMSO, ET_3N, CH_2Cl_2, −78 °C, 93%; (v) ethylene glycol, benzene, APTS, reflux, 96%; (vi) BBr_3, CH_2Cl_2, −78 °C, 76%; (vii) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, 40–56%; (viii) Et_3N, acetonitrile, 72%.

debenzylation leading to alcohol **23** and its subsequent oxidation to aldehyde **24**, and the N terminus by Fmoc cleavage leading to secondary amine **25**. Immediately, we were forced to realise that the high steric hindrance found in **22** significantly inhibited palladium-catalysed hydrogenation of the benzyl group. In fact, classic conditions at 1 bar hydrogen and 10% palladium on carbon caused no reaction. All attempts under numerous conditions with catalysts such as Pd/C, PtO_2, or Raney nickel were to no avail. When the pressure was raised above 1 bar, the Fmoc group started to get cleaved. We thus turned to tribromoborane as an alternative deprotection agent for benzyl-protected alcohols. Usually, the use of this reagent can be regarded as much more strenuous to any given substrate than catalytic hydrogenation. However, in this particular case the substrate **22** presents an ethylenglycoldiether motive, and the associated chelating properties[17] are conducive to mild cleavage of the benzyl group as depicted in Scheme 3. Nonetheless, the reaction necessitated rigorous optimisation before giving satisfactory yields: after treatment with BBr_3 at −70 °C and complete consumption of starting material, the aggressive reactant had to be destroyed by transferring the entire mixture at −78 °C via a cannula into a solution of sodium bicarbonate at 0 °C. This protocol turned out to be remarkably effective. The reaction should be stopped before 100% consumption is achieved, and the desired alcohol **23** (76% yield) can be separated by column chromatography from remaining **22** (19% yield), which, in turn, can easily be reintroduced into a subsequent batch ready for deprotection. Thereby achieved yields of **23** are significantly higher than those reported in the literature.[18]



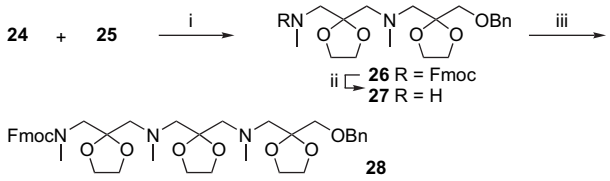
Scheme 3. Mechanism of debenzylation.

In spite of the literature precedence of a Swern oxidation carried out on a molecule with the same hydroxymethyldioxolane moiety as found in **23**,[19] the latter did not give satisfactory results upon exposure to the same conditions. Using Pfitzner–Moffat conditions[20] (DCC instead of oxalyl chloride) did not improve the yield. Compound **23** also

resisted oxidation by PCC or PDC. Finally, the reactant of Dess and Martin[21] was applied, albeit with mediocre results (40–56% yield according to the batch). The most likely reason for the reduced yield must be seen in the electron-withdrawing effect of the ketal moiety in the alpha position to the aldehyde group; the latter thus tends to get hydrated as is found in alpha-fluorinated or -chlorinated aldehydes and ketones. These hydrated forms are often found to have much higher water solubility and may accordingly be lost during work-up. However, the application of the Dess–Martin reagent has been retained for its ease of execution and because no purification step is needed.

2.3. Coupling by reductive amination

Reductive aminations can be achieved by use of two general types of independent reductants: molecular hydrogen and complex hydrides.[22] In view of the presence of a benzyl and an Fmoc group, application of hydrogen can be ruled out. Among the complex hydrides only those with a sufficiently low reactivity can be considered so as to avoid the possible reduction of the aldehyde component. We focussed on testing cyanoborohydride ($NaBH_3CN$),[23] triacetoxyborohydride ($NaBH(OAc)_3$)[24] and the borane/pyridine adduct (BH_3/Py).[25] Whatever the nature of the complex hydride, reductive aminations are usually carried out at room temperature. Parameters that can be modified for optimisation are (a) the nature of the solvent (the above-mentioned complex hydrides are stable in protic solvents, even when acidified), (b) the potential presence or rigorous absence of water and (c) the acidification of the medium and the potential addition of a Lewis acid.[23] While certain authors chose to shift the equilibrium towards imine or immonium formation by use of zeolites (for its dehydrating[26] or catalytic[27] properties), others acidified their medium by adding glacial acetic acid.[24] However, the latter may produce conflicting results depending on the system to which it is applied. In fact, the acid also activates aldehyde groups for reduction, and it was observed that $NaBH_3CN$, while not acting on aldehydes at pH 6–8, becomes an efficient reductant at pH 3–4.[23] In the majority of cases, the formation and subsequent reduction of the immonium ion is much more rapid than aldehyde reduction. Yet in the case of sterically hindered aldehydes, competition by the aldehyde reduction path becomes a problem.[24]



Scheme 4. Synthesis of trimer **28**. *Reagents and conditions*: (i) BH_3/Py, 4 Å molecular sieves, MeOH, 60%; (ii) Et_3N, acetonitrile, 92%; (iii) **24**, BH_3/Py, 4 Å molecular sieves, MeOH, 57%.

In view of the considerable steric hindrance in our case, a significant amount of work had to go into the search for conditions minimising reduction of aldehyde **24** (Scheme 4). This study was greatly facilitated by LCMS analysis (Fig. 3). Table 1 illustrates the effect of variation of reactant and conditions. It becomes easily apparent that the reductant BH_3/Py in MeOH does not cause any aldehyde reduction. Its Lewis-acid character constitutes an additional advantage in that it makes addition of a Brönstedt-acid catalyst obsolete. While this reaction is particularly slow (48 h), the reaction components do not appear to degrade during this period.

Thus obtained dimer **26** was subsequently deprotected on the amino terminus by use of triethylamine (92%) and coupled

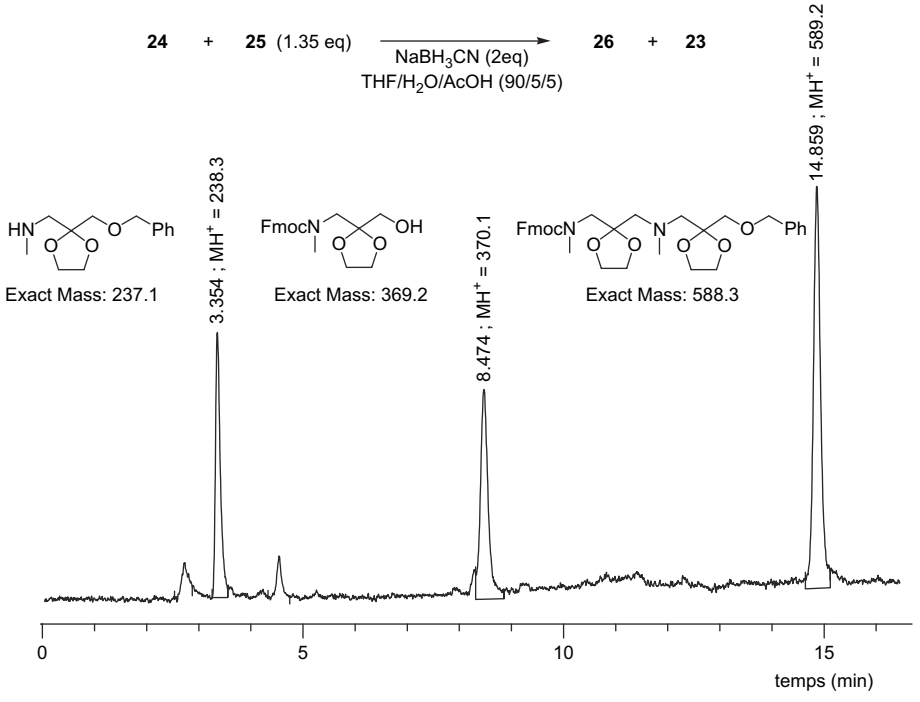
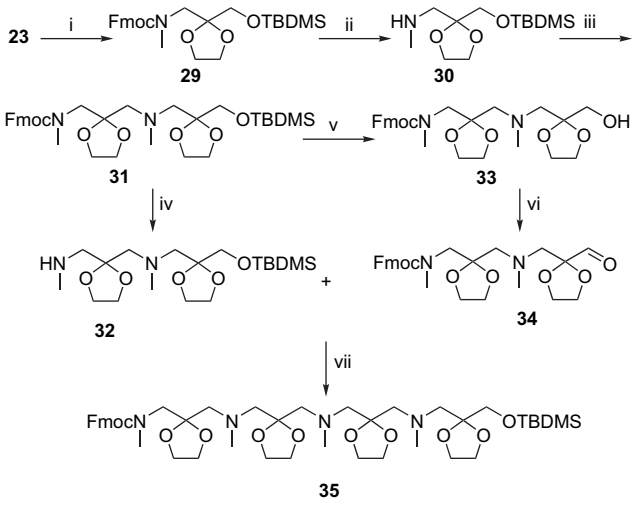


Figure 3. LCMS chromatogram of dimer formation using reaction conditions different from those finally retained (Column Zorbax SB-CN; eluant: H_2O+ HCO_2H (0, 1%)/acetonitrile; 1:0–0:1 in 15 min).

Table 1. Optimisation of coupling conditions: minimisation of aldehyde reduction

Reductive agent	Solvent	AcOH	H_2O	Ratio of peak areas **26/23**
$NaBH_3CN$	THF	5%	5%	2.27
$NaBH_3CN$	CH_2Cl_2			0.38
BH_3/Py	CH_2Cl_2			0.66
BH_3/Py	MeOH			No alcohol
BH_3/Py	THF	5%		6.36
BH_3/Py	THF	5%	5%	18.16
$NaHB(OAc)_3$	CH_2Cl_2			1.42
$NaHB(OAc)_3$	MeOH			1.57
$NaHB(OAc)_3$	THF	5%		3.39
$NaHB(OAc)_3$	THF	5%	5%	0.75

with aldehyde **24** to furnish trimer **28** in 57% yield. Such an experiment should demonstrate the feasibility of step-by-step construction of the oligomer as is found in solid-phase synthesis of heteropolymers, but does not allow for rapid synthesis of an oligomer of appreciable size. A convergent synthesis using two dimers of the type **26** turned out to be impossible because the benzyl group was surprisingly resistant to the use of BBr_3. In view of the limited access to dimer **26**, it appeared prudent to protect alcohol **23** with a more readily cleavable protecting group, namely the TBDMS group. The resulting silyl ether **29** (Scheme 5) was deprotected with piperidine instead of triethylamine since the latter reacts much more slowly and thus causes multiple products of decomposition. However, use of piperidine has an inconvenient consequence, in fact, it is well-known that the fluorene formed during deprotection reacts with piperidine to give fluorenylmethylpiperidine[28] that unfortunately cannot be removed by chromatography since the desired secondary amine **30** proved to be very labile on silica gel. On the other hand, the presence of fluorenylmethylpiperidine in the subsequent coupling step causes formation of a large proportion of the alkylation product of piperidine by aldehyde **24**. In the end, two to three cycles of precipitation/filtration of fluorenylmethylpiperidine in methanol at −78 °C were sufficient to completely remove the side product as evidenced by NMR.



Scheme 5. Synthesis of tetramer **35**. *Reagents and conditions*: (i) TBDMSCl, Et_3N, DMAP, CH_2Cl_2, 97%; (ii) piperidine, acetonitrile, 93%; (iii) **24**, $NaBH(AcO)_3$, $TiCl(Oi\text{-}Pr)_3$, CH_2Cl_2, 44%; (iv) piperidine, acetonitrile, 45%; (v) BF_3/OEt_2, acetonitrile, 73%; (vi) oxalyl chloride, DMSO, ET_3N, CH_2Cl_2, −78 °C, 78%; (vii) BH_3/Py, zeolite 4A, MeOH, 42%.

Surprisingly, the presence of a silyl group in the reactant **30** as compared to the benzyl group in **25** led to mediocre coupling yields towards dimer **31**. The efficient conditions elaborated for the coupling to dimer **26** were thus of no great use in this new reaction. No side product explaining this reduction in yield could be detected by LCMS analysis. Finally, coupling conditions employing the Lewis acid tri-isopropoxytitanium chloride were retained (44% yield). The thus obtained dimer was coupled to a tetramer by first deprotecting **31** using BF_3 etherate, oxidising the resulting alcohol **33** to aldehyde **34** under Swern conditions, and finally coupling it to the deprotected secondary amine **32** using the conditions that proved successful in the coupling to **26**. The tetramer **35** was obtained in 42% yield.

3. Conclusion

We have presented here the design of an original polymer backbone on the basis of a weak functional group interaction between a tertiary amine and a ketone moiety. This interaction has been amply characterised in the course of the last 50 years, but never for its capacity to show cooperative effects when present in multiple copies on the same molecule. Right from the start, the heavily functionalised structure of the initially chosen monomers and their corresponding triply protected forms made the need for thorough synthetic optimisation likely. After initially failing in developing a synthesis starting from ethyl bromopyruvate, we have succeeded in discovering an efficient synthetic path towards a protected monomer using glycidol. This building block is stable over extended periods of time, lends itself to perfectly selective deprotection, and gives mediocre (42%) to satisfactory (60%) yields during equimolar solution-phase coupling depending on the identity and the complexity of the reaction partners. We have thus prepared a dimer, a trimer and a tetramer. The deprotection of each reaction partner in these syntheses and the coupling behaviour vary considerably in each case. The proximity of the functional groups on the backbone caused complications such as difficulty during debenzylation and reductive amination, effects that can be attributed at the same time to electronic and steric influences. However, this same proximity was chosen precisely for the eventual observation of a folding pattern that involves favourable formation of chair-like six-membered rings in the secondary structure (Fig. 2) and that is congruent with beta-sheet formation in proteins. Grafting of these oligomers onto beta-turn mimics, deprotection of the ketone groups on the backbone and structural characterisation are in progress.

4. Experimental

4.1. General

All reactions were carried out in anhydrous solvents in dried glassware. CH_2Cl_2 and Et_3N were distilled under argon on CaH_2. Compounds **14** and **15** were prepared according to the literature protocols.[16] ^1H and ^{13}C NMR spectra were recorded on a Bruker DPX 200 spectrometer (200 MHz) and a Varian Unity 500 spectrometer (500 MHz). Coupling patterns in the ^1H NMR spectra are designated as s, singlet; d,

doublet; dd, double doublet; t, triplet; m, multiplet. HRMS were recorded by the Centre de Spectrométrie de Masse, Université de Lyon, France. LRMS were recorded on an Agilent 1100 Series LC/MSD apparatus. For those compounds existing as a mixture of rotamers, the signal corresponding to equivalent protons or carbons on different rotamers is separated by 'and'.

4.1.1. Aminoketone 17. A solution of **15** (500 mg, 2.51 mmol) and water (15 μL, 0.83 mmol, 0.3 equiv) in acetone (10 mL) was stirred for 16 h with an Amberlyst-15® resin (400 mg). The resin was removed by filtration. After cooling the mixture at 0 °C, K_2CO_3 (1.04 g, 7.53 mmol, 3 equiv) and *N*-methylbenzylamine (364 mg, 3.01 mmol, 1.2 equiv) were added. The mixture was stirred for 20 min, allowed to warm to room temperature and stirred for 20 min. The solvent was removed in vacuo and the residue was taken in water (15 mL). The aqueous layer was extracted with ethyl acetate (3×15 mL). The combined organic layers were washed with brine (10 mL), dried over sodium sulfate and the solvent was removed in vacuo. Compound **17** was obtained as a pale yellow oil after flash chromatography using CH_2Cl_2/ethyl acetate 65:35 as an eluant (210 mg, 43%). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.30 (s, 3H), 3.24 (s, 2H), 3.56 (s, 2H), 4.35 (s, 2H), 7.24–7.31 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 42.9, 62.0, 63.3, 67.0, 126.6, 127.2, 128.5, 137.2, 209.4.

4.1.2. Benzyl ether 18b. To a stirred solution of glycidol (17.2 mL, 0.255 mol) and benzylbromide (40.4 mL, 0.338 mol, 1.3 equiv) in dry DMF (650 mL) at 0 °C under argon atmosphere was added sodium hydride (60% dispersion in mineral oil, 10.19 g, 0.255 mol, 1 equiv). The mixture was allowed to warm to room temperature and stirred overnight. The solvent was removed in vacuo and the residue was taken up with water (500 mL). The aqueous layer was extracted with CH_2Cl_2 (3×250 mL). The combined organic layers were washed with brine (60 mL), dried over sodium sulfate and the solvent was removed in vacuo. Compound **18b** was obtained as a colourless oil after flash chromatography using cyclohexane/ethyl acetate 85:15 as an eluant (63.7 g, 91%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.61 (m, 1H), 2.80 (m, 1H), 3.19 (m, 1H), 3.44 (dd, J=6 Hz, J'=11 Hz, 1H), 3.78 (dd, J=3 Hz, J'=11 Hz, 1H), 4.56 (d, J=12 Hz, 1H), 4.62 (d, J=12 Hz, 1H), 7.3–7.4 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 44.28, 50.87, 70.84, 73.33, 127.77 and 128.45, 137.94; HRMS (EI) *m/z*: calcd for $C_{10}H_{12}O_2$: 164.0837; found: 164.0837.

4.1.3. Amino alcohol 19. To a stirred solution of methylamine (40 wt % solution in water, 650 mL) at 0 °C was slowly added a solution of compound **18b** (26.18 g, 0.159 mol) in a minimum of CH_2Cl_2. The mixture was allowed to warm to room temperature and stirred overnight. The solvent was removed in vacuo. Compound **19** was obtained as a colourless oil (31.05 g, 100%). For the characterisation, the ammonium salt can be obtained with a solution of HCl (gas) in diethylether. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.67 (s, 3H), 3.05 (m, 2H), 3.53 (m, 2H), 4.38 (m, 1H), 5.49 (m, 2H), 7.30–7.34 (m, 5H), 8.66 (s (L), 1H), 9.31 (s (L), 1H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 33.70, 52.38, 65.66, 71.79, 73.46, 127.85, 128.39, 137.51; HRMS (CI) *m/z*: calcd for $C_{11}H_{18}NO_2$: 196.1338; found: 196.1339.

4.1.4. Fmoc-protected amino alcohol 20. To a stirred solution of compound **19** (35.203 g, 180 mmol) in 1,4-dioxane (750 mL) was added a solution of $NaHCO_3$ (10 wt % solution in water, 750 mL) and 9-fluorenylmethyl chloroformate (48.901 g, 0.189 mol, 1.05 equiv). The mixture was stirred overnight, then diluted with water (1.8 L) and extracted with CH_2Cl_2 (3×700 mL). The combined organic layers were washed with brine (500 mL), dried over sodium sulfate and the solvent was removed in vacuo. Compound **20** was obtained as a colourless oil after flash chromatography using pentane/ethyl acetate 2:1 as an eluant (68.5 g, 91%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.91 and 2.98 (2s, 3H), 3.06–3.24 (m, 2H), 3.43–3.47 (m, 2H), 4.02 (m, 1H), 4.20–4.25 (m, 1H), 4.41–4.82 (m, 2H), 4.55 (s, 2H), 7.32–7.41 (m, 9H), 7.59 (m, 2H), 7.7–7.8 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 36.01, 47.25, 51.50 and 52.63, 66.68 and 67.50, 69.23 and 69.77, 71.87, 73.38, 119.80, 124.90, 126.99, 127.59, 127.67, 128.37, 137.77, 141.26, 143.91, 156.12 and 157.55; HRMS (CI) *m/z*: calcd for $C_{26}H_{28}NO_4$: 418.2018; found: 418.2019.

4.1.5. Ketone 21. To a stirred solution of oxalyl chloride (5.30 mL, 0.063 mol, 1.7 equiv) in CH_2Cl_2 (190 mL) under argon atmosphere and at −78 °C was slowly added DMSO (9.2 mL, 0.130 mol, 3.5 equiv). After 15 min a solution of **20** (15.51 g, 0.037 mol, 1 equiv) in CH_2Cl_2 (140 mL) in a separate round bottom flask under argon atmosphere and at −78 °C was slowly transferred via a cannula to the first flask. The mixture was stirred for 2 h at −78 °C. Triethylamine (37 mL, 0.265 mol, 7.2 equiv) was added and the solution was stirred for 30 min at −78 °C and 30 min at 0 °C. CH_2Cl_2 (750 mL) was added and the solution was washed with saturated NH_4Cl solution (100 mL) and brine (100 mL), dried over sodium sulfate and evaporated to dryness. Compound **21** was obtained as a colourless oil after flash chromatography using pentane/ethyl acetate 4:1 then 2:1 as an eluant (14.05 g, 93%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.90 and 3.00 (2s, 3H), 3.86 and 4.02 (2s, 2H), 4.14 (s, 1H), 4.28–4.30 (m, 2H), 3.90 and 4.75 (2d, J=6.5 Hz), 4.51 and 4.60 (2s, 2H), 7.30–7.40 (m, 9H), 7.49 (m, 1H), 7.62 (m, 1H), 7.71 (m, 1H), 7.77 (m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 35.52 and 36.00, 47.15, 55.81 and 56.25, 66.87 and 67.77, 73.61, 74.05 and 74.21, 119.82, 124.64 and 125.02, 127.01, 127.61, 127.85, 128.09, 128.52, 136.83, 141.23, 143.89, 155.95 and 156.60, 203.62 and 204.13; HRMS (CI) *m/z*: calcd for $C_{26}H_{26}NO_4$: 416.1862; found: 416.1865.

4.1.6. Ketal 22. A solution of compound **21** (18.74 g, 45 mmol), *p*-toluenesulfonic acid (6.60 g, 38 mmol, 0.85 equiv) and ethylene glycol (50 mL, 900 mmol, 20 equiv) in benzene (400 mL) was stirred under reflux for 3.5 h. During this time, the water was removed with a Dean–Stark apparatus. The solution was washed with water (100 mL) and brine (2×100 mL). The aqueous layer was then extracted with ethyl acetate (2×100 mL). The combined organic layers were washed with brine (100 mL), dried over sodium sulfate and the solvent was removed in vacuo. Compound **22** was obtained as a colourless oil after flash chromatography using pentane/diethylether 4:6 as an eluant (19.69 g, 96%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.03 (s, 3H), 3.37 and 3.51 (2s, 2H), 3.55 and 3.60 (2s, 2H), 3.89–4.01 (m, 4H), 4.22–4.26 (m, 1H), 4.41–4.43 (m,

2H), 4.57 and 4.60 (2s, 2H), 7.29–7.34 (m, 7H), 7.38–7.42 (m, 2H), 7.61–7.67 (m, 2H), 7.76–7.79 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 36.01 and 36.62, 47.36, 51.37 and 51.77, 65.41 and 65.50, 67.38, 71.59 and 71.71, 73.63, 108.91 and 109.21, 119.86, 124.98, 126.95, 127.54, 128.29, 138.01, 141.28 and 144.13, 156.86; HRMS (CI) *m/z*: calcd for $C_{28}H_{30}NO_5$: 460.2124; found: 460.2121.

4.1.7. Alcohol 23. To a stirred solution of **22** (11.61 g, 31 mmol) in CH_2Cl_2 (230 mL) at −78 °C under argon atmosphere was added dropwise a solution of boron tribromide in CH_2Cl_2 (31 mL, C=1 mol/L, 1 equiv). After 4 h, the solution was transferred to saturated $NaHCO_3$ solution (500 mL) at 0 °C. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3×100 mL). The combined organic layers were washed with brine (60 mL), dried over sodium sulfate and the solvent was removed in vacuo. Compound **23** was obtained as a colourless oil after flash chromatography using cyclohexane/ethyl acetate 2:1, then 1:1 as an eluant (7.09 g, 76%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.99 (s, 3H), 3.36 (d, *J*=7 Hz, 2H), 3.46 (s, 2H), 3.81 (t, *J*= 7 Hz, 1H), 3.93–3.99 (m, 4H), 4.25 (t, *J*=6.5 Hz, 1H), 4.47 (d, *J*=6.5 Hz, 2H), 7.32 (m, 2H), 7.41 (m, 2H), 7.59 (m, 2H), 7.78 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 35.63 and 36.15, 46.80, 50.53, 61.96, 64.63 and 64.99, 66.85 and 67.28, 108.82 and 109.17, 119.53, 124.45, 126.63, 127.27, 140.84, 143.35, 156.25 and 157.23; HRMS (CI) *m/z*: calcd for $C_{21}H_{24}NO_5$: 370.1654; found: 370.1657.

4.1.8. Aldehyde 24. To a stirred solution of $NaHCO_3$ (4.80 g, 57.1 mmol, 3.5 equiv) and **23** (6.05 g, 16.3 mmol) in CH_2Cl_2 (150 mL) at 0 °C under argon atmosphere was added Dess–Martin periodinane (12.27 g, 28.9 mmol, 1.8 equiv). After 1.5 h, aqueous $Na_2S_2O_3$ (75 mL) was added followed by saturated $NaHCO_3$ solution (75 mL). The mixture was stirred for 30 min. The layers were separated and the aqueous layer was extracted with diethylether (3×150 mL). The combined organic layers were washed with brine (60 mL), dried over sodium sulfate and the solvent was removed in vacuo (3.37 g, 56%). The crude product was used without further purification. Its NMR spectra are congruent with the presence of a minor amount of the hydrated form. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.97 and 3.02 (2s, 3H), 3.51 and 3.70 (2s, 2H), 3.94–4.07 (m, 4H), 4.25 (m, 1H), 4.39–4.48 (m, 2H), 7.32 (t, *J*=7.5 Hz, 2H), 7.40 (t, *J*=7.0 Hz, 2H), 7.58 (d, *J*=7.5 Hz, 2H), 7.76 (d, *J*=7.5 Hz, 2H), 9.03 and 9.42 (2s, 0.7H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 36.37, 47.13, 50.34, 65.85, 67.61, 106.35, 119.84, 124.84, 126.95, 127.56, 141.20, 143.82, 156.69, 195.19; HRMS (CI) *m/z*: calcd for $C_{21}H_{22}NO_5$: 368.1498; found, 368.1497.

4.1.9. Amine 25. Triethylamine (3 mL, 21.5 mmol) was added dropwise to a stirred solution of **22** (435 mg, 0.95 mmol) in acetonitrile (10 mL). The mixture was stirred for 48 h before removing the solvent in vacuo. Compound **25** was obtained as a yellow oil after purification by neutral-alumina chromatography using CH_2Cl_2, then CH_2Cl_2/MeOH 100:20 as an eluant (162 mg, 72%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.43 (s, 3H), 2.79 (s, 2H), 3.46 (s, 2H), 3.96 (s, 4H), 4.54 (s, 2H), 7.20–7.34 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 36.70, 54.87, 65.26, 71.12, 73.26, 108.82, 127.31, 127.48, 128.06, 137.96; HRMS (CI) *m/z*: calcd for $C_{13}H_{20}NO_3$: 238.1443; found: 238.1442.

4.1.10. Dimer 26. To a stirred solution of aldehyde **24** (473 mg, 1.29 mmol) and amine **25** (366 mg, 1.54 mmol, 1.2 equiv) in methanol (15 mL) under argon atmosphere was added dropwise BH_3/Py (0.143 mL, 1.42 mmol, 1.1 equiv) and 4 Å molecular sieves. After 24 h, an additional sample of BH_3/Py (0.090 mL, 0.90 mmol, 0.7 equiv) was added. After another 24 h the mixture was filtered, the filtrate was diluted with saturated $NaHCO_3$ (15 mL), stirred for 30 min and extracted with diethylether (3×30 mL). The combined organic layers were washed with brine (20 mL), dried over sodium sulfate and the solvent was removed in vacuo. Compound **26** was obtained as a colourless oil after flash chromatography using pentane/ethyl acetate 10:3 as an eluant (455 mg, 60%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.41 (s, 3H), 2.55 and 2.59 (s, 2H), 2.64 (m, 2H), 2.98 (s, 3H), 3.56–3.59 (m, 4H), 3.82–3.86 (m, 4H), 3.962 (m, 4H), 4.22–4.26 (m, 1H), 4.38–4.42 (m, 2H), 4.58 (d, *J*=22 Hz, 2H), 7.30–7.40 (m, 9H), 7.61–7.76 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 35.82 and 36.59, 45.07 and 47.11, 51.94, 53.23, 61.41, 62.32 and 62.59, 64.40, 64.62, 64.84, 64.99, 66.93 and 67.17, 71.15, 73.20, 109.74, 110.42 and 110.72, 119.58, 124.70, 124.94, 126.69, 127.20, 127.26, 127.92, 138.15, 140.95, 143.94, 156.56 and 156.72; HRMS (ESI) *m/z*: calcd for $C_{34}H_{41}N_2O_7$: 589.2914; found: 589.2916.

4.1.11. Amine 27. To a stirred solution of **26** (227 mg, 0.39 mmol) in acetonitrile (4 mL) was added dropwise 3 mL of triethylamine. The mixture was stirred for 48 h before the solvent was removed in vacuo. Compound **27** was obtained as a yellow oil after purification by neutral-alumina chromatography using ethyl acetate, then methanol as an eluant (130 mg, 92%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.42 (s, 3H), 2.54 (s, 3H), 2.69 (s, 2H), 2.70 (s, 2H), 3.02 (s, 2H), 3.46 (s, 2H), 3.92–4.00 (m, 8H), 4.59 (s, 2H), 7.20–7.35 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 36.40, 44.94, 55.19, 61.53, 62.30, 64.51, 64.88, 71.05, 73.28, 109.76, 110.21, 127.18, 127.23, 127.99, 138.08; HRMS (ESI) *m/z*: calcd for $C_{19}H_{31}N_2O_5$: 367.2233; found: 367.2234.

4.1.12. Trimer 28. To a stirred solution of amine **27** (87 mg, 0.24 mmol) and aldehyde **24** (105 mg, 0.29 mmol, 1.2 equiv) in methanol (3 mL) under argon atmosphere was added dropwise BH_3/Py (0.027 mL, 0.27 mmol, 1.1 equiv) and 4 Å molecular sieves. After 48 h the mixture was filtered, diluted with saturated $NaHCO_3$ (7 mL), stirred for 30 min and extracted with diethylether (3×10 mL). The combined organic layers were washed with brine (20 mL), dried over sodium sulfate and the solvent was removed in vacuo. Compound **28** was obtained as a colourless oil after flash chromatography (97 mg, 57%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.39 (s, 3H), 2.40 and 2.41 (2s, 3H), 2.56–2.60 (m, 4H), 2.64 (s, 2H), 2.66 (s, 2H), 3.02 and 3.03 (2s, 3H), 3.58 and 3.60 (2s, 2H), 3.64 and 3.68 (2s, 2H), 3.85–3.96 (m, 12H), 4.22–4.27 (m, 1H), 4.37–4.41 (m, 2H), 4.59 (d, *J*=13.6 HZ, 2H), 7.28–7.33 (m, 6H), 7.36–7.40 (m, 2H), 7.60–7.61 (m, 1H), 7.69–7.77 (m, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 36.16 and 36.93, 45.45, 47.38, 52.33, 61.79, 62.15, 62.26, 62.74 and 62.92, 64.65, 64.89, 65.17, 67.20 and 67.57, 71.89, 73.52, 110.16, 110.82 and 111.10, 111.81, 119.83, 124.97 and 125.25, 126.92 and 127.30,

127.40, 127.49, 128.16, 138.51, 141.23, 144.25, 156.90 and 157.11; HRMS (ESI) *m/z*: calcd for $C_{40}H_{52}N_3O_9$: 718.3704; found: 718.3706.

4.1.13. Silyl ether 29. To a stirred solution of **23** (5.59 g, 15.1 mmol), triethylamine (2.3 mL, 16.4 mmol, 1.1 equiv) and DMAP (100 mg, 0.82 mmol, 0.05 equiv) in CH_2Cl_2 at 0 °C under argon atmosphere was added dropwise a solution of *tert*-butylchlorodimethylsilane (4.1 g, 27 mmol, 1.8 equiv) in CH_2Cl_2 (6 mL). The mixture was allowed to warm to room temperature and stirred for 3 h. The precipitated ammonium salts were filtrated and washed with diethylether (4×15 mL). The combined organic layers were washed with water (2×25 mL) and brine (25 mL), dried over sodium sulfate and the solvent was removed in vacuo. Compound **29** was obtained as a colourless oil after flash chromatography using cyclohexane/ethyl acetate 10:1, then 10:4 (7.12 g, 97%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.06 (s, 6H), 0.89 (s, 9H), 3.03 (s, 3H), 3.52 (s, 1H), 3.53 (s, 2H), 3.60 (s, 1H), 3.87–3.99 (m, 4H), 4.22–4.27 (m, 1H), 4.41 (d, *J*=7.0 Hz, 2H), 7.31 (t, *J*=7.3 Hz, 2H), 7.40 (t, *J*=7.4 Hz, 2H), 7.61 (d, *J*=7.5 Hz, 1H), 7.67 (d, *J*=7.4 Hz, 1H), 7.76 (d, *J*=7.3 Hz, 2H), ^{13}C NMR ($CDCl_3$, 50 MHz): δ −5.34, 18.35, 25.91, 36.07 and 36.73, 47.42, 51.10 and 51.45, 65.45 and 65.60, 67.47, 67.60, 109.43 and 109.76, 119.93, 125.09, 127.03, 127.62, 141.33, 144.22, 156.97; HRMS (CI) *m/z*: calcd for $C_{26}H_{38}NO_5Si$: 484.2519; found: 484.2516.

4.1.14. Amine 30. To a stirred solution of **29** (3.92 g, 8.1 mmol) in acetonitrile (43 mL) was added dropwise 4.3 mL of piperidine. After 3 h, the solvent was removed in vacuo and the solid was mixed with cold methanol at −78 °C, transferred to a mortar, and well homogenised. The mixture was filtered and the solid was washed with cold methanol at −78 °C. The filtrate was taken up and the cycle of evaporation/mixing/filtration was repeated two or three times until the disappearance of the signal of 9-fluorenylmethylpiperidine in the corresponding NMR spectra (1.96 g, 93%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.07 (s, 6H), 0.90 (s, 9H), 2.47 (s, 3H), 2.78 (s, 2H), 3.62 (s, 2H), 4.01 (s, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ −5.51, 18.20, 25.77, 36.66, 54.55, 65.16, 65.48, 109.245; HRMS (CI) *m/z*: calcd for $C_{12}H_{28}NO_3Si$: 262.1838; found: 262.1840.

4.1.15. Dimer 31. To a solution of **30** (494 mg, 1.89 mmol) in CH_2Cl_2 (10 mL) under argon atmosphere was added a solution of **24** (833 mg, 2.27 mmol, 1.2 equiv) in CH_2Cl_2 (3 mL), tri-isopropoxytitanium chloride (1.1 mL, 3.27 mmol, 1.7 equiv) and sodium triacetoxyborohydride (2.0 g, 9.44 mmol, 5 equiv). The mixture was stirred for 2 h then diluted with diethylether (45 mL) and treated with saturated $NaHCO_3$ solution (30 mL). The layers were separated and the aqueous layer was extracted with diethylether (2×30 mL). The combined organic layers were washed with brine (20 mL), dried over sodium sulfate and the solvent was removed in vacuo. Compound **30** was obtained as a colourless oil after flash chromatography using pentane/diethylether 90:10, then 50:50 as an eluant (503 mg, 44%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.05 and 0.07 (2s, 6H), 0.88 and 0.90 (2s, 9H), 2.42 (s, 3H), 2.56–2.61 (m, 4H), 3.03 (s, 3H), 3.63–3.69 (m, 4H), 3.89–3.95 (m, 8H), 4.22–4.28 (m, 1H), 4.40 (m, 2H), 7.30 (t, *J*=7.4 Hz, 2H), 7.38–7.39 (m, 2H), 7.65 (d, *J*=14.5 Hz, 1H), 7.73 (d, *J*=14.2 Hz, 1H), 7.75–7.77 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ −5.54, 18.12, 25.72, 35.92 and 36.704, 45.17, 47.23, 52.07, 61.31, 62.52 and 62.79, 64.73, 65.04 (peak with shoulder), 67.03 and 67.31, 110.23, 110.58 and 110.85, 119.64, 124.78 and 125.03, 126.76, 127.33, 141.07, 144.07, 156.69 and 156.88; HRMS (CI) *m/z*: calcd for $C_{33}H_{49}N_2O_7Si$: 613.3309; found: 613.3307.

4.1.16. Amine 32. To a stirred solution of **31** (323 mg, 0.53 mmol) in acetonitrile (2 mL) was added dropwise 0.5 mL of piperidine. After 3 h, the solvent was removed in vacuo and the solid was mixed with cold methanol (−78 °C) in a mortar. The mixture was filtered and the solid was washed with cold methanol (−78 °C). The filtrate was taken up and the cycle of evaporation/mixing/filtration was repeated two or three times until there was no signal of 9-fluorenylmethylpiperidine in NMR spectra (91 mg, 45%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.07 (s, 6H), 0.90 (s, 9H), 2.42 (s, 3H), 2.49 (s, 3H), 2.62 (s, 2H), 2.63 (s, 2H), 2.83 (s, 2H), 3.64 (s, 2H), 3.951–3.969 (m, 8H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ −5.45, 18.22, 25.81, 36.73, 45.12, 55.54, 61.52, 62.54, 64.69, 65.07, 65.16, 110.30, 110.38; HRMS (CI) *m/z*: calcd for $C_{18}H_{39}N_2O_5Si$: 391.2628; found: 391.2627.

4.1.17. Alcohol 33. To a stirred solution of **31** (286 mg, 0.47 mmol) in acetonitrile (5.5 mL) at 0 °C under argon atmosphere was added dropwise BF_3/etherate (48 wt %, 0.197 mL, 1.6 equiv). The mixture was allowed to warm to room temperature, stirred for 2 h, subsequently diluted with ethyl acetate (30 mL) and treated with 10 mL of water. The layers were separated and the organic layer was washed with brine (2×10 mL), dried over sodium sulfate and the solvent was removed in vacuo. Compound **33** was obtained as a colourless oil after flash chromatography using CH_2Cl_2, then CH_2Cl_2/MeOH 100:2 as an eluant (170 mg, 73%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.42 (s, 3H), 2.47 and 2.60 (2s, 2H), 2.67 and 2.73 (2s, 2H), 2.99 (s, 3H), 3.50 and 3.52 (2s, 2H), 3.60 and 3.64 (2s, 2H), 3.87–4.00 (m, 8H), 4.24–4.27 (m, 1H), 4.42–4.46 (m, 2H), 7.31 (t, *J*=7.5 Hz, 2H), 7.39 (t, *J*=7.5 Hz, 2H), 7.59–7.65 (m, 2H), 7.76 (d, *J*=7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 35.94 and 36.57, 45.39, 47.22, 52.05, 62.31, 62.31, 62.90, 64.48, 65.00, 67.27, 109.23, 110.78, 119.79, 124.85, 126.88, 127.48, 141.18, 143.99, 156.72; HRMS (CI) *m/z*: calcd for $C_{27}H_{35}N_2O_7$: 499.2443; found: 499.2443.

4.1.18. Aldehyde 34. To a stirred solution of oxalyl chloride (0.153 mL, 1.78 mmol, 1.5 equiv) in CH_2Cl_2 (20 mL) under argon atmosphere and at −78 °C was slowly added DMSO (0.292 mL, 4.11 mmol, 3.5 equiv). After 5 min a solution of **33** (594 mg, 1.19 mmol) in CH_2Cl_2 (12 mL) was added dropwise. After 20 min, triethylamine (1.15 mL, 8.53 mmol, 7.2 equiv) was added and the solution was stirred for 30 min at −78 °C and 30 min at 0 °C. CH_2Cl_2 (750 mL) was added and the solution was washed with saturated NH_4Cl solution (2×25 mL), dried over sodium sulfate and evaporated to dryness. Compound **34** was obtained as a colourless oil after flash chromatography using CH_2Cl_2, then CH_2Cl_2/MeOH 100:1 as an eluant (460 mg, 78%). Its NMR spectra are congruent with the presence of a minor amount of the hydrated form. ^{1}H NMR ($CDCl_3$,

500 MHz): δ 2.39–2.49 (m, 3H), 2.59 and 2.93 (2s, 2H), 2.93 and 2.97 (2s, 2H), 2.99–3.01 (m, 3H), 3.44–3.48 (m, 2H), 3.83–4.01 (m, 8H), 4.24 (m, 1H), 4.41–4.44 (m, 2H), 7.32 (m, 2H), 7.39 (m, 2H), 7.60 (d, J=7.5 Hz, 1H), 7.67 (d, J=7.5 Hz, 1H), 7.76 (d, J=7.5 Hz, 2H), 9.49 and 9.53 (2s, 0.5H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 36.09 and 36.72, 44.88, 47.33, 52.17 and 52.34, 61.38, 62.39, 65.06, 65.31, 67.32, 106.68 and 107.24, 110.53 and 110.70, 119.84, 124.95, 126.93, 127.52, 141.24, 144.12, 156.87, 197.34; HRMS (CI) *m/z*: calcd for $C_{27}H_{33}N_2O_7$: 497.2288; found: 497.2287.

4.1.19. Tetramer 35. To a solution of **34** (66 mg, 0.133 mmol) and **32** (62 mg, 156 mmol, 1.2 equiv) in methanol (5 mL) under argon atmosphere was added dropwise BH_3/Py (0.015 mL, 0.143 mmol, 1.1 equiv) and 4 Å molecular sieves. After 48 h the mixture was filtered, treated with saturated $NaHCO_3$ solution (5 mL), stirred for 30 min and extracted with diethylether (3×15 mL). The combined organic layers were washed with brine (10 mL), dried over sodium sulfate and the solvent was removed in vacuo. Compound **35** was obtained as a colourless oil after flash chromatography using CH_2Cl_2, methanol/CH_2Cl_2 100:2, and then 100:10 as an eluant (49 mg, 42%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.06 (s, 6H), 0.89 (s, 9H), 2.404–2.428 (m, 9H), 2.520 (s, 1H), 2.581–2.660 (m, 12H), 2.782 (s, 1H), 3.030–3.040 (m, 3H), 3.650–3.706 (m, 4H), 3.850–3.967 (m, 16H), 4.230–4.272 (m, 1H), 4.382–4.415 (m, 2H), 7.28–7.31 (m, 2H), 7.37–7.40 (m, 2H), 7.60–7.62 (m, 1H), 7.70–7.72 (m, 1H), 7.74–7.76 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ −5.42, 18.24, 25.84, 36.09 and 36.86, 45.27, 45.41, 45.52, 47.29, 52.21, 61.83, 62.25, 62.91, 64.57, 64.81, 64.99, 65.26, 65.72, 67.26, 109.23, 110.38, 110.76 and 111.01, 111.82, 119.78, 124.85, 126.86, 127.43, 141.17, 144.14, 156.73 and 157.03; HRMS (ESI) *m/z*: calcd for $C_{45}H_{71}N_4O_{11}Si$: 871.4889; found: 871.4884.

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Supplementary data

^{1}H, ^{13}C NMR and mass spectral data are available in the electronic supplementary information (ESI). Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.12.081.

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