



Tuning the Stacking Properties of C_3 -Symmetrical Molecules by Modifying a Dipeptide Motif

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Abstract: C_3 -symmetrical molecules are described which consists of a 1,3,5-benzenetricarboxamide core extended with dipeptide fragments bearing peripheral mesogenic groups. Small structural modifications in the dipeptide fragment have been performed to demonstrate their influence on the stability of the stacks and on the order within the self-assemblies formed. Seven C_3 -symmetrical discs have been investigated, all with different combinations of glycine, L- and/or D-phenylalanine in the dipeptide fragments. Characterization of these discotics in the neat state using differential scanning calorimetry (DSC), X-ray diffraction (XRD) and polarized optical microscopy (POM) and in solution with circular dichroism (CD), UV-visible spectroscopy, low-

concentration proton nuclear magnetic resonance and IR spectroscopy reveals that there is a clear trend in the stack stability, going from the glycine-phenylalanine motifs to the phenylalanine-phenylalanine ones. The combination of a larger hydrophobic core, more confinement of space and the possibility of additional π - π interactions leads to more stable stacks. Surprisingly, the weakest stacks consist of discotics of which the center is extended with L-phenylalanyl-glycines and not of discotics of which the center is extended with the glycyl-L-phenylalanine se-

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quences. Furthermore, the XRD investigations show that it is difficult to form well-ordered self-assemblies in the neat state. And, CD measurements point out that some of the discs have a very complex energy landscape in solution. These observations suggest that small differences in the balance between the secondary interactions originating from the benzenetricarboxamide core and the dipeptide fragments, have a strong influence on the order within the stack. From these results it can be concluded that subtle modifications in the peptide fragments of the discs cause significant changes in the stacking properties, stressing the importance of understanding the self-assembly mechanism of each discotic in order to clarify its self-assembly behavior.

Introduction

Self-assembled architectures are envisioned to serve as important building blocks in the fields of biology as well as materials science.^[1a-k] The interplay of secondary interactions fulfills a key role in the formation of stable conformers that still can express their reversible nature. It is known that minor changes in the molecule may dramatically influence the subtle balance of non-covalent interactions between molecules, in most extreme cases resulting in the loss of re-

versibility or preventing stable self-assembled structures to be formed.^[2a-e] The challenge is to develop new molecules that self-assemble and allow functionalization and fine-tuning of the structure in an easily accessible manner.

Peptide fragments are widely used as structuring elements in self-assembled architectures, because of their biocompatibility, hydrogen bonding properties and versatile nature.^[3a-j] Amphiphilic dendritic dipeptides that self-assemble into helical pores were described by Percec and co-workers.^[4] Stupp and collaborators reported peptide amphiphiles that self-assemble into nanofibers and they demonstrated the ability of this system to tolerate chemical modifications by changing the peptide sequence.^[5] In the group of van Esch excellent low molecular weight hydrogelators were developed that possess a cyclohexane/benzene core extended with a dipeptide fragment.^[6] They showed that the properties of the gels could be easily tuned by changing the hydrophobic substituents or the number of hydrogen bonding moieties. Recently, Kimizuka and co-workers also reported C_3 -symmetrical con-

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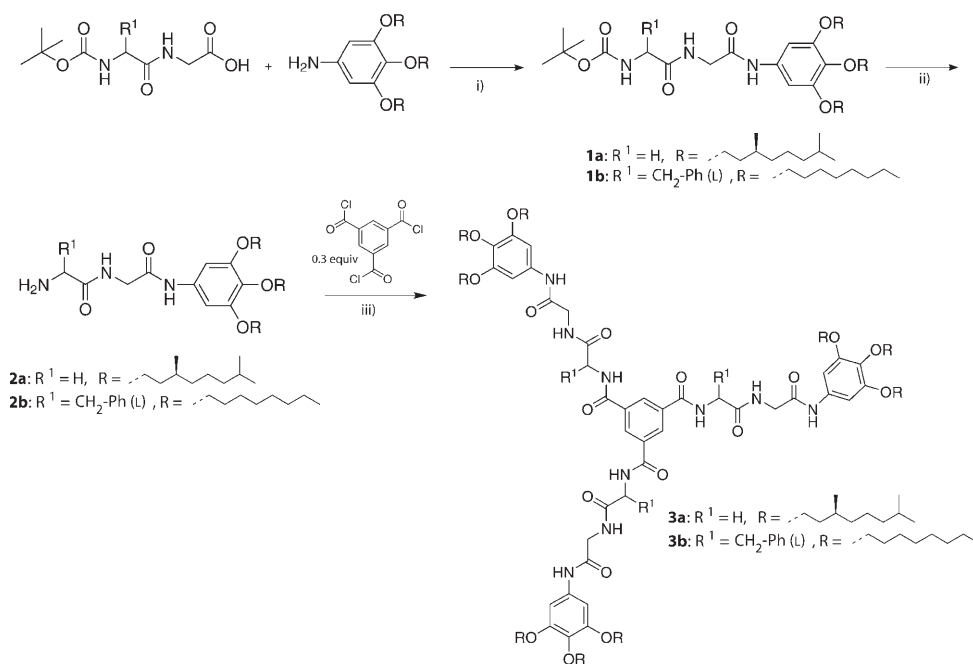
jugates that bear three β -sheet forming peptides (FKFEFKFE) that form antiparallel β -sheets in water.^[7] These C_3 -symmetrical peptide conjugates spontaneously self-assemble into viral-sized peptide nanospheres.

In our laboratory, self-assembly of various 1,3,5-benzenetricarboxamide derivatives, which have a strong tendency to form columnar aggregates in solution, has been extensively studied.^[8a-d] In our present design the 1,3,5-benzenetricarboxamide center is extended with dipeptide fragments, providing additional driving forces for self-assembly (like hydrogen bonding and hydrophobic interactions). We selected three amino acids, glycine, D-phenylalanine and L-phenylalanine: glycine, because it is achiral, D- and L-phenylalanine, because they are chiral, as well as hydrophobic and may offer additional π - π interactions. In order to determine whether it is possible to tune the stack stability and the order within the stack by modifying the peptide fragment a small library of dipeptide discotics was synthesized. The stability of the stacks strongly depends on the dipeptide fragment incorporated. As expected, most stable stacks were obtained when two phenylalanines were used to extend the center. Surprisingly, the weakest stacks consist of discotics of which the center is extended with L-phenylalanyl-glycines and not of discotics extended with the glycyl-L-phenylalanine motifs. The formed self-assemblies are not very well-ordered in the neat state. And, some of the self-assembled structures show very complex energy landscapes in solution. This indicates that small differences in the balance between the secondary interactions originating from the benzenetricarboxamide core and the dipeptide fragments, have a strong influence on the order within the stack.

Results and Discussion

Synthesis of C_3 -symmetrical discotics: C_3 -symmetrical discotics **3a,b** were prepared as depicted in Scheme 1. 3,4,5-Triocetyloxyaniline^[9] and 3,4,5-tri((S)-3,7-dimethyloctyloxy)aniline^[10] were synthesized according to literature procedures. Direct coupling of the desired Boc-protected dipeptides with the anilines was accomplished using HBTU as a coupling reagent and DIPEA as a base and yielded $\approx 65\%$ of pure compounds **1a,b**. In these two cases, racemization is excluded due to the presence of an achiral glycine at the C-terminus of the peptide fragments. Deprotection of **1a,b** with trifluoroacetic acid, followed by a basic work-up, gave **2a,b** in yields of $\approx 90\%$. Finally, discotics **3a,b** were obtained after coupling of compounds **2a,b** with 0.3 molar equivalents of trimesyl chloride in the presence of triethylamine as a base.

In addition, C_3 -symmetrical discotics **8a-e** were synthesized as depicted in Scheme 2. Due to the presence of a chiral center at the C-terminus of the dipeptide fragment, these dipeptides have to be introduced via a one-by-one coupling strategy to avoid racemization. First, a single phenylalanine was reacted with 3,4,5-trioctyloxyaniline using HBTU as a coupling reagent and DIPEA as a base. The Boc group was then removed with trifluoroacetic acid, followed by a basic work-up to give the free amines **5a,b**. Repetition of these consecutive steps with the desired amino acids and compounds **5a,b** as starting materials, gave dipeptide amines **7a-e**. Chiral HPLC was used to screen all Boc-protected intermediates (**6a-e**) for their enantiomeric purity (for HPLC traces see Supporting Information). The enantiomeric excess of all Boc-protected intermediates varied be-



Scheme 1. Synthetic route towards discotics (**3a,b**) with a glycine at the C-terminus of the dipeptide fragment: i) HBTU, DIPEA, DMF, RT, overnight; ii) 1) TFA, RT, 1 h, 2) basic work-up; iii) Et₃N, CH₂Cl₂, RT, overnight.

tween 99 and 100%. Finally, discotics **8a–e** were obtained after coupling of compounds **7a–e** with 0.3 molar equivalents of trimesyl chloride in the presence of triethylamine as a base.

Self-assembly of discotics **3a,b** and **8a–e** in the neat state:

The self-assembly behavior of all C₃-symmetrical molecules was examined in the neat state with differential scanning calorimetry (DSC), X-ray diffraction (XRD) and polarized optical microscopy (POM).^[11] The DSC data of the second heating run (rate 10°Cmin^{−1}) for compounds **3a,b** and **8a–e** are shown in Table 1 (for DSC traces of the third heating run (rate 40°Cmin^{−1}) see Supporting Information). POM results showed that compound **3a** melts at 240°C, but the clearing is accompanied by decomposition of the sample; therefore, we measured DSC up to 220°C. Upon heating the sample from −100 to 220°C a glass transition temperature was found at 113°C. Compound **3b** was heated in the second run at a speed of 10°Cmin^{−1} from −100 to 160°C. It exhibits a transition with an onset at 133°C and, upon cooling, a transition at 132°C was observed. Remarkably, no hysteresis of the transition was observed upon cooling,

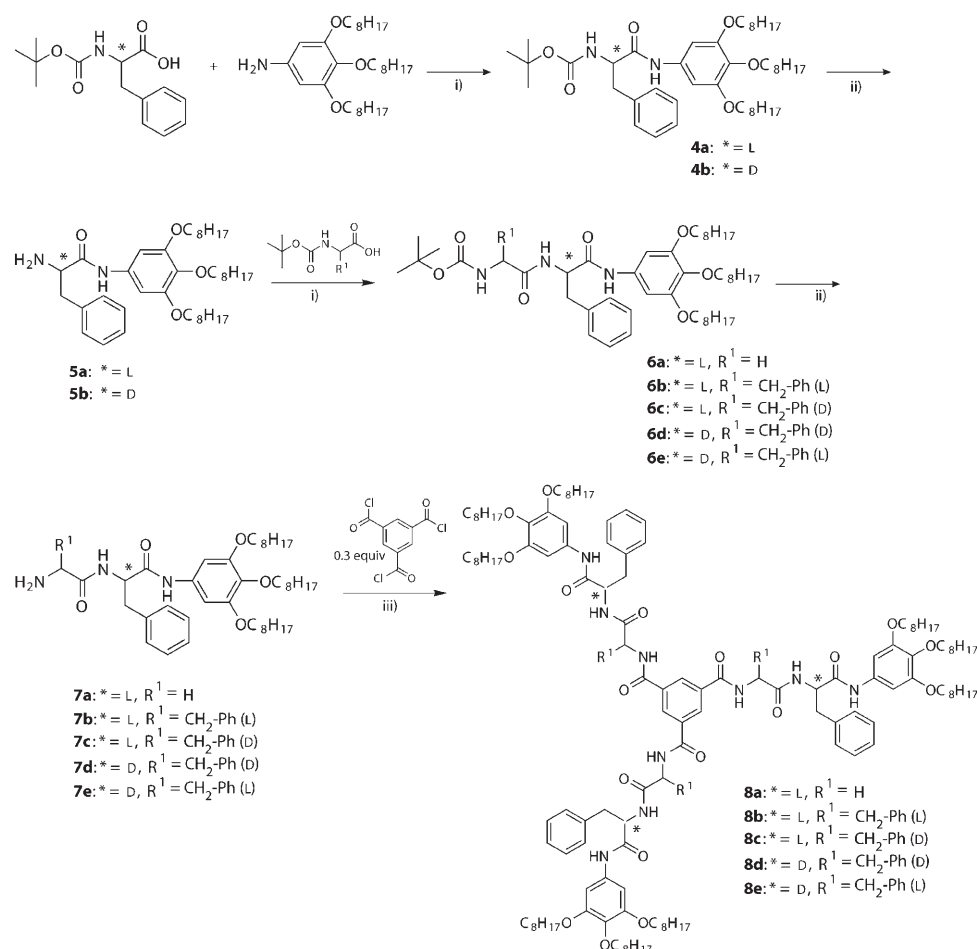
Table 1. Phase-transition behavior for compounds **3a,b** and **8a–e** (second heating run; 10°Cmin^{−1}).^[a]

Compound		<i>T</i> _{onset} [°C] (ΔH [kJ mol ^{−1}])	
3a	— ^[b]	113	M ^[c]
3b	K	133 (14)	I
8a	K	186 (18)	I
8b	K	115 (6.8) ^[d]	M ^[c]
8c	K	175/186 (16) ^[e]	I
8d	— ^[f]	—	— ^[c]
8e	K ^[g]	175/184(13) ^[e]	I

[a] —=phase is not observed; K=crystalline phase; M=unidentified mesophase; I=isotropic phase. [b] A *T*_g is observed. [c] At the clearing temperature decomposition of the sample takes place. [d] Temperature of transition maximum instead of transition onset. [e] The onset temperatures of overlapping peaks with corresponding total enthalpies. [f] Cooling the sample down to −100°C did not show any transition. [g] An enantiotropic transition with an onset at 110(0.7) was present, probably originating from an undetectably small amount of impurity.

which normally indicates a transition to a mesophase instead of a transition to a crystalline phase. However, slowly cooling from the isotropic state did not result in a texture for **3b**

and it was also not possible to induce formation of the mesophase by pressing on the sample. Discotic **8a** was heated at a speed of 10°Cmin^{−1} from −100 to 230°C and showed a broad K–I transition at 186°C. The cooling run, in contrast, showed a sharp transition with an onset at 176°C. Polarized optical microscopy pointed out that a monotropic mesophase is present at around 202°C. The texture of the mesophase could be grown as shown in Figure 1. Probably, the enthalpy associated with this I–M transition is too small to be detected with DSC. Enantiomers **8b** and **8d** start to show some decomposition around 240°C, before reaching the clearing point (around 305°C); therefore these discotics were heated from −100 to 220°C in DSC. Discotic **8b** shows a reversible transition with a maximum at 115°C in the heating run and a maximum at 107°C in the cooling run. Surprisingly, **8d** did not exhibit any transition upon cooling to −100°C. Enantiomers **8c** and **8e** melt around 210°C. Upon heating discotic **8e** from −100 to 220°C three



Scheme 2. Synthetic route towards discotics (**8a–e**) with a phenylalanine at the C-terminus of the dipeptide fragment: i) HBTU, DIPEA, DMF, RT, overnight; ii) 1) TFA, RT, 1 h, 2) basic work-up; iii) Et₃N, CH₂Cl₂, RT, overnight.

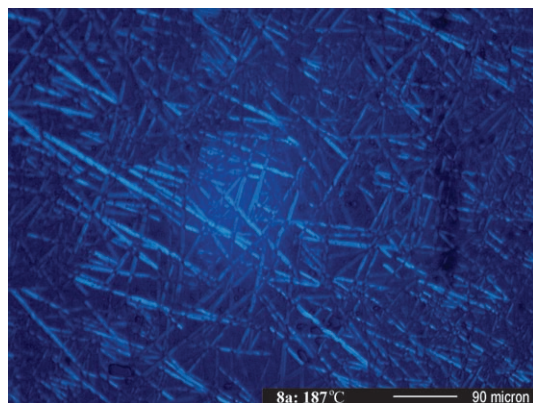


Figure 1. Polarized optical microscopy texture for compound **8a**.

transitions could be discerned, a small transition with a maximum at 110 °C and a transition that is overlapping the transition to the isotropic state with a maximum at 181 °C. Upon cooling, just one I–K transition was observed with a maximum at 153 °C. The DSC curve of discotic **8e** is similar to the one of **8c**, except for the small transition at 110 °C in the heating run, which is missing. Most likely, this small peak originates from a small amount of impurity, which could not be detected or identified with the aid of MALDI-TOF MS and GPC.

Discotics **3a,b** and **8a,b,e** were also investigated with X-ray diffraction. The data are gathered in Table 2. The XRD patterns of compounds **3a,b** consist of an intense peak and a diffuse halo in the small and the wide angle region, respectively. The position of the former is temperature independent up to the clearing point and corresponds to a distance of 32 Å for **3a** and 27 Å for **3b**, which is in the range of the dimensions of the molecules. The diffuse halo is attributed to the aliphatic chains in the periphery although the associated spacings, 4.8 Å for **3a** and 4.6 Å for **3b** at room temperature, are somehow larger than the expected 4.4–4.6 Å. An increase in the temperature leads to an increase in the distance corresponding to the halo. The pattern of compound **8a** in the virgin state comprises an intense peak at 37 Å and a hump centered at 17.5 Å in the small angle region and a non-symmetric halo in the wide angle region, with its center at 4.5 Å and a sharper edge towards smaller angles. When heating above the isotropic transition temperature of 186 °C, the new phase exhibits the same pattern, but with the intense peak corresponding to 28–29 Å and the hump becoming weaker and broader. The diffuse halo becomes symmetric and the distance associated to it increases to 4.9 Å. Upon cooling back to room temperature the spacing of the peak remains at 28–29 Å, the hump is recovered as a broad peak with a spacing of 16 Å and the diffuse halo moves back to 4.5 Å. The XRD pattern of **8b** stays invariant from room temperature to 190 °C. No change is observed when the compound undergoes the DSC transition at 115 °C. The XRD pattern comprises two broad peaks with spacings in an approximate ratio 2:1, at 30 and 16 Å, respectively. In the wide angle region the halo is not symmetric and exhibits

a sharper edge towards the smaller angles. The XRD pattern of compound **8e** shows an intense peak whose corresponding spacing increases from 35 Å at room temperature to 41 Å at 185 °C. However, at a temperature as high as 211 °C there is a second phase, as proven by an intense peak appearing with a smaller spacing (22 Å) than the virgin peak, still present at this temperature but vanishing with time or upon further heating. When cooling to room temperature the pattern of the pristine sample is recovered. It has to be noted that the spacing corresponding to the diffuse halo is in all cases larger than that expected for the molten alkyl chains in a liquid crystalline phase. The lack of reflections prevents the assignment of any phase, but also excludes a well-ordered crystalline state for all of the compounds. In some cases the intense reflection in the small angle region corresponds to a spacing comparable to the expected diameter of these molecules, pointing to a columnar phase, which would be disordered in any case due to the absence of a peak with spacing of 3.3–4.0 Å. Another remarkable observation, which holds for all presented materials, is that the XRD patterns do not disappear at temperatures well above the clearing point as measured by POM. This behavior has been previously reported^[12a–c] and has been attributed to the local stacking of discs persisting above the clearing point.

Table 2. The XRD data of compounds **3a,b** and **8a,b,e**.

Compound	<i>T</i> [°C]	<i>d</i> [Å] ^[a]
3a ^[b]	25	32.7 (s), 4.8 (h)
	130	32.4 (s), 4.9 (h)
3b	25	26.5 (s), 4.6 (h)
	152	27.2 (s), 4.8 (h)
8a	pristine	36.8 (s), 17.8 (br), 4.5 (h)
	200	29.2 (s), 17.5 (br), 4.9 (h)
	25	28.1 (s), 16.2 (br), 4.5 (h)
8b	64	30.0, 15.8, 4.9 (h)
	120	30.8, 16.0, 4.9 (h)
8e	25	34.9 (s), 4.9 (h)
	211	21.8 (s), 5.0 (h)

[a] s = sharp; br = broad; h = halo. [b] As an example, the XRD diagrams of **3a** at different temperatures are included in the Supporting Information.

Self-assembly of discotics **3a,b and **8a–e** in solution:** The self-assembly behavior of all C₃-symmetrical molecules was examined with CD, UV/Vis, ¹H NMR and IR spectroscopy in dilute solutions in chloroform and in heptane. From ordinary solubility experiments, it became clear that a trend in stability of these molecules was noticeable. Compounds **8b** and **8d**, containing two phenylalanines with equal chirality, are neither soluble in chloroform nor in heptane, even at concentrations in the micromolar range. Therefore, it was not possible to characterize these discotics in solution. Discotics **8c** and **8e**, both carrying two phenylalanines with opposite chirality, are only soluble in chloroform and not in heptane. Compound **8a** is soluble in both solvents, but to dissolve **8a** in heptane external heating is needed. Finally,

3a and **3b** which both contain a glycine at the C-terminus of the dipeptide fragment are easily dissolved in both solvents.

CD and UV/Vis at room temperature: The CD and UV/Vis spectra of discotics **3a,b** and **8a,c,e** in chloroform and of **3a,b** and **8a** in heptane are shown in Figure 2. Compound **3a** does not show a Cotton effect neither in heptane nor in chloroform. Presumably, the glycyglycine tails are too flexible, which makes it impossible to transfer the chiral information embedded in the alkyl chains to a higher level of organization. In heptane, **3b** induces a coupled CD curve centered at 242 nm with a negative extreme at 255 nm and a positive extreme at 234 nm, while in chloroform a much smaller CD effect was observed with a negative extreme at 262 nm. Compound **8a** also displays a coupled CD curve in heptane, of which the effect is even stronger compared with **3b**. This curve is centered at 235 nm and shows a broad negative CD band around 263 nm. The CD spectrum of **8a** in chloroform is less active than the CD spectrum in heptane, as was also observed for discotic **3b**. Compound **8c** shows a Cotton effect in chloroform that decreases going to smaller wavelengths, while compound **8e** in chloroform shows a Cotton effect that increases going to smaller wavelengths. From Figure 2 it can be deduced that the CD spectra of **8c** and **8e** are mirror images, as expected since **8c** and **8e** are enantiomers.

Temperature dependence of CD and UV/Vis measurements in chloroform: Temperature dependent CD and UV/Vis measurements revealed that discotics **3b** and **8a,c,e** do not show a temperature dependent behavior in chloroform neither with UV/Vis nor with CD. To investigate whether the weak, temperature insensitive Cotton effects in chloroform originate from molecularly dissolved discotics or less-ordered self-assembled structures, IR spectra in chloroform (Table 3) and ¹H NMR spectra in deuterated chloroform (Figure 3) were recorded. The measurements were performed using solutions with similar concentrations as used for the CD measurements. The NH-stretch vibrations in chloroform are very broad for all samples measured. The maximum of the broad peak can in general be found around 3322 cm⁻¹, which is indicative for hydrogen bonding. The ¹H NMR measurements also suggest that self-assemblies are still present, because all peaks in the spectra are broadened as can clearly be seen from the signals above δ 7.5 ppm, corresponding to the chemical shifts of the aromatic protons of the core and the protons of the amide groups.

Temperature dependence of CD and UV/Vis measurements in heptane: Temperature dependent CD and UV/Vis measurements revealed that solutions of compounds **3b** and **8a** in heptane do show a temperature dependent Cotton effect, while the optical density is not temperature dependent. The graphs depicted in Figure 4 are heating curves of **3b** and **8a**, starting from 10 to 80 °C in steps of 10 °C at λ = 255 and 263 nm, respectively. The heating curve of **3b** shows two plateaus, one at low temperatures with Δε = -36 L mol⁻¹ cm⁻¹

and one at higher temperatures with Δε = -13 L mol⁻¹ cm⁻¹, and a melting temperature around 62 °C. The cooling curve of **3b** lies exactly on top of the heating curve and these temperature scans are reproducible, meaning that the system is in thermodynamic equilibrium. The heating curve of **8a** only shows a plateau at low temperatures with Δε = -53 L mol⁻¹ cm⁻¹. At 80 °C the second plateau is still not reached. Furthermore, the cooling curve of **8a** is completely different from the heating curve and is not reproducible at all. IR and ¹H NMR spectroscopy were used to judge whether helically ordered self-assemblies or molecularly dissolved discotics of **3b** and **8a** are present in heptane at 70 °C. The IR spectra were taken in heptane, while the ¹H NMR spectra were measured in deuterated cyclohexane, both at similar concentrations as used in the CD measurements. According to the NH-stretch vibrations of **3b** and **8a**, which appear as sharp peaks at ν̄ 3286 and 3272 cm⁻¹, respectively, hydrogen bonding is still present at 70 °C suggesting that self-assemblies are still present (Table 4). The completely broadened ¹H NMR spectra in deuterated cyclohexane at 70 °C (Figure 5) also confirm this observation. Presumably, the deaggregation of the stacks in heptane is a multiple-step process of which just the first step, going from well-ordered to less-ordered self-assemblies, can be monitored with CD due to the restricted temperature window. This also explains why the optical density is not temperature dependent in this temperature frame.

In general, the UV/Vis and CD measurements in combination with IR and ¹H NMR demonstrate that discotics **3b** and **8a,c,e** do aggregate and that it is not possible to reach the molecularly dissolved state not even in chloroform at 50 °C. The transition observed in the temperature dependent CD measurements of **3b** in heptane was proven to be a transition from well-ordered self-assembled architectures to less-ordered ones. It was proven that **3b** is in thermodynamic equilibrium during this transition, while **8a** is not. An explanation for the different behavior of **3b** and **8a** might originate from the structures of the molecules. They contain a 1,3,5-benzenetricarboxamide center that wants to self-assemble in a ship-screw-type of fashion, in order to make sure that both π-π interactions and hydrogen bonding can take place. And they also contain a dipeptide fragment of which it is known that it prefers to form hydrogen bonds perpendicular to its backbone, like in a β-sheet. This might result in an ongoing competition between the center of the discotic and the dipeptide fragment depending on the strength of the interactions between the different moieties. For compound **3b**, there is apparently one dominant conformation. This probably means that the supramolecular interactions of either the 1,3,5-benzenetricarboxamide center or the dipeptide fragment are far more dominant, so competition is not an issue. In the case of **8a** there obviously is competition, meaning that the strengths of the interactions are in the same order of magnitude. This might explain why several different CD spectra, heating and cooling runs were recorded.

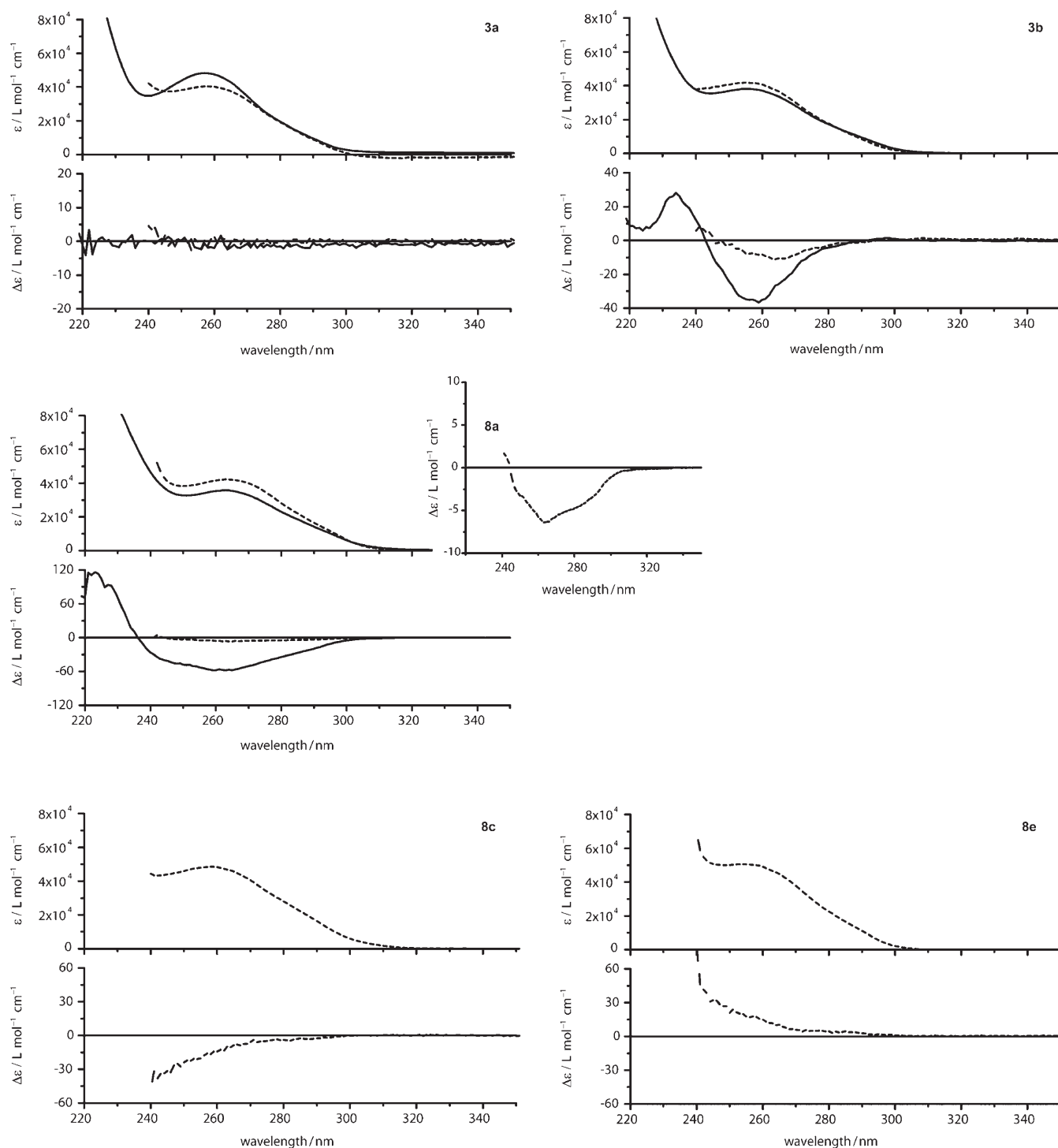


Figure 2. UV/Vis and CD spectra for compounds **3a,b** and **8a,c,e** in heptane, 4×10^{-5} M (—) and chloroform, 4×10^{-5} M (----). The insertion in graph **8a** is an enlargement of the CD spectrum of **8a** in chloroform.

Table 3. Wavenumbers σ [cm^{-1}] of the N-H stretch vibrations of **3b** and **8a,c,e** in the solid state and in 2×10^{-5} M chloroform solutions at 20 °C.

Compound	3b	8a	8c	8e
σ solid state	3315	3300	3267	3276
σ chloroform	3322	3327	3322	3322

Stability of the self-assemblies: It was demonstrated that the stability of all self-assemblies is very high, nevertheless a clear trend in stability of the stacks could be observed. Characterization in the neat state pointed out that the clearing temperatures increase going from discotic **3b** to **8a** to **8c,e** to **8b,d** (Figure 6). Discotic **3a** does not fit in this series at

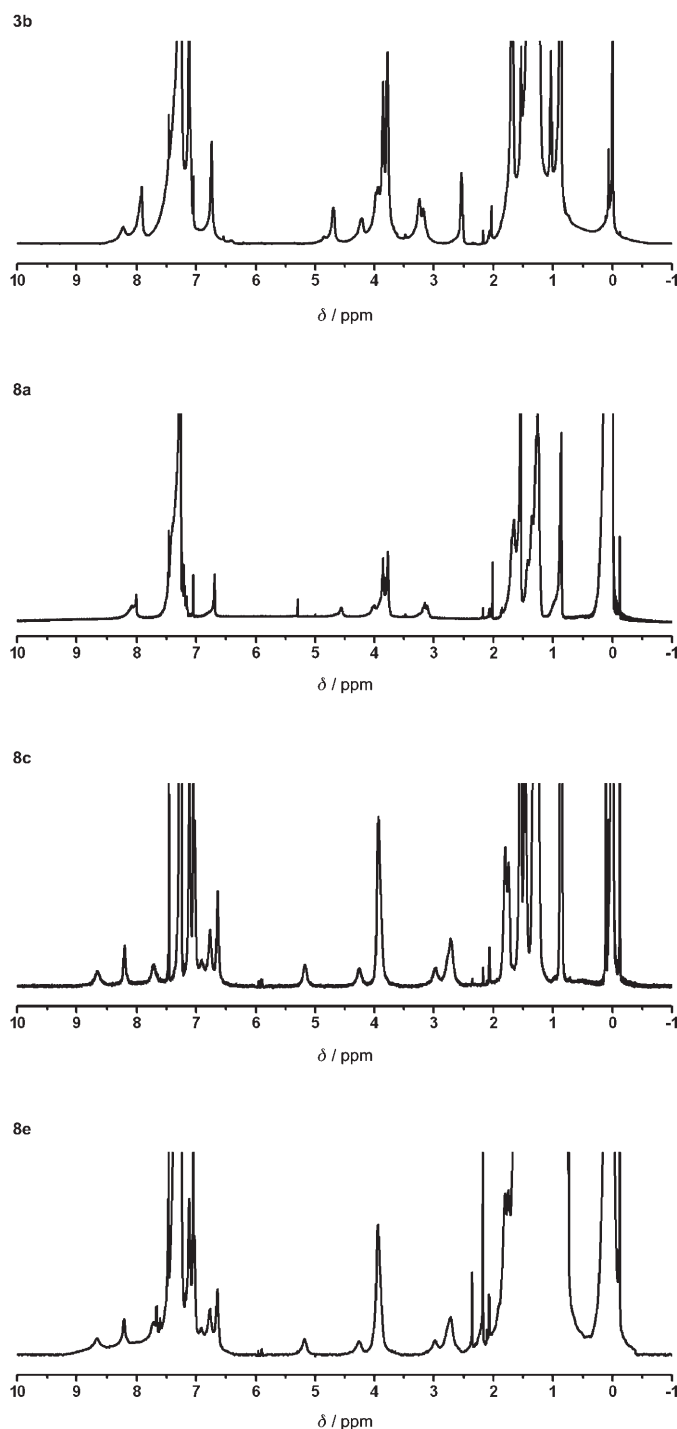


Figure 3. ¹H NMR spectra at 25 °C of compounds **3b** and **8a,c,e**; 2×10^{-5} M in CDCl₃.

all. Its behavior is totally different from the other discotics showing a glass transition temperature, while all the other molecules become crystalline at a certain point. The clearing temperature, on the other hand, is very high and the clearance is accompanied by decomposition of the sample. In this way, the behavior of **3a** resembles the behavior of **8b** and **8d**, which also decompose before the isotropic state could

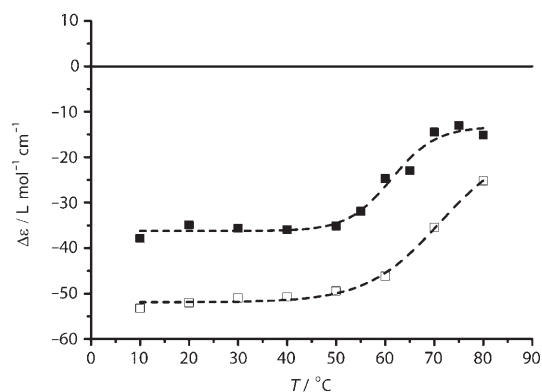


Figure 4. Temperature dependent CD measurements for compounds **3b** (■) and **8a** (□) at $\lambda = 255$ and 263 nm, respectively, in heptane, 2×10^{-5} M from 10 °C in steps of 10 to 80 °C.

Table 4. Wavenumbers σ [cm⁻¹] of the N-H stretch vibrations of **3b** and **8a** in the solid state and in 2×10^{-5} M heptane solutions at 70 °C.

Compound	3b	8a
σ solid state	3315	3300
σ heptane	3286	3272

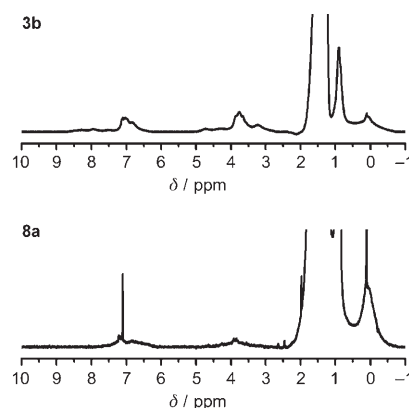


Figure 5. ¹H NMR spectra at 70 °C for compounds **3b**, 2×10^{-5} M C₆D₁₂ and **8a**, 2×10^{-5} M in C₆D₁₂.

be reached, meaning that strong interactions are present preventing the molecules to flow. The solubility experiments in chloroform and in heptane show the same trends as observed in the neat state; the solubility decreases going from discotic **3b** to **8a** to **8c,e** to **8b,d** (Figure 6). Again, discotic **3a** behaves completely different compared with the other molecules. Discotic **3a** does not show a Cotton effect neither in chloroform nor in heptane. Probably, the glycyglycine tails of **3a** are too flexible, which makes it impossible to transfer the chiral information embedded in the alkyl tails to a higher level of organization. This does not necessarily mean that aggregation, in which the transfer of chirality to a higher level of organization is not possible, cannot be present in solution. In contrast, according to the high stability in the neat state, it is most likely that self-assemblies are

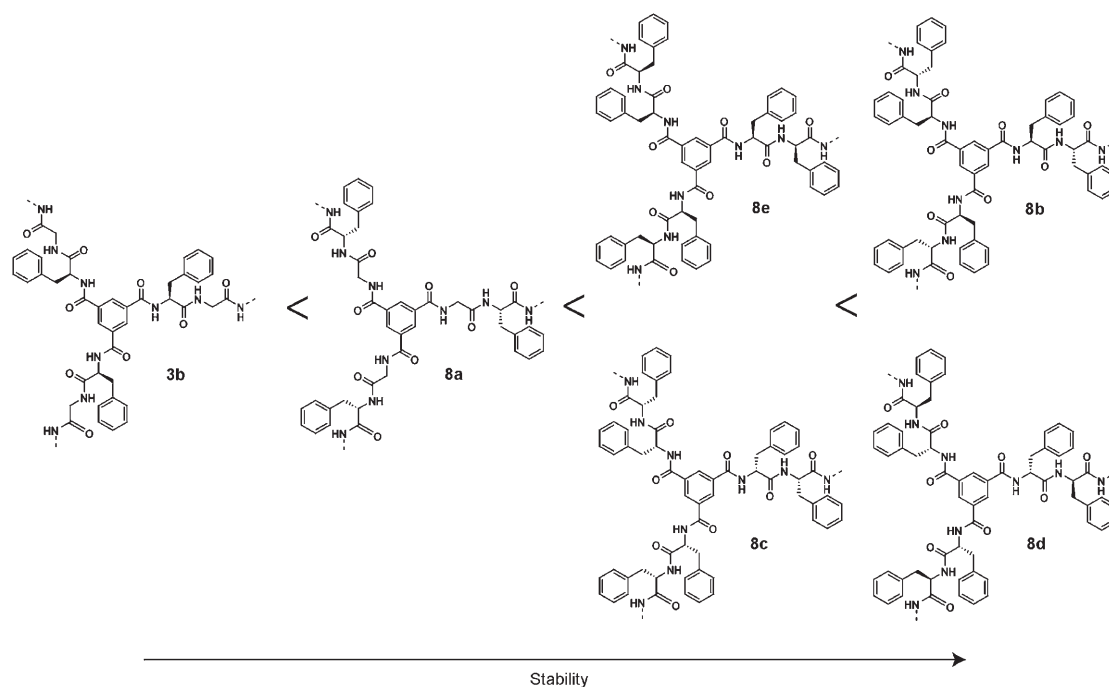


Figure 6. Cores of compounds **3b** and **8a–e** shown in order of increasing stability.

present also in solution. Figure 6 demonstrates that the stack stability increases when two phenylalanines are present in the core (**8b–e**). Explanations for the increased stability might be that two phenylalanines provide more confinement of space, additional π – π interactions and/or extra chiral information. The measurements also reveal that the stack stability is higher when two phenylalanines with equal chirality (**8b,d**) are present compared with two phenylalanines with opposite chirality (**8c,e**), which might be due to more efficient packing when two phenylalanines with equal chirality are introduced. Unexpectedly, the data also point out that when a combination of L-phenylalanine and glycine is used, the stack stability is higher when the L-phenylalanine is placed remote from the core. To explain this observation it is necessary to understand the self-assembly mechanism in more detail. When the center starts to self-assemble first followed by the mesogenic groups at the periphery, it would be more beneficial to have the phenylalanine close to the center to enlarge the core and provide a more confined packing. Nevertheless, the opposite is observed, which suggests that stacking is not initiated from the center of the discotics, but from the periphery. Preliminary investigation of the stacking mechanism of **3b** in solution with CD spectroscopy also supports this hypothesis.

Conclusion

This paper reports on the syntheses of a series of C_3 -symmetrical molecules that contain a 1,3,5-benzenetricarboxamide core extended with dipeptide fragments bearing peripheral mesogenic groups. The complete library of discotics

was investigated both in the neat state as well as in solution. Although all discotics form very stable self-assemblies, a clear trend in the stability of the different stacks has been observed depending on the dipeptide fragment incorporated. The self-assemblies appeared not to be very well-ordered in the neat state. Furthermore, some of the self-assembled structures show very complex energy landscapes in solution. This indicates that small differences in the balance between the secondary interactions, which originate from the benzenetricarboxamide core and the dipeptide fragments, have a strong influence on the order within the stack. To conclude, the stability and the chiral behavior of the discs depend on their environments and on the strength of the different secondary interactions embedded in the structure of the molecules. The balance of these supramolecular interactions is very subtle and a small modification can already make the difference between thermodynamically stable or completely frustrated stacks. The results presented here show that it is possible to tune the stacking properties of these dipeptide discotics by modifying the dipeptide fragments, but the results also stress the importance of understanding the self-assembly mechanisms in order to clarify the self-assembly behavior of the different C_3 -symmetrical molecules.

Experimental Section

Unless stated otherwise, all reagents and chemicals were obtained from commercial sources and used without further purification. The aniline derivatives were synthesized according to described literature procedures.^[9–10] Water was demineralised prior to use. Dichloromethane and

THF were obtained by distillation over Merck molecular sieves (4 Å). ¹H NMR, ¹H,¹H COSY and ¹⁹F NMR spectra were recorded on a Varian Gemini 300 spectrometer, a Varian Mercury Vx 400 spectrometer or a Varian Unity Inova 500 spectrometer at 298 K. Chemical shifts are given in ppm (δ) values relative to tetramethylsilane (TMS). Splitting patterns are designated as s, singlet; d, doublet; dd, double doublet; t, triplet; q, quartet; m, multiplet. Neat state IR spectra were measured at 298 K on a Perkin-Elmer 1605 FT-IR spectrophotometer. Matrix assisted laser desorption/ionization mass spectra were obtained on a PerSeptive Biosystems Voyager DE-PRO spectrometer using α-cyano-4-hydroxycinnamic acid (CHCA) and 2-[(2E)-3-(4-*tert*-butylphenyl)-2-methylprop-2-enylidene]malononitrile (DCTB) as matrices. Elemental analyses were carried out using a Perkin Elmer 2400. GPC measurements were performed on a Shimadzu system with a mixed column (2 × PL gel 3 μm, 100 Å), with a flow of 1 mL min⁻¹, and THF as the eluting solvent. The injection volume was 50 μL and photodiode array detection (260 nm) was applied. Chiral HPLC was performed on a Shimadzu system consisting of a Shimadzu LC-10 ADvp pump, a Spark Midas autosampler and a Shimadzu SPD-10 ADvp UV/Vis detector. Two chiral HPLC columns were used a Daicel Chiralcel OD (0.46 × 25 cm) and a DNBP (covalent, 5 μm; 0.46 × 25 cm), both with hexane/isopropanol 9:1 as the eluent. UV/Vis spectra were obtained on a Perkin Elmer Lambda 40 spectrometer. CD measurements were performed on a Jasco J-600 spectropolarimeter connected to a Jasco PTC-348WI temperature controller. Infrared spectra of the liquid samples were recorded using a Biorad FTS 6000 spectrometer. The heatable cell used to perform the measurements was controlled by a home made temperature controller and fitted with KBr windows and a Teflon spacer that makes the pathlength 1 mm. Each spectrum was recorded with a resolution of 4 cm⁻¹, co-adding 200 scans. The optical properties of the neat state were determined using a Jenaval polarization microscope equipped with a Linkam THMS 600 heating device and a Polaroid digital camera model PDMC-2. DSC data were collected on a Perkin Elmer Pyris 1 under nitrogen atmosphere. The X-ray measurements were carried out on a home-built system consisting of a sealed X-ray tube (Cu_{Kα} radiation), a primary graphite monochromator, a pinhole collimator, a sample stage, and a Siemens Hi-Star area detector. All components were mounted on an optical bench to provide maximal flexibility and easy alignment. Samples were prepared in a 0.9 mm diameter Lindemann capillary tube and mounted in a home-built furnace, based on a TMS94 Linkam hot stage. Wide angle X-ray (WAXS) patterns were recorded with a sample-to-detector distance of 8.1 cm.

N^o-(*tert*-Butyloxycarbonyl)-N^o-[3,4,5-tri((S)-3,7-dimethyloctyloxy)phenyl]glycylglycinamide (1a): DIPEA (0.26 mL, 1.49 mmol) and BocGly-GlyOH (0.16 g, 0.69 mmol) were added subsequently to a magnetically stirred solution of HBTU (0.28 g, 0.74 mmol) in dry DMF (1.5 mL). The mixture was stirred for 5 min after which 3,4,5-tri((S)-3,7-dimethyloctyl)-aniline (0.21 g, 0.37 mmol) was added. Stirring was continued overnight at room temperature. The reaction mixture was slowly added to a mixture of diethyl ether (25 mL), acidic water (pH < 3, 25 mL) and ice. The organic layer was washed with sat. KCl (15 mL), 1 N NaOH (3 × 15 mL) and 10 mM NaHCO₃ (3 × 15 mL), dried over MgSO₄ and the organic solvent was evaporated in vacuo. The crude product was purified by column chromatography (silica, 4% methanol in dichloromethane) to yield the pure compound as a transparent, sticky oil (0.19 g, 0.24 mmol, 65%). ¹H NMR (CDCl₃): δ = 8.30 (s, 1H, aromatic amide NH), 7.00 (brt, 1H, aliphatic amide NH), 6.87 (s, 2H, *ortho*-H), 5.26 (t, 1H, carbamate NH), 4.08 (d, 2H, *J* = 5.7 Hz, CH₂CONHAr), 4.0–3.8 (m, 6H, OCH₂), 3.84 (d, 2H, *J* = 5.7 Hz, (CH₃)₃OCONHCH₂), 1.9–0.8 ppm (m, 66H, alkyl H [57H] + C(CH₃)₃ [9H]); ¹³C NMR (CDCl₃): δ = 170.3, 166.8, 156.6, 153.3, 135.0, 133.4, 99.2, 81.1, 71.9, 67.5, 44.9, 44.1, 39.5, 39.4, 37.7, 37.5, 37.5, 36.6, 30.0, 29.9, 28.4, 28.1, 24.9, 24.9, 22.9, 22.8, 22.7, 19.7, 19.7 ppm; FT-IR (ATR): $\tilde{\nu}$ = 3314, 2954, 2926, 2870, 1688 1663, 1608, 1505, 1428, 1383, 1367, 1290, 1226, 1169, 1117 cm⁻¹; MALDI-TOF: *m/z*: calcd for: 775.61; found: 775.50 [M]⁺, 798.50 [M+Na]⁺; elemental analysis calcd (%) for C₄₅H₈₁N₃O₇: C 69.64, H 10.52, N 5.41; found: C 69.91, H 10.62, N 5.41.

N^o-(*tert*-Butyloxycarbonyl)-N^o-(3,4,5-trioctyloxy-phenyl)-L-phenylalanyl-glycinamide (1b): DIPEA (3.0 mL, 17 mmol) and Boc-L-PheGly-OH (2.41 g, 7.48 mmol) were added subsequently to a magnetically stirred so-

lution of HBTU (3.18 g, 8.38 mmol) in dry DMF (17 mL). The mixture was stirred for 5 min after which 3,4,5-trioctyloxyaniline (1.98 g, 4.15 mmol) was added. Stirring was continued overnight at room temperature. The reaction mixture was slowly added to a mixture of diethyl ether (200 mL), acidic water (pH < 3, 200 mL) and ice. The organic layer was washed with sat. KCl (150 mL), 1 N NaOH (3 × 150 mL) and 10 mM NaHCO₃ (3 × 150 mL) and dried over MgSO₄. The crude product was purified by column chromatography (silica, 2% methanol in dichloromethane) and subsequently washed with methanol to yield the pure compound as an off-white solid material (2.00 g, 2.56 mmol, 62%). ¹H NMR (CDCl₃): δ = 8.27 (s, 1H, aromatic amide NH), 7.4–7.1 (m, 5H, Ar), 6.87 (s, 2H, *ortho*-H), 6.58 (brt, 1H, aliphatic amide NH), 4.93 (d, 1H, *J* = 5.1 Hz, carbamate NH), 4.28 (q, 1H, C_αH), 4.1–3.8 (m, 8H, NHCH₂CO [2H] + OCH₂ [6H]), 3.10 (dd + dd, 2H, CH₂Ar), 1.9–1.2 (m, 45H, (CH₂)₆ [36H] + C(CH₃)₃ [9H]), 0.86 ppm (t, 9H, CH₃); ¹³C NMR (CDCl₃): δ = 172.2, 166.8, 156.1, 153.2, 136.2, 135.1, 133.4, 129.2, 129.1, 127.5, 99.4, 81.2, 73.6, 69.2, 56.8, 44.2, 37.7, 32.0, 32.0, 30.4, 29.7, 29.5, 29.4, 28.4, 26.3, 26.2, 22.8, 22.8, 14.2 ppm; FT-IR (ATR): $\tilde{\nu}$ = 3296, 2924, 2855, 1683, 1653, 1606, 1525, 1504, 1428, 1379, 1365, 1228, 1114, 1022, 697 cm⁻¹; MALDI-TOF: *m/z*: calcd for 781.56; found: 781.46 [M]⁺; elemental analysis calcd (%) for C₄₆H₇₃N₃O₇: C 70.64, H 9.67, N 5.37; found: C 70.72, H 9.56, N 5.32.

N^o-[3,4,5-Tri((S)-3,7-dimethyloctyloxyphenyl)]glycylglycinamide (2a): Compound 1a (1.63 g, 2.10 mmol) was dissolved in TFA (10 mL). The solution was purged with argon for 15 min, after which the mixture was stirred for another 45 min. The reaction mixture was concentrated in vacuo. A mixture of diethyl ether, 1 N NaOH and ice was added and the layers were separated. The organic layer was washed several times with 1 N NaOH and dried over MgSO₄ to give the pure title compound (1.30 g, 1.92 mmol, 92%). ¹H NMR (CDCl₃): δ = 8.58 (s, 1H, aromatic amide NH), 8.12 (brt, 1H, aliphatic amide NH), 6.82 (s, 2H, *ortho*-H), 4.10 (d, 2H, *J* = 5.6 Hz, NHCH₂CO), 4.0–3.9 (m, 6H, OCH₂), 3.45 (s, 2H, H₂NCH₂), 1.90–0.8 ppm (m, 59H, alkyl H [57H] + NH₂ [2H]); ¹³C NMR (CDCl₃): δ = 174.4, 167.1, 153.3, 135.0, 133.5, 98.9, 71.9, 67.5, 44.7, 39.5, 39.4, 37.7, 37.5, 37.5, 36.5, 29.9, 29.8, 28.1, 24.9, 24.9, 22.9, 22.8, 22.7, 19.7 ppm; FT-IR (ATR): $\tilde{\nu}$ = 3286, 2954, 2926, 2870, 1698, 1655, 1620, 1604, 1527, 1555, 1504, 1466, 1426, 1383, 1366, 1233, 1115, 834 cm⁻¹; MALDI-TOF: *m/z*: calcd for: 675.55; found: 675.55 [M]⁺, 698.55 [M+Na]⁺; elemental analysis calcd (%) for C₄₀H₇₃N₃O₅: C 71.07, H 10.88, N 6.22; found: C 70.95, H 10.80, N 6.09.

N^o-(3,4,5-Trioctyloxyphenyl)-L-phenylalanyl-glycinamide (2b): Compound 1b (0.80 g, 1.02 mmol) was dissolved in TFA (10 mL). The solution was purged with argon for 15 min, after which the mixture was stirred for another 45 min. The reaction mixture was concentrated in vacuo. A mixture of ethyl acetate, 1 N NaOH and some ice was added. The organic layer was washed with 1 N NaOH several times and dried over MgSO₄ to give the pure title compound (0.63 g, 0.92 mmol, 90%). ¹H NMR (CDCl₃): δ = 8.75 (s, 1H, aromatic amide NH), 8.20 (brt, 1H, aliphatic amide NH), 7.4–7.1 (m, 5H, Ar), 6.83 (s, 2H, *ortho*-H), 4.10 (d, 2H, *J* = 4.8 Hz, NHCH₂CO), 4.0–3.8 (m, 6H, OCH₂), 3.70 (m, 1H, C_αH), 3.72 + 2.77 (dd + dd, 2H, CH₂Ar), 1.9–1.2 (m, 38H, (CH₂)₆ [36H] + NH₂ [2H]), 0.86 ppm (m, 9H, CH₃); ¹³C NMR (CDCl₃): δ = 175.8, 170.0, 153.2, 137.2, 134.9, 133.4, 129.2, 128.9, 127.1, 99.0, 73.5, 69.1, 56.2, 44.7, 40.8, 31.9, 31.8, 30.3, 29.6, 29.4, 29.3, 26.1, 26.1, 22.7, 22.7, 14.1 ppm; FT-IR (ATR): $\tilde{\nu}$ = 3289, 2923, 2855, 1694, 1648, 1603, 1555, 1502, 1426, 1384, 1227, 1115, 700 cm⁻¹; MALDI-TOF: *m/z*: calcd for: 682.51; found: 682.36 [M+H]⁺, 704.35 [M+Na]⁺; elemental analysis calcd (%) for C₄₁H₆₇N₃O₅: C 72.21, H 9.90, N 6.16; found: C 71.55, H 9.60, N 6.08.

N^o,N^o,N^o-(1,3,5-Benzenetricarbonyl)tris[N^o-(3,4,5-tri((S)-3,7-dimethyloctyloxy)phenyl)]glycylglycinamide (3a): A solution of 1,3,5-benzenetricarbonyl trichloride (0.13 g, 0.51 mmol) in dry dichloromethane (5 mL) was added dropwise to a solution of 2a (1.20 g, 1.77 mmol) and triethylamine (0.5 mL, 3.6 mmol) in dry dichloromethane (15 mL). After stirring overnight and evaporation of the dichloromethane the product was purified using column chromatography (silica, 2.5% methanol in ethyl acetate) to yield the title compound as a pink solid material (0.70 g, 0.32 mmol, 63%). The product was characterized using GPC (THF, 260 nm, purity based on UV > 98%): ¹H NMR ([D₈]THF): δ = 9.03 (brs,

6H, NH'' [3H] + NH [3H]), 8.42 (s, 3H, *ortho*-H), 8.23 (brt, 3H, NH'), 6.84 (s, 6H, *ortho*-H'), 4.0–3.8 (m, 30H, ArCONHCH₂ [6H] + CH₂CONHAr [6H] + OCH₂ [18H]), 1.7–0.7 ppm (m, 171H, alkyl H); ¹³C NMR ([D₈]THF): δ = 171.8, 170.4, 168.5, 155.3, 137.0, 136.6, 131.4, 101.1, 73.2, 46.3, 45.5, 41.8, 41.6, 40.0, 39.8, 38.8, 32.1, 32.1, 30.3, 24.5, 24.4, 21.5, 21.3 ppm; FT-IR (ATR): $\tilde{\nu}$ = 3314, 2954, 2926, 2870, 1656, 1603, 1533, 1504, 1427, 1383, 1226, 1114 cm⁻¹; MALDI-TOF: *m/z*: calcd for: 2182.65; found: 2182.70 [M]⁺, 2205.65 [M+Na]⁺; elemental analysis calcd (%) for C₁₂₆H₂₁₃N₉O₁₈: C 70.65, H 10.02, N 5.88; found: C 70.33, H 10.04, N 5.63.

N^o,N^o,N^o-(1,3,5-Benzenetricarbonyl)tris[N^o-(3,4,5-trioctyloxy)phenyl]-L-phenylalanylglycinamide (3b): A solution of 1,3,5-benzenetricarbonyl trichloride (66.7 mg, 0.25 mmol) in dry dichloromethane (2.5 mL) was added dropwise to a solution of **2b** (0.60 g, 0.88 mmol) and triethylamine (0.3 mL, 2.2 mmol) in dry dichloromethane (7.5 mL). After stirring overnight and evaporation of the dichloromethane the product was purified using column chromatography (silica, ethyl acetate/pentane 4:1) to yield the title compound as an off-white solid material (0.37 g, 0.17 mmol, 67%). The product was characterized using GPC (THF, 260 nm, purity based on UV > 99%). ¹H NMR ([D₆]DMSO, T = 323 K): δ = 9.73 (s, 3H, NH''), 8.87 (d, 3H, J = 7.2 Hz, NH), 8.49 (brt, 3H, NH'), 8.31 (s, 3H, *ortho*-H), 7.4–7.1 (m, 15H, Ar), 6.93 (s, 6H, *ortho*-H'), 4.79 (m, 3H, C_αH), 4.0–3.6 ppm (m, 24H, NHCH₂CO [6H] + OCH₂ [18H]), 3.2–3.0 (dd + dd, 6H, CH₂Ar), 1.8–1.0 (m, 108H, (CH₂)₆), 0.84 ppm (t, 27H, CH₃); ¹³C NMR ([D₆]DMSO, T = 323 K): δ = 171.5, 167.2, 165.7, 152.3, 138.1, 134.6, 134.4, 133.1, 129.1, 128.1, 126.2, 97.8, 72.4, 68.1, 55.8, 42.8, 37.3, 31.3, 31.2, 29.8, 29.4, 28.9, 28.8, 28.7, 25.6, 25.6, 22.1, 15.1 ppm; FT-IR (ATR): $\tilde{\nu}$ = 3300, 2924, 2855, 1645, 1603, 1536, 1503, 1427, 1380, 1226, 1112, 699 cm⁻¹; MALDI-TOF: *m/z*: calcd for: 2200.51; found: 2200.49 [M]⁺, 2223.44 [M+Na]⁺; elemental analysis calcd (%) for C₁₃₂H₂₀₁N₉O₁₈: C 72.00, H 9.20, N 5.72; found: C 71.63, H 9.30, N 5.44.

N^o-(tert-Butyloxycarbonyl)-N^o-(3,4,5-trioctyloxyphenyl)-L-phenylalaninamide (4a): DIPEA (3.0 mL, 17 mmol) and Boc-L-PheOH (2.04 g, 7.69 mmol) were added subsequently to a magnetically stirred solution of HBTU (3.24 g, 8.54 mmol) in dry DMF (17 mL). This mixture was stirred for 5 min after which 3,4,5-trioctyloxyaniline (2.00 g, 4.19 mmol) was added. Stirring was continued overnight at room temperature. The reaction mixture was slowly added to a mixture of diethyl ether (200 mL), acidic water (pH < 3, 200 mL) and ice. The organic layer was washed with sat. KCl (80 mL), 1 N NaOH (3 × 80 mL) and 10 mM NaHCO₃ (3 × 80 mL) and dried over MgSO₄. The crude product was used as such for the preparation of **5a**.

N^o-(tert-Butyloxycarbonyl)-N^o-(3,4,5-trioctyloxyphenyl)-D-phenylalaninamide (4b): DIPEA (3.0 mL, 17 mmol) and Boc-D-Phe-OH (2.01 g, 7.57 mmol) were added subsequently to a magnetically stirred solution of HBTU (3.20 g, 8.44 mmol) in dry DMF (17 mL). This mixture was stirred for 5 min after which 3,4,5-trioctyloxyaniline (2.04 g, 4.28 mmol) was added. Stirring was continued overnight at room temperature. The reaction mixture was slowly added to a mixture of diethyl ether (200 mL), acidic water (pH < 3, 200 mL) and ice. The organic layer was washed with sat. KCl (80 mL), 1 N NaOH (3 × 80 mL) and 10 mM NaHCO₃ (3 × 80 mL) and dried over MgSO₄. The crude product was used as such for the preparation of **5b**.

N^o-(3,4,5-Trioctyloxyphenyl)-L-phenylalaninamide (5a): Crude **4a** (4.2 g) was dissolved in TFA (25 mL). The solution was purged with argon for 15 min, after which the mixture was stirred for another 45 min. The reaction mixture was concentrated in vacuo. A mixture of diethyl ether, 1 N NaOH and ice was added. The organic layer was washed with 1 N NaOH several times and dried over MgSO₄ to give the pure title compound (2.23 g, 3.56 mmol, 85% after two reactions). ¹H NMR (CDCl₃): δ = 9.28 (s, 1H, aromatic amide NH), 7.4–7.2 (m, 5H, Ar), 6.87 (s, 2H, *ortho*-H), 4.1–3.9 (m, 6H, OCH₂), 3.70 (m, 1H, C_αH), 3.35 + 2.75 (dd + dd, 2H, CH₂Ar), 1.9–1.2 (m, 38H, (CH₂)₆ [36H] + NH₂ [2H]), 0.89 ppm (t, 9H, CH₃); ¹³C NMR (CDCl₃): δ = 172.1, 153.2, 137.8, 134.7, 133.3, 129.3, 128.8, 127.0, 98.4, 73.5, 69.0, 56.9, 40.7, 31.9, 31.8, 30.2, 29.6, 29.4, 29.3, 26.1, 26.1, 22.7, 22.7, 14.1 ppm; FT-IR (ATR): $\tilde{\nu}$ = 3273, 2950, 2919, 2850, 1653, 1642, 1600, 1534, 1506, 1465, 1429, 1389, 1231, 1115, 743, 702 cm⁻¹; MALDI-TOF: *m/z*: calcd for: 625.49; found: 625.44 [M+H]⁺, 647.43

[M+Na]⁺; elemental analysis calcd (%) for C₃₉H₆₄N₂O₄: C 74.95, H 10.32, N 4.48; found: C 74.92, H 10.52, N 4.28.

N^o-(3,4,5-Trioctyloxyphenyl)-D-phenylalaninamide (5b): Crude **4b** (4.3 g) was dissolved in TFA (25 mL). The solution was purged with argon for 15 min, after which the mixture was stirred for another 45 min. The reaction mixture was concentrated in vacuo. A mixture of diethyl ether, 1 N NaOH and ice was added. The organic layer was washed with 1 N NaOH several times and dried over MgSO₄ to give the pure title compound (2.24 g, 3.58 mmol, 85% after two reactions). ¹H NMR (CDCl₃): δ = 9.28 (s, 1H, aromatic amide NH), 7.4–7.2 (m, 5H, Ar), 6.87 (s, 2H, *ortho*-H), 4.1–3.9 (m, 6H, OCH₂), 3.70 (m, 1H, C_αH), 3.35 + 2.75 (dd + dd, 2H, CH₂Ar), 1.9–1.2 (m, 38H, (CH₂)₆ [36H] + NH₂ [2H]), 0.89 ppm (t, 9H, CH₃); ¹³C NMR (CDCl₃): δ = 172.1, 153.2, 137.8, 134.7, 133.3, 129.3, 128.8, 127.0, 98.4, 73.5, 69.1, 56.9, 40.7, 31.9, 31.8, 30.3, 29.6, 29.4, 29.3, 26.2, 26.1, 22.7, 22.7, 14.1 ppm; FT-IR (ATR): $\tilde{\nu}$ = 3270, 2950, 2919, 2850, 1652, 1642, 1600, 1536, 1506, 1465, 1430, 1389, 1231, 1115, 743, 702 cm⁻¹; MALDI-TOF: *m/z*: calcd for: 624.49; found: 624.38 [M+H]⁺; elemental analysis calcd (%) for C₃₉H₆₄N₂O₄: C 74.95, H 10.32, N 4.48; found: C 75.22, H 10.57, N 4.37.

N^o-(tert-Butyloxycarbonyl)-N^o-(3,4,5-trioctyloxyphenyl)-glycyl-L-phenylalaninamide (6a): DIPEA (0.6 mL, 3.5 mmol) and BocGlyOH (0.29 g, 1.66 mmol) were added subsequently to a magnetically stirred solution of HBTU (0.69 g, 1.82 mmol) in dry DMF (3.6 mL). This mixture was stirred for 5 min after which **5a** (0.57 g, 0.91 mmol) was added. Stirring was continued overnight at room temperature. The reaction mixture was slowly added to a mixture of diethyl ether (100 mL), acidic water (pH < 3, 100 mL) and ice. The organic layer was washed with sat. KCl (80 mL), 1 N NaOH (3 × 80 mL) and 10 mM NaHCO₃ (3 × 80 mL) and dried over MgSO₄. The crude product was purified by column chromatography (silica, 3% methanol in dichloromethane) to yield the pure compound as a sticky yellow solid material (0.56 g, 0.72 mmol, 79%). The product was characterized using chiral HPLC (isocratic, 10% isopropanol in hexane, purity based on UV > 99%). ¹H NMR (CDCl₃): δ = 7.85 (s, 1H, aromatic amide NH), 7.4–7.2 (m, 5H, Ar), 6.74 (s, 2H, *ortho*-H), 6.66 (d, 1H, J = 7.6 Hz, aliphatic amide NH), 5.07 (brt, 1H, carbamate NH), 4.78 (q, 1H, C_αH), 4.0–3.6 (m, 8H, NHCH₂CO [2H] + OCH₂ [6H]), 3.29 + 3.07 (dd + dd, 2H, CH₂Ar), 1.8–1.1 (m, 45H, (CH₂)₆ [36H] + C(CH₃)₃ [9H]), 0.88 ppm (t, 9H, CH₃); ¹³C NMR (CDCl₃): δ = 169.7, 168.9, 156.4, 153.1, 136.4, 135.0, 133.2, 129.4, 128.9, 127.2, 99.1, 80.7, 73.6, 69.1, 54.9, 44.7, 38.2, 32.0, 32.0, 30.4, 29.7, 29.5, 29.4, 28.3, 28.1, 26.2, 26.2, 22.8, 22.8, 14.2 ppm; FT-IR (ATR): $\tilde{\nu}$ = 3285, 2955, 2924, 2855, 1649, 1607, 1549, 1504, 1428, 1389, 1367, 1228, 1169, 1114, 698 cm⁻¹; MALDI-TOF: *m/z*: calcd for: 781.56; found: 781.57 [M]⁺; elemental analysis calcd (%) for C₄₆H₇₅N₃O₇: C 70.64, H 9.67, N 5.37; found: C 70.64, H 9.85, N 5.32.

N^o-(tert-Butyloxycarbonyl)-N^o-(3,4,5-trioctyloxyphenyl)-L-phenylalanylglycyl-L-phenylalaninamide (6b): DIPEA (0.7 mL, 4.0 mmol) and Boc-L-Phe-OH (0.50 g, 1.88 mmol) were added subsequently to a magnetically stirred solution of HBTU (0.80 g, 2.11 mmol) in dry DMF (4 mL). This mixture was stirred for 5 min after which **5a** (0.66 g, 1.05 mmol) was added. Stirring was continued overnight at room temperature. The reaction mixture was slowly added to a mixture of diethyl ether (100 mL), acidic water (pH < 3, 100 mL) and ice. The organic layer was washed with sat. KCl (60 mL), 1 N NaOH (3 × 60 mL) and 10 mM NaHCO₃ (3 × 60 mL) and dried over MgSO₄. The crude product was purified by column chromatography (silica, 3% methanol in dichloromethane) and subsequently washed with methanol to yield the pure compound as a white solid material (0.68 g, 0.78 mmol, 74%). The product was characterized using chiral HPLC (isocratic, 10% isopropanol in hexane, purity based on UV > 99%). ¹H NMR (CDCl₃): δ = 7.98 (s, 1H, aromatic amide NH), 7.4–6.9 (m, 10H, Ar), 6.87 (s, 2H, *ortho*-H), 6.27 (d, 1H, J = 7.2 Hz, aliphatic amide NH), 4.9–4.7 (m, 2H, carbamate NH [1H] + C_αH [1H]), 4.26 (q, 1H, C_αH), 4.0–3.8 (m, 6H, OCH₂), 3.37 + 2.89 (dd + dd, 2H, C_αHCH₂Ar) + 3.04 (m, 2H, C_αHCH₂Ar), 1.8–1.2 (m, 45H, (CH₂)₆ [36H] + C(CH₃)₃ [9H]), 0.88 ppm (t, 9H, CH₃); ¹³C NMR (CDCl₃): δ = 171.0, 168.5, 156.0, 153.1, 136.2, 135.8, 134.9, 133.5, 129.4, 129.3, 129.2, 129.0, 127.7, 127.3, 99.1, 81.2, 73.6, 69.1, 56.5, 53.9, 37.4, 37.0, 32.0, 32.0, 30.4, 29.7, 29.5, 29.4, 28.4, 28.2, 26.3, 26.2, 22.8, 22.8, 14.3 ppm; FT-IR (ATR): $\tilde{\nu}$ = 3284, 2922, 2854, 1690, 1647, 1603, 1527, 1506, 1429,

1367, 1229, 1170, 1116, 697 cm⁻¹; MALDI-TOF: *m/z*: calcd for: 871.61; found: 871.61 [*M*]⁺; elemental analysis calcd (%) for C₅₃H₈₁N₃O₇: C 72.98, H 9.36, N 4.82; found: C 73.03, H 9.56, N 4.76.

N^o-(tert-Butyloxycarbonyl)-N^o-(3,4,5-trioctyloxyphenyl)-D-phenylalanyl-L-phenylalaninamide (6c): DIPEA (0.8 mL, 4.6 mmol) and Boc-D-PheOH (0.57 g, 2.15 mmol) were added subsequently to a magnetically stirred solution of HBTU (0.91 g, 2.40 mmol) in dry DMF (5 mL). This mixture was stirred for 5 min after which **5a** (0.75 g, 1.20 mmol) was added. Stirring was continued overnight at room temperature. The reaction mixture was slowly added to a mixture of diethyl ether (80 mL), acidic water (pH < 3, 80 mL) and ice. The organic layer was washed with sat. KCl (40 mL), 1 N NaOH (3 × 40 mL) and 10 mM NaHCO₃ (3 × 40 mL) and dried over MgSO₄. The crude product was purified by column chromatography (silica, 2% methanol in dichloromethane) and subsequently washed with methanol to yield the pure compound as a white solid material (0.78 g, 0.90 mmol, 75%). The product was characterized using chiral HPLC (isocratic, 10% isopropanol in hexane, purity based on UV > 99%). ¹H NMR (CDCl₃): δ = 7.99 (s, 1H, aromatic amide NH), 7.4–6.9 (m, 10H, Ar), 6.72 (s, 2H, *ortho*-H), 6.15 (d, 1H, *J* = 6.4 Hz, aliphatic amide NH), 4.96 (brd, 1H, carbamate NH), 4.76 (q, 1H, C_{α2}H), 4.08 (q, 1H, C_{α1}H), 4.0–3.8 (m, 6H, OCH₂), 3.26 + 2.80 (dd + dd, 2H, C_{α2}HCH₂Ar), 3.00 (m, 2H, C_{α1}HCH₂Ar), 1.8–1.2 (m, 45H, (CH₂)₆ [36H] + C(CH₃)₃ [9H]), 0.88 ppm (t, 9H, CH₃); ¹³C NMR (CDCl₃): δ = 171.5, 168.5, 155.8, 153.1, 136.4, 136.3, 135.3, 133.1, 129.6, 129.4, 129.0, 129.0, 127.4, 127.3, 99.9, 81.0, 73.6, 69.3, 57.2, 54.5, 37.7, 37.0, 32.0, 32.0, 30.4, 29.7, 29.5, 29.4, 28.3, 26.3, 26.2, 22.8, 22.8, 14.3 ppm; FT-IR (ATR): $\tilde{\nu}$ = 3295, 2921, 2852, 1688, 1648, 1603, 1526, 1508, 1428, 1388, 1367, 1231, 1170, 1130, 1117, 700 cm⁻¹; MALDI-TOF: *m/z*: calcd for: 871.61; found: 871.64 [*M*]⁺; elemental analysis calcd (%) for C₅₃H₈₁N₃O₇: C 72.98, H 9.36, N 4.82; found: C 73.31, H 9.45, N 4.77.

N^o-(tert-Butyloxycarbonyl)-N^o-(3,4,5-trioctyloxyphenyl)-D-phenylalanyl-D-phenylalaninamide (6d): DIPEA (1.1 mL, 6.3 mmol) and Boc-D-PheOH (0.75 g, 2.83 mmol) were added subsequently to a magnetically stirred solution of HBTU (1.19 g, 3.14 mmol) in dry DMF (7 mL). This mixture was stirred for 5 min after which **5b** (0.98 g, 1.57 mmol) was added. Stirring was continued overnight at room temperature. The reaction mixture was slowly added to a mixture of diethyl ether (80 mL), acidic water (pH < 3, 80 mL) and ice. The organic layer was washed with sat. KCl (40 mL), 1 N NaOH (3 × 40 mL) and 10 mM NaHCO₃ (3 × 40 mL) and dried over MgSO₄. The crude product was purified by column chromatography (silica, 2% methanol in dichloromethane) and subsequently washed with methanol to yield the pure compound as a white solid material (1.04 g, 1.19 mmol, 76%). The product was characterized using chiral HPLC (isocratic, 10% isopropanol in hexane, purity based on UV > 99%). ¹H NMR (CDCl₃): δ = 7.97 (s, 1H, aromatic amide NH), 7.4–6.9 (m, 10H, Ar), 6.87 (s, 2H, *ortho*-H), 6.26 (d, 1H, *J* = 6.5 Hz, aliphatic amide NH), 4.9–4.7 (m, 2H, carbamate NH [1H] + C_{α2}H [1H]), 4.26 (q, 1H, C_{α1}H), 4.0–3.8 (m, 6H, OCH₂), 3.37 + 2.89 (dd + dd, 2H, C_{α2}HCH₂Ar) + 3.04 (m, 2H, C_{α1}HCH₂Ar), 1.8–1.2 (m, 45H, (CH₂)₆ [36H] + C(CH₃)₃ [9H]), 0.88 ppm (t, 9H, CH₃); ¹³C NMR (CDCl₃): δ = 170.9, 168.5, 156.1, 153.1, 136.2, 135.8, 134.9, 133.5, 129.4, 129.3, 129.2, 129.1, 127.7, 127.3, 99.1, 81.2, 73.6, 69.1, 56.5, 53.8, 37.4, 37.0, 32.0, 32.0, 30.4, 29.7, 29.5, 29.4, 28.2, 26.3, 26.2, 22.8, 22.8, 14.3 ppm; FT-IR (ATR): $\tilde{\nu}$ = 3289, 2922, 2852, 1691, 1648, 1602, 1527, 1506, 1428, 1388, 1367, 1297, 1229, 1168, 1129, 1116, 697 cm⁻¹; MALDI-TOF: *m/z*: calcd for: 871.61; found: 871.45 [*M*]⁺; elemental analysis calcd (%) for C₅₃H₈₁N₃O₇: C 72.98, H 9.36, N 4.82; found: C 73.22, H 9.39, N 4.75.

N^o-(tert-Butyloxycarbonyl)-N^o-(3,4,5-trioctyloxyphenyl)-L-phenylalanyl-D-phenylalaninamide (6e): DIPEA (1.1 mL, 6.3 mmol) and Boc-L-PheOH (0.76 g, 2.86 mmol) were added subsequently to a magnetically stirred solution of HBTU (1.20 g, 3.16 mmol) in dry DMF (7 mL). This mixture was stirred for 5 min after which **5b** (0.99 g, 1.58 mmol) was added. Stirring was continued overnight at room temperature. The reaction mixture was slowly added to a mixture of diethyl ether (80 mL), acidic water (pH < 3, 80 mL) and ice. The organic layer was washed with sat. KCl (40 mL), 1 N NaOH (3 × 40 mL) and 10 mM NaHCO₃ (3 × 40 mL) and dried over MgSO₄. The crude product was purified by column chromatography (silica, 2% methanol in dichloromethane) and

subsequently washed with methanol to yield the pure compound as a white solid material (0.70 g, 0.80 mmol, 51%). The product was characterized using chiral HPLC (isocratic, 10% isopropanol in hexane, purity based on UV > 99%). ¹H NMR (CDCl₃): δ = 7.98 (s, 1H, aromatic amide NH), 7.4–6.9 (m, 10H, Ar), 6.72 (s, 2H, *ortho*-H), 6.15 (d, 1H, *J* = 6.5 Hz, aliphatic amide NH), 4.96 (brd, 1H, carbamate NH), 4.76 (q, 1H, C_{α2}H), 4.08 (q, 1H, C_{α1}H), 4.0–3.8 (m, 6H, OCH₂), 3.26 + 2.80 (dd + dd, 2H, C_{α2}HCH₂Ar), 3.00 (m, 2H, C_{α1}HCH₂Ar), 1.8–1.2 (m, 45H, (CH₂)₆ [36H] + C(CH₃)₃ [9H]), 0.88 ppm (t, 9H, CH₃); ¹³C NMR (CDCl₃): δ = 171.4, 168.5, 155.8, 153.1, 136.4, 136.3, 135.3, 133.1, 129.6, 129.4, 129.0, 129.0, 127.4, 127.3, 99.9, 81.0, 73.6, 69.3, 57.2, 54.5, 37.7, 37.0, 32.0, 32.0, 30.4, 29.7, 29.5, 29.4, 28.3, 26.3, 26.2, 22.8, 22.8, 14.3 ppm; FT-IR (ATR): $\tilde{\nu}$ = 3289, 2922, 2852, 1691, 1648, 1602, 1527, 1506, 1428, 1388, 1367, 1297, 1229, 1168, 1129, 1116, 697 cm⁻¹; MALDI-TOF: *m/z*: calcd for: 871.61; found: 871.55 [*M*]⁺; elemental analysis calcd (%) for C₅₃H₈₁N₃O₇: C 72.98, H 9.36, N 4.82; found: C 73.00, H 9.36, N 4.80.

N^o-[3,4,5-Trioctyloxyphenyl]glycyl-L-phenylalaninamide (7a): Compound **6a** (0.48 g, 0.61 mmol) was dissolved in TFA (6 mL). The solution was purged with argon for 15 min, after which the mixture was stirred for another 45 min. The reaction mixture was concentrated in vacuo. A mixture of diethyl ether, 1 N NaOH and ice was added. The organic layer was washed with 1 N NaOH several times and dried over MgSO₄ to give the pure title compound (0.38 g, 0.56 mmol, 91%). ¹H NMR (CDCl₃): δ = 8.10 (s, 1H, aromatic amide NH), 7.91 (d, 1H, *J* = 7.5 Hz, aliphatic amide NH), 7.4–7.1 (m, 5H, Ar), 6.66 (s, 2H, *ortho*-H), 4.71 (q, 1H, C_{α1}H), 4.0–3.8 (m, 6H, OCH₂), 3.35 (m, 2H, NH₂CH₂CO), 3.18 (dd + dd, 2H, CH₂Ar), 1.9–1.2 (m, 38H, (CH₂)₆ [36H] + NH₂ [2H]), 0.89 ppm (t, 9H, CH₃); ¹³C NMR (CDCl₃): δ = 173.8, 169.0, 153.2, 137.0, 135.0, 133.3, 129.5, 129.4, 128.8, 127.1, 99.1, 73.6, 69.2, 55.3, 44.6, 37.7, 32.0, 32.0, 30.4, 29.7, 29.5, 29.4, 26.3, 26.2, 22.8, 22.8, 14.2 ppm; FT-IR (ATR): $\tilde{\nu}$ = 3272, 2922, 2854, 1647, 1602, 1533, 1506, 1466, 1427, 1388, 1230, 1116, 700 cm⁻¹; MALDI-TOF: *m/z*: calcd for: 681.51; found: 681.46 [*M*]⁺, 721.49 [*M*+K]⁺; elemental analysis calcd (%) for C₄₁H₆₇N₃O₅: C 72.21, H 9.90, N 6.16; found: C 71.48, H 9.80, N 6.16.

N^o-[3,4,5-Trioctyloxyphenyl]-L-phenylalanyl-L-phenylalaninamide (7b): Compound **6b** (0.27 g, 0.31 mmol) was dissolved in TFA (3 mL). The solution was purged with argon for 15 min, after which the mixture was stirred for another 45 min. The reaction mixture was concentrated in vacuo. A mixture of ethyl acetate, 1 N NaOH and some ice was added. The organic layer was washed with 1 N NaOH several times and dried over MgSO₄ to give the pure title compound (0.22 g, 0.29 mmol, 93%). ¹H NMR (CDCl₃): δ = 8.32 (s, 1H, aromatic amide NH), 7.97 (d, 1H, *J* = 4.4, aliphatic amide NH), 7.4–7.1 (m, 10H, Ar), 6.69 (s, 2H, *ortho*-H), 4.77 (q, 1H, C_{α2}H), 4.0–3.8 (m, 6H, OCH₂), 3.61 (d, 1H, *J* = 5.6 Hz, C_{α1}H), 3.23 + 3.11 (dd + dd, 2H, C_{α2}HCH₂Ar), 3.11 + 2.45 (dd + dd, 2H, C_{α1}HCH₂Ar), 1.9–1.2 (m, 38H, (CH₂)₆ [36H] + NH₂ [2H]), 0.88 ppm (m, 9H, CH₃); ¹³C NMR (CDCl₃): δ = 175.4, 168.9, 153.2, 136.8, 135.0, 133.3, 129.5, 129.3, 128.9, 128.8, 127.1, 99.1, 73.6, 69.2, 56.3, 55.2, 40.7, 37.7, 32.0, 32.0, 30.4, 29.7, 29.5, 29.4, 26.3, 26.2, 22.8, 22.8, 14.2 ppm; FT-IR (ATR): $\tilde{\nu}$ = 3283, 2954, 2923, 2855, 1644, 1605, 1539, 1506, 1467, 1455, 1428, 1387, 1231, 1116, 698 cm⁻¹; MALDI-TOF: *m/z*: calcd for: 771.55; found: 771.53 [*M*]⁺; elemental analysis calcd (%) for C₄₈H₇₃N₃O₅: C 74.67, H 9.53, N 5.44; found: C 73.78, H 9.45, N 5.54.

N^o-[3,4,5-Trioctyloxyphenyl]-D-phenylalanyl-L-phenylalaninamide (7c): Compound **6c** (0.30 g, 0.34 mmol) was dissolved in TFA (3.5 mL). The solution was purged with argon for 15 min, after which the mixture was stirred for another 45 min. The reaction mixture was concentrated in vacuo. A mixture of ethyl acetate, 1 N NaOH and some ice was added. The organic layer was washed with 1 N NaOH several times and dried over MgSO₄ to give the pure title compound (0.24 g, 0.31 mmol, 91%). ¹H NMR (CDCl₃): δ = 8.26 (s, 1H, aromatic amide NH), 7.90 (d, 1H, *J* = 7.6, aliphatic amide NH), 7.4–7.1 (m, 10H, Ar), 6.69 (s, 2H, *ortho*-H), 4.70 (q, 1H, C_{α2}H), 4.0–3.8 (m, 6H, OCH₂), 3.57 (m, 1H, C_{α1}H), 3.23 + 2.74 (m, 4H, CH₂Ar), 1.9–1.2 (m, 38H, (CH₂)₆ [36H] + NH₂ [2H]), 0.88 ppm (m, 9H, CH₃); ¹³C NMR (CDCl₃): δ = 175.5, 168.9, 153.2, 137.4, 137.0, 135.0, 133.3, 129.4, 129.3, 128.9, 128.9, 127.1, 99.1, 73.6, 69.2, 56.3, 55.4, 40.9, 37.3, 32.0, 32.0, 30.4, 29.7, 29.5, 29.4, 26.3, 26.2, 22.8, 14.2 ppm; FT-IR (ATR): $\tilde{\nu}$ = 3271, 2922, 2853, 1643, 1603, 1535, 1506, 1467, 1454,

1431, 1387, 1230, 1118, 698 cm^{-1} ; MALDI-TOF: m/z : calcd for: 771.55; found: 771.64 $[M]^+$; elemental analysis calcd (%) for $\text{C}_{48}\text{H}_{73}\text{N}_3\text{O}_5$: C 74.67, H 9.53, N 5.44; found: C 74.82, H 9.51, N 5.29.

$N^{\text{O}}, N^{\text{W}}, N^{\text{WW}}$ -(3,4,5-Triethoxyphenyl)-D-phenylalanyl-D-phenylalaninamide (7d): Compound **6d** (0.30 g, 0.34 mmol) was dissolved in TFA (3.5 mL). The solution was purged with argon for 15 min, after which the mixture was stirred for another 45 min. The reaction mixture was concentrated in vacuo. A mixture of ethyl acetate, 1N NaOH and some ice was added. The organic layer was washed with 1N NaOH several times and dried over MgSO_4 to give the pure title compound (0.24 g, 0.31 mmol, 91 %). ^1H NMR (CDCl_3): δ = 8.08 (s, 1H, aromatic amide NH), 7.93 (d, 1H, J = 7.6, aliphatic amide NH), 7.4–7.1 (m, 10H, Ar), 6.68 (s, 2H, *ortho*-H), 4.70 (q, 1H, $\text{C}_{\alpha 2}\text{H}$), 4.0–3.8 (m, 6H, OCH_2), 3.60 (m, 1H, $\text{C}_{\alpha 1}\text{H}$), 3.23 (m, 2H, $\text{C}_{\alpha 2}\text{HCH}_2\text{Ar}$), 3.11 + 2.45 (dd + dd, 2H, $\text{C}_{\alpha 1}\text{HCH}_2\text{Ar}$), 1.9–1.2 (m, 38H, $(\text{CH}_2)_6$ [36H] + NH_2 [2H]), 0.88 ppm (m, 9H, CH_3); ^{13}C NMR (CDCl_3): δ = 175.4, 168.9, 153.2, 137.4, 137.0, 135.0, 133.3, 129.5, 129.3, 128.9, 128.8, 127.1, 99.1, 73.6, 69.2, 56.3, 55.2, 40.7, 37.5, 32.0, 32.0, 30.4, 29.7, 29.5, 29.4, 26.3, 26.2, 22.8, 22.8, 14.2 ppm; FT-IR (ATR): $\tilde{\nu}$ = 3283, 2955, 2922, 2855, 1646, 1606, 1540, 1506, 1467, 1455, 1430, 1231, 1119, 698 cm^{-1} ; MALDI-TOF: m/z : calcd for: 771.55; found: 771.60 $[M]^+$; elemental analysis calcd (%) for $\text{C}_{48}\text{H}_{73}\text{N}_3\text{O}_5$: C 74.67, H 9.53, N 5.44; found: C 74.35, H 9.53, N 5.36.

$N^{\text{O}}, N^{\text{W}}, N^{\text{WW}}$ -(3,4,5-Triethoxyphenyl)-L-phenylalanyl-D-phenylalaninamide (7e): Compound **6e** (0.78 g, 0.90 mmol) was dissolved in TFA (9 mL). The solution was purged with argon for 15 min, after which the mixture was stirred for another 45 min. The reaction mixture was concentrated in vacuo. A mixture of ethyl acetate, 1N NaOH and some ice was added. The organic layer was washed with 1N NaOH several times and dried over MgSO_4 to give the pure title compound (0.49 g, 0.63 mmol, 71 %). ^1H NMR (CDCl_3): δ = 8.13 (s, 1H, aromatic amide NH), 7.90 (d, 1H, J = 7.6, aliphatic amide NH), 7.4–7.1 (m, 10H, Ar), 6.68 (s, 2H, *ortho*-H), 4.70 (q, 1H, $\text{C}_{\alpha 2}\text{H}$), 4.0–3.8 (m, 6H, OCH_2), 3.57 (m, 1H, $\text{C}_{\alpha 1}\text{H}$), 3.23 + 2.74 (m, 4H, CH_2Ar), 1.9–1.2 (m, 38H, $(\text{CH}_2)_6$ [36H] + NH_2 [2H]), 0.87 ppm (m, 9H, CH_3); ^{13}C NMR (CDCl_3): δ = 175.6, 168.9, 153.3, 137.3, 137.0, 135.1, 133.3, 129.4, 129.4, 128.9, 128.9, 127.1, 99.1, 73.6, 69.3, 56.3, 55.5, 40.8, 37.0, 32.0, 32.0, 30.4, 29.7, 29.5, 29.4, 26.3, 26.2, 22.8, 22.8, 14.2 ppm; FT-IR (ATR): $\tilde{\nu}$ = 3265, 2924, 2855, 1644, 1614, 1603, 1555, 1504, 1467, 1454, 1427, 1379, 1229, 1115, 698 cm^{-1} ; MALDI-TOF: m/z : calcd for: 771.55; found: 771.58 $[M]^+$; elemental analysis calcd (%) for $\text{C}_{48}\text{H}_{73}\text{N}_3\text{O}_5$: C 74.67, H 9.53, N 5.44; found: C 74.81, H 9.62, N 5.32.

$N^{\text{O}}, N^{\text{W}}, N^{\text{WW}}$ -(1,3,5-Benzenetricarbonyl)-tris($N^{\text{O}}, N^{\text{W}}, N^{\text{WW}}$ -(3,4,5-triethoxyphenyl)-glycyl-L-phenylalaninamide (8a): A solution of 1,3,5-benzenetricarbonyl trichloride (45.4 mg, 0.17 mmol) in dry THF (1.7 mL) was added dropwise to a solution of **7a** (0.39 g, 0.57 mmol) and triethylamine (0.2 mL, 1.43 mmol) in dry THF (5 mL). After stirring overnight and evaporation of THF, the product was purified using column chromatography (silica, THF/hexane 2:1). Subsequently, the product was recrystallized from a mixture of THF/methanol 2:3 to yield the title compound as a white solid material (0.12 g, 0.05 mmol, 32 %). The product was characterized using GPC (THF, 260 nm, purity based on UV $\approx$ 100 %). ^1H NMR ($[\text{D}_6]\text{DMSO}$, T = 323 K): δ = 9.71 (s, 3H, NH''), 8.78 (t, 3H, NH), 8.48 (s, 3H, *ortho*-H), 8.18 (d, 3H, J = 7.5 Hz, NH'), 7.3–7.1 (m, 15H, Ar), 6.91 (s, 6H, *ortho*-H'), 4.66 (q, 3H, $\text{C}_{\alpha}\text{H}$), 4.0–3.7 (m, 24H, NHCH_2CO [6H] + OCH_2 [18H]), 3.1 + 2.9 (m, 6H, CH_2Ar), 1.8–1.0 (m, 108H, $(\text{CH}_2)_6$), 0.85 ppm (t, 27H, CH_3); ^{13}C NMR ($[\text{D}_6]\text{DMSO}$, T = 323 K): δ = 169.2, 168.4, 165.5, 152.1, 137.3, 134.3, 134.1, 133.6, 128.9, 127.8, 126.1, 98.6, 72.3, 68.2, 54.6, 42.6, 37.5, 31.0, 31.0, 29.6, 28.7, 28.6, 28.5, 28.4, 25.4, 25.3, 21.8, 21.8, 13.6 ppm; FT-IR (ATR): $\tilde{\nu}$ = 3280, 2923, 2854, 1651, 1604, 1536, 1506, 1467, 1428, 1386, 1228, 1116, 699 cm^{-1} ; MALDI-TOF: m/z : calcd for: 2200.51; found: 2200.36 $[M]^+$; 2223.38 $[M+\text{Na}]^+$; elemental analysis calcd (%) for $\text{C}_{132}\text{H}_{201}\text{N}_9\text{O}_{18}$: C 72.00, H 9.20, N 5.72; found: C 71.41, H 9.22, N 5.77.

$N^{\text{O}}, N^{\text{W}}, N^{\text{WW}}$ -(1,3,5-Benzenetricarbonyl)-tris($N^{\text{O}}, N^{\text{W}}, N^{\text{WW}}$ -(3,4,5-triethoxyphenyl)-L-phenylalanyl-L-phenylalaninamide (8b): A solution of 1,3,5-benzenetricarbonyl trichloride (33.4 mg, 0.13 mmol) in dry THF (1.3 mL) was added dropwise to a solution of **7b** (0.30 g, 0.39 mmol) and triethylamine (0.1 mL, 0.7 mmol) in dry dichloromethane (4 mL). After stirring overnight the reaction mixture was filtered to yield the title compound as an

off-white solid material (0.19 g, 0.07 mmol, 59 %). ^1H NMR ($[\text{D}_6]\text{DMSO}$, T = 323 K): δ = 9.74 (s, 3H, NH''), 8.60 (d, 3H, J = 8.0 Hz, NH), 8.24 (s, 3H, *ortho*-H), 8.16 (d, 3H, J = 7.5 Hz, NH'), 7.3–7.0 (m, 30H, Ar), 6.87 (s, 6H, *ortho*-H'), 4.79 (q, 3H, $\text{C}_{\alpha}\text{H}$), 4.69 (q, 3H, $\text{C}_{\alpha 2}\text{H}$), 4.0–3.7 (m, 18H, OCH_2), 3.1 + 2.9 (m, 12H, CH_2Ar), 1.8–1.0 (m, 108H, $(\text{CH}_2)_6$), 0.84 ppm (t, 27H, CH_3); ^{13}C NMR ($[\text{D}_6]\text{DMSO}$, T = 323 K): δ = 170.6, 169.1, 165.2, 152.1, 137.7, 137.1, 134.2, 134.1, 133.6, 128.9, 127.8, 126.1, 125.9, 98.6, 72.3, 68.2, 54.6, 37.5, 37.0, 31.0, 31.0, 29.6, 28.6, 28.5, 28.4, 25.3, 21.8, 13.5 ppm; FT-IR (ATR): $\tilde{\nu}$ = 3273, 2923, 2854, 1639, 1603, 1532, 1506, 1467, 1455, 1428, 1387, 1230, 1117, 697 cm^{-1} ; MALDI-TOF: m/z : calcd for: 2471.65; found: 2471.78 $[M]^+$, 2494.75 $[M+\text{Na}]^+$, 2511.73 $[M+\text{K}]^+$; elemental analysis calcd (%) for $\text{C}_{153}\text{H}_{219}\text{N}_9\text{O}_{18}$: C 74.33, H 8.93, N 5.10; found: C 74.06, H 8.94, N 5.04.

$N^{\text{O}}, N^{\text{W}}, N^{\text{WW}}$ -(1,3,5-Benzenetricarbonyl)-tris($N^{\text{O}}, N^{\text{W}}, N^{\text{WW}}$ -(3,4,5-triethoxyphenyl)-D-phenylalanyl-L-phenylalaninamide (8c): A solution of 1,3,5-benzenetricarbonyl trichloride (30.0 mg, 0.11 mmol) in dichloromethane (1.2 mL) was added dropwise to a solution of **7c** (0.29 g, 0.37 mmol) and triethylamine (0.1 mL, 0.7 mmol) in dry dichloromethane (3.5 mL). After stirring overnight and evaporation of the dichloromethane, the compound was separated from the crude mixture using column filtration (silica, 2 % methanol in dichloromethane). Subsequently, reflux in methanol for 30 min and filtration afforded the product as a white solid in pure form (0.20 g, 0.08 mmol, 71 %). The product was characterized using GPC (THF, 260 nm, purity based on UV > 99 %). ^1H NMR ($[\text{D}_6]\text{DMSO}$, T = 373 K): δ = 9.43 (s, 3H, NH''), 8.27 (d, 3H, J = 8.5 Hz, NH), 8.18 (s, 3H, *ortho*-H), 8.03 (d, 3H, J = 7.5 Hz, NH'), 7.3–7.0 (m, 30H, Ar), 6.88 (s, 6H, *ortho*-H'), 4.77 (q, 3H, $\text{C}_{\alpha}\text{H}$), 4.69 (q, 3H, $\text{C}_{\alpha 2}\text{H}$), 4.0–3.7 (m, 18H, OCH_2), 3.1–2.9 (m, 12H, CH_2Ar), 1.8–1.0 (m, 108H, $(\text{CH}_2)_6$), 0.84 ppm (t, 27H, CH_3); ^{13}C NMR ($[\text{D}_6]\text{DMSO}$, T = 373 K): δ = 170.2, 168.7, 165.0, 151.9, 137.2, 136.9, 134.3, 134.1, 133.6, 128.5, 128.4, 128.1, 127.3, 125.6, 125.5, 99.5, 72.1, 68.5, 54.6, 54.2, 37.4, 37.0, 30.6, 30.5, 29.2, 28.4, 28.2, 28.0, 28.0, 25.0, 25.0, 21.3, 21.3, 13.0 ppm; FT-IR (ATR): $\tilde{\nu}$ = 3267, 2954, 2922, 2854, 1640, 1603, 1536, 1505, 1467, 1455, 1430, 1388, 1231, 1117, 697 cm^{-1} ; MALDI-TOF: m/z : calcd for: 2471.65; found: 2471.88 $[M]^+$, 2494.94 $[M+\text{Na}]^+$, 2510.92 $[M+\text{K}]^+$; elemental analysis calcd (%) for $\text{C}_{153}\text{H}_{219}\text{N}_9\text{O}_{18}$: C 74.33, H 8.93, N 5.10; found: C 74.35, H 8.87, N 4.90.

$N^{\text{O}}, N^{\text{W}}, N^{\text{WW}}$ -(1,3,5-Benzenetricarbonyl)-tris($N^{\text{O}}, N^{\text{W}}, N^{\text{WW}}$ -(3,4,5-triethoxyphenyl)-D-phenylalanyl-D-phenylalaninamide (8d): A solution of 1,3,5-benzenetricarbonyl trichloride (5.8 mg, 21.8 μmol) in dichloromethane (0.2 mL) was added dropwise to a solution of **7d** (52.6 mg, 68.1 μmol) and triethylamine (20 μL , 143 μmol) in dry dichloromethane (0.7 mL). After stirring overnight the reaction mixture was filtered to yield the title compound as an off-white solid material (20 mg, 8.09 μmol , 37 %). ^1H NMR ($[\text{D}_6]\text{DMSO}$, T = 323 K): δ = 9.75 (s, 3H, NH''), 8.61 (d, 3H, J = 8.0 Hz, NH), 8.24 (s, 3H, *ortho*-H), 8.18 (d, 3H, J = 8.0 Hz, NH'), 7.3–7.0 (m, 30H, Ar), 6.87 (s, 6H, *ortho*-H'), 4.79 (q, 3H, $\text{C}_{\alpha}\text{H}$), 4.69 (q, 3H, $\text{C}_{\alpha 2}\text{H}$), 4.0–3.7 (m, 18H, OCH_2), 3.1–2.9 (m, 12H, CH_2Ar), 1.8–1.0 (m, 108H, $(\text{CH}_2)_6$), 0.84 ppm (t, 27H, CH_3); ^{13}C NMR ($[\text{D}_6]\text{DMSO}$, T = 323 K): δ = 170.6, 169.0, 165.2, 152.1, 137.7, 137.0, 134.2, 134.1, 133.6, 128.9, 128.9, 127.8, 127.8, 126.1, 125.9, 98.6, 72.3, 68.2, 54.6, 37.6, 37.0, 31.0, 31.0, 29.5, 28.6, 28.6, 28.5, 28.4, 25.3, 25.3, 21.8, 21.8, 13.5 ppm; FT-IR (ATR): $\tilde{\nu}$ = 3275, 2923, 2855, 1639, 1603, 1532, 1506, 1467, 1455, 1428, 1387, 1230, 1116, 697 cm^{-1} ; MALDI-TOF: m/z : calcd for: 2471.65; found: 2471.78 $[M]^+$, 2494.75 $[M+\text{Na}]^+$; elemental analysis calcd (%) for $\text{C}_{153}\text{H}_{219}\text{N}_9\text{O}_{18}$: C 74.33, H 8.93, N 5.10; found: C 74.15, H 8.95, N 4.94.

$N^{\text{O}}, N^{\text{W}}, N^{\text{WW}}$ -(1,3,5-Benzenetricarbonyl)-tris($N^{\text{O}}, N^{\text{W}}, N^{\text{WW}}$ -(3,4,5-triethoxyphenyl)-L-phenylalanyl-D-phenylalaninamide (8e): A solution of 1,3,5-benzenetricarbonyl trichloride (44.2 mg, 0.17 mmol) in dichloromethane (1.7 mL) was added dropwise to a solution of **7e** (0.43 g, 0.56 mmol) and triethylamine (0.16 mL, 1.15 mmol) in dry dichloromethane (5 mL). After stirring overnight and evaporation of the dichloromethane, the product was purified using column chromatography (silica, 2 % methanol in dichloromethane) and subsequently washed with acetonitrile to yield the title compound as an off-white solid material (0.23 g, 0.09 mmol, 55 %). The product was characterized using GPC (THF, 260 nm, purity based on UV $\approx$ 100 %). ^1H NMR ($[\text{D}_6]\text{DMSO}$, T = 373 K): δ = 9.43 (s, 3H, NH''), 8.27 (d, 3H, J = 8.0 Hz, NH), 8.18 (s, 3H, *ortho*-H), 8.03 (d, 3H, J = 6.5 Hz,

NH'), 7.3–7.0 (m, 30H, Ar), 6.88 (s, 6H, *ortho*-H'), 4.77 (q, 3H, C₆₁H), 4.69 (q, 3H, C₆₂H), 4.0–3.7 (m, 18H, OCH₂), 3.1–2.9 (m, 12H, CH₂Ar), 1.8–1.0 (m, 108H, (CH₂)₆), 0.84 ppm (t, 27H, CH₃); ¹³C NMR ([D₆]DMSO, T = 373 K): δ = 170.2, 168.7, 165.0, 152.0, 137.2, 136.9, 134.3, 134.2, 133.6, 128.6, 128.5, 128.1, 127.4, 125.7, 125.6, 99.6, 72.1, 68.5, 54.6, 54.2, 37.4, 37.1, 30.6, 30.5, 29.2, 28.4, 28.2, 28.1, 28.0, 28.0, 25.0, 25.0, 21.3, 21.3, 13.0 ppm; FT-IR (ATR): $\tilde{\nu}$ = 3276, 2923, 2854, 1640, 1603, 1537, 1505, 1467, 1455, 1429, 1387, 1230, 1116, 697 cm⁻¹; MALDI-TOF: *m/z*: calcd for: 2471.65; found: 2471.05 [M]⁺, 2494.07 [M+Na]⁺; elemental analysis calcd (%) for C₁₅₃H₂₁₉N₉O₁₈: C 74.33, H 8.93, N 5.10; found: C 73.72, H 8.85, N 4.87.

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