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Enhanced gelation property due to intra-molecular hydrogen bonding in a new series of bis(amino acid)-functionalized pyridine-2,6-dicarboxamide organogelators

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Abstract—A series of pyridine-2,6-dicarboxamide derivatives containing two α-amino acid pendant groups was prepared and characterized. Three of the synthesized compounds obtained from this series, all having aromatic amino acid side chains, were found to be excellent organogelators toward aromatic solvents (mgc∼10–20 mg/mL), alcoholic solvents (mgc∼4–15 mg/mL), and CCl_4 (mgc∼4–10 mg/mL). It was found that the intra-molecular hydrogen bonds between the pyridine dicarboxamide N–Hs and the pyridine N atom were the key structural elements for gel formation. This series of compounds represented one of the rare examples where both inter- and intra-molecular hydrogen bonds were needed for effective gel formation. FTIR, ^{1}H NMR, and CD spectroscopy revealed that both hydrogen bonding and π–π aromatic stacking were the driving forces for gelation.

1. Introduction

The gelation of organic solvents by low molecular weight organic compounds is one of the most intriguing self assembly processes in chemistry.[1] Gelation is typified by the formation of a stable three dimensional, non-covalent network structure through the intricate interactions (e.g., ionic, hydrogen bonding, π–π stacking and/or the hydrophobic effect) between the gelator–gelator, gelator–solvent, and solvent–solvent molecules. To a certain extent, the gelation power of a gelator depends mainly on gelator–gelator and gelator–solvent interactions. While the gelator–solvent interaction is sometimes difficult to assess or quantify, gelator–gelator interactions have been frequently and successfully used as the principal driving force to explain the gelation mechanism.[1a] It has been rationalized that the inter-molecular interactions between the many gelator molecules have to be delicately balanced in such a way that their crystallization/precipitation as a result of exceedingly strong inter-molecular interaction, or dissolution because of extremely weak interaction, can be prevented. The other major factor that controls the crystallization process, in addition to inter-molecular interactions, is the crystal packing of the gelator molecules. In order to avoid crystallization, structurally flexible units are generally used to create disorder in the crystal packing and to prevent the gelator from precipitation in the gelled state. It is therefore not surprising to find that many strong organogelators are found to possess branching or non-branching long chain alkyl groups (≥8 carbon atoms) in part of their structures.[2,3]

Among the various driving forces for gelation, inter-molecular hydrogen bonding is highly directional and energetically stronger than π–π stacking and hydrophobic interactions. It is actually one of the major driving forces in the gelation of carbohydrate-,[4] nucleic acid-,[1f] and amino acid-based gelators.[1e] What is not often observed, however, is the presence of intra-molecular hydrogen bonding in a gelator molecule. As anticipated, the presence of intra-molecular hydrogen bonding in a gelator molecule would invariably lead to greater structural rigidity, and consequently better crystallinity, and a higher tendency toward precipitation. Here we wish to report an unusual finding that intra-molecular hydrogen bonding can actually be a pre-requisite structural element for effective gel formation in a series of bis(amino acid)-functionalized[3,5] pyridine-2,6-dicarboxamide organogelator molecules **1**.

The amino acid gelator molecules **1** were accidentally found during our ongoing investigative work on the structural diversity and conformational property of amino acid-based dendrons. Our group recently reported a library of α-amino acid-based dendrons **2**[6] and β-alanine-based dendrimers[7] (e.g., **3**) and showed that they self-assembled to form

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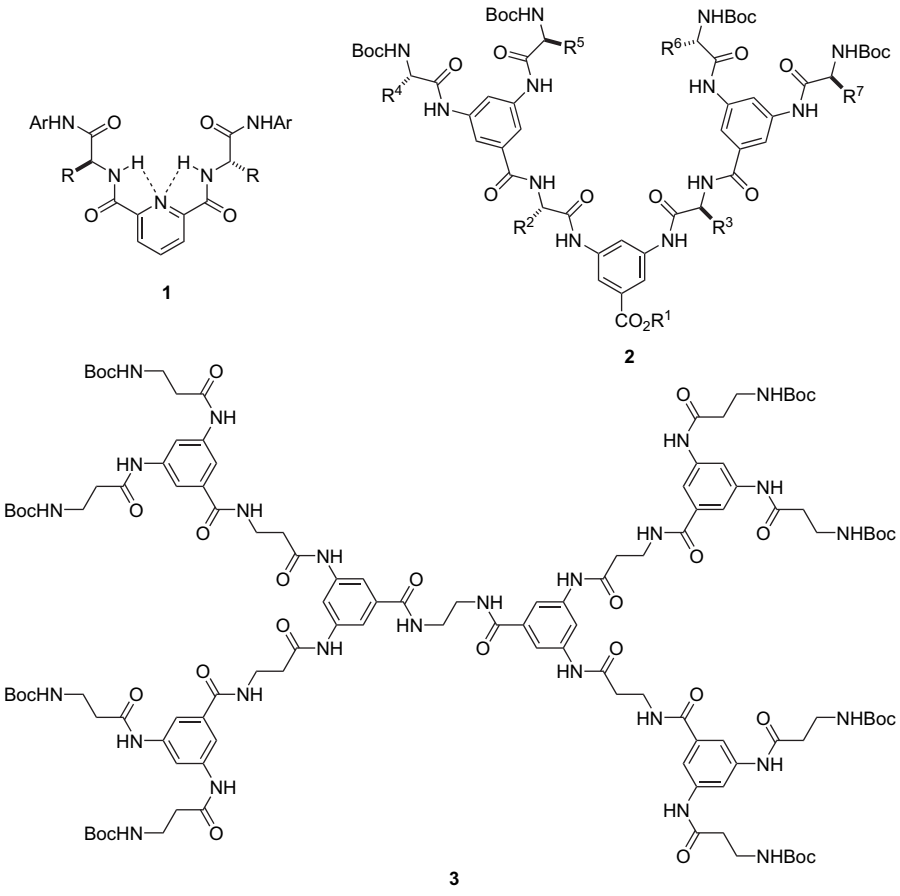
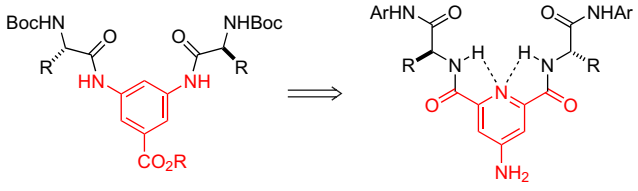


aggregates in many organic solvents. Furthermore, the α-amino acid-based dendrons **2**, bearing different amino acid moieties within the dendritic skeleton, were found to be powerful organogelators with minimum gelation concentration (mgc) as low as 2 mg/mL. We also demonstrated that their gelation strength was strongly dependent on the nature of the focal point functionality (i.e., R^1) and the amino acid side chain residues (i.e., R^2–R^7). Despite the presence of many hydrogen bonding amide functionalities, these compounds were shown to be devoid of higher order secondary structure in polar solvents. Inspired by the work of Parquette,[8] we decided to introduce conformational rigidity into our α-amino acid-based dendrons **2** by replacing the 3,5-diaminobenzamide branching unit with a 4-aminopyridine-2,6-dicarboxamide unit (Scheme 1). The latter functional moiety was known to exist predominantly in the *syn–syn* conformation due to the formation of two intramolecular hydrogen bonds of the carboxamide N–Hs with the pyridine N atom. In a pilot study, a series of G1 α-amino acid-based pyridine-2,6-dicarboxamides **1** was prepared as model compounds to examine their conformational behavior.[9] As expected, the conformational rigidity of the two carboxamide groups was instilled into the system and was confirmed by spectroscopic studies. However, as reported in this paper, to our surprise, these derivatives **1** still maintained their powerful gelation ability in many organic solvents. Furthermore, it was found that the gelation ability disappeared if the two intra-molecular hydrogen bonds were removed from the system. Hence, the target bis(amino acid) functionalized pyridine-2,6-dicarboxamides **1** constitute a rare class of organogelator, which requires both intra- and inter-molecular hydrogen bonding for effective gel formation.[10] The gelation mechanism, as well as the morphology of the resulting organogels was examined by various spectroscopic techniques.



Scheme 1. Modification of central core.

2. Results and discussion

2.1. Synthesis

The general synthetic route to the target compounds **1**-aa bearing different amino acid pendant chains (Table 1) was shown in Scheme 2. Boc-protected or Cbz-protected amino acids **4**-aa were coupled to 3,5-dimethylaniline in the presence of 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ) to give the corresponding protected amino amides **5**-aa in 65–92% yield. The Boc- and Cbz-protecting groups were then removed by trifluoroacetic acid (TFA), or catalytic hydrogenolysis, respectively, to furnish the diamino esters **6**-aa. Finally, coupling of **6**-aa with pyridine-2,6-dicarboxylic acid in the presence of EEDQ gave the target compounds **1**-aa in yields ranging from 58 to 79% (overall yield from amino

Table 1. List of target organogelators

Compound	R
1-Gly	H
1-Ala	Me
1-Val	*i*-Pr
1-Leu	CH_2(*i*-Pr)
1-Phe	Bn
1-Asp β-benzyl ester	CH_2CO_2Bn
1-Tyr	$CH_2C_6H_4OH$
1-Ser	CH_2OH
1-Asn	CH_2CONH_2
1-Pro	—[a]

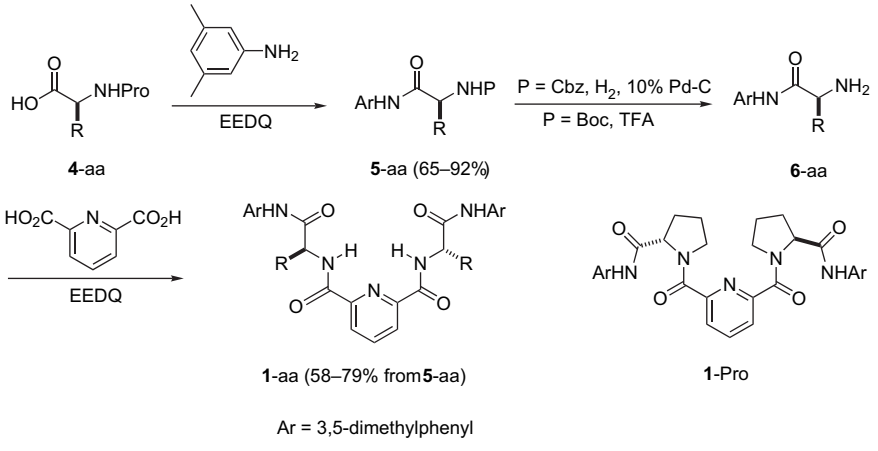
[a] For structure see Scheme 2.

amide **5**-aa). The proline derived compound **1**-Pro, having a backbone structure that was very different from the other amino acid derived target compounds, was synthesized in a similar manner in overall 39% yield from Cbz-proline.

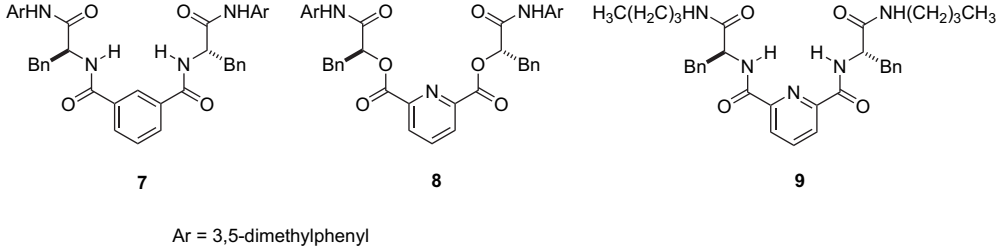
We also prepared three phenylalanine derived structural analogues **7**–**9** in order to investigate the structural requirements for optimal gelation. Compound **7** has the central pyridine ring replaced by a phenyl ring. For compound **8**, the linkages between the amino acid pendant groups and the pyridine ring are replaced by an ester instead of an amide functionality. We also prepared compound **9** in order to examine the effect of the amide functionality at the amino acid carboxyl end on gelation by replacing the *N*-(3,5-dimethylphenyl) groups with *N*-butyl groups. The synthetic routes for these compounds were very similar to those described for compounds **1** except that the more reactive 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide methiodide (EDCI) was used as the coupling reagent for the synthesis of compound **8**. The synthetic details are given in Section 4.

2.2. Characterization

2.2.1. NMR spectroscopy. The structural identities of all intermediates and target compounds were characterized by ^{1}H and ^{13}C NMR spectroscopy. Due to the poor solubility of some of the target compounds, their NMR spectra were recorded in DMSO-d_6 solution. The ^{1}H NMR spectra of the organogelators were found to possess three characteristic features. One was a set of invariable C–H signals originating from the common pyridine-2,6-dicarboxamide central core and two anilide functionalities at the amino acid carboxyl end (Fig. 1). The second was the signals due to the N–H protons of the pyridine-2,6-dicarboxamide and the anilide functionalities, which varied slightly in chemical shift values according to the nature of the amino acid side chain. While the anilide N–H signals were located at the expected chemical shift region (δ 8.4–8.6 in $CDCl_3$; δ 10.0–10.1 in DMSO-d_6), the amide N–H signals were significantly downfield shifted (δ 8.3–8.7 in $CDCl_3$; δ 9.0–9.8 in DMSO-d_6), indicating that they were hydrogen bonded to the pyridine N atom. This finding was consistent with data reported in the literature.[8,9] Finally, the third characteristic feature was a set of variable 'fingerprint' signals due to the protons originating from the different amino acid side chains. For example, the ^{1}H NMR spectrum of compound **1**-Val showed the presence of the isopropyl side chain as a doublet at δ 1.17 and a multiplet at δ 2.40–2.49. Likewise, the 'feature' signals of **1**-Asn were found at δ 2.82 (CH_2), 4.94 (CH), 7.07 ($CONH_2$), and 7.60 ($CONH_2$). Compound **1**-Pro, due to the absence of the carboxamide N–Hs and hence the removal of conformational locking by intra-molecular hydrogen bonds, existed as a mixture of rotamers as shown by ^{1}H NMR study.



Scheme 2. General synthetic routes to target organogelators **1**.



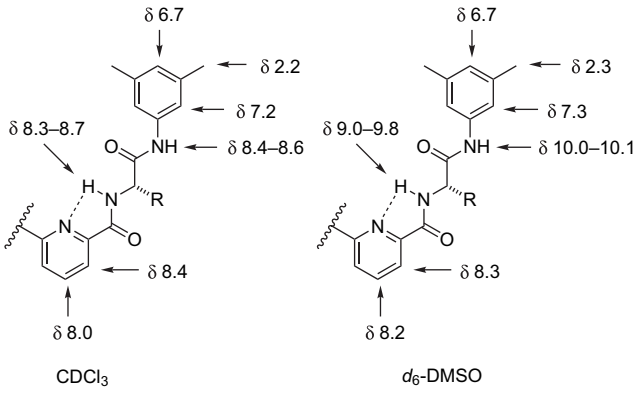


Figure 1. ^{1}H NMR spectral features of the target organogelators.

The ^{1}H NMR spectrum of **1**-Asp β-benzyl ester deserves additional comments, as the carboxamide N–H signal was even further downfield shifted to δ 9.47 ($CDCl_3$) due to the presence of extra intra-molecular hydrogen bonding interactions with the carboxyl oxygen atoms of the β-benzyl esters (Fig. 2). Furthermore, this doublet signal remained at the same position (δ 9.47) over a concentration range of 0.7–44.6 mM in $CDCl_3$. On the other hand, the chemical shift value of the corresponding amide N–Hs of the benzene-1,3-dicarboxamide analogue **7**, due to an absence of intra-molecular hydrogen bonding, was upfield shifted to δ 8.89 (DMSO-d_6). ^{1}H NMR titration study of a $CDCl_3$ solution of **1**-Asp β-benzyl ester with DMSO-d_6 revealed the presence of two N–Hs of different microenvironments. The carboxamides N–Hs (H_a) that were hydrogen bonded to the pyridine N experienced little change of chemical shift ($\Delta\delta<0.05$) upon addition of the hydrogen bond acceptor solvent DMSO-d_6, indicating that they formed very stable intra-molecular hydrogen bonds. However, the chemical shift values of the anilide N–Hs (H_b) showed significant downfield shifts upon addition of DMSO-d_6, suggesting that the initially non-hydrogen bonded H_bs began to form intermolecular hydrogen bonds in the presence of acceptor solvent molecules.

The ^{13}C NMR spectra of the target compounds also shared a common spectral feature; the chemical shift values of the carbon nuclei due to the common backbone skeleton were nearly the same. Hence, the carbon signals of the pyridine ring were found to be situated between δ 124 and 149 ppm, while the aromatic carbon signals of the 3,5-dimethylanilide moiety were found between δ 116 and 139 ppm. Two sets of C=O signals, located at $\sim\delta$ 164 and 170 were found. Similar to the ^{1}H NMR spectroscopic analysis, the chemical identities of the amino acid side chains could also be ascertained by their respective 'fingerprint' ^{13}C NMR signals.

2.2.2. Mass spectrometric analysis. The structures of the gelators were characterized by fast atom bombardment (FAB) mass spectroscopy or secondary ion mass spectrometry (L-SIMS). In addition to molecular ions in the form of M^+ or $(M+H)^+$, dimeric M_2^+ or $(M_2+H)^+$ ions were also found (Fig. 3), suggesting the presence of molecular aggregates in the solution state. The exact mass of the molecular ion peak matched well with the theoretical value.

2.3. Gelation properties

As described earlier, the target compounds were prepared to investigate their conformational behavior. It was therefore unexpected to find them capable of forming gels with organic solvents, particularly in view of their relatively rigid structures as compared to the 3,5-diaminobenzoic acid derived organogelators.[5e,6] Nonetheless, their gelation properties were subsequently revealed and therefore examined in various solvents (Table 2). Among the many amino acid derivatives, those containing aromatic side chain such as **1**-Phe and **1**-Asp β-benzyl ester were the best organogelators. The remaining compounds were either too soluble or too insoluble in the solvent system and some of them precipitated from solution after cooling. In particular, those carrying highly hydrophilic side chains, such as **1**-Asn and **1**-Ser were poorly soluble. It was of interest to note that **1**-Tyr, even though it possessed two aromatic side chains, was a poor organogelator. This was probably due to the two extra phenolic groups that increased its tendency to precipitate from solution. Similar to the 3,5-diaminobenzoic acid dendritic organogelators, strong gels were formed from **1**-Phe and **1**-Asp β-benzyl ester in aromatic solvents (Fig. 4). Although

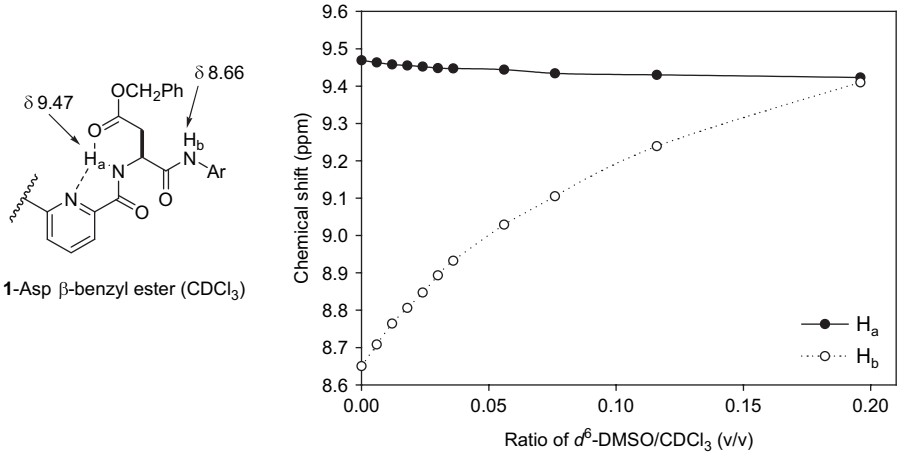


Figure 2. (Left) ^{1}H NMR data of the N–Hs in **1**-Asp β-benzyl ester. (Right) DMSO-d_6 ^{1}H NMR titration study of **1**-Asp β-benzyl ester (c=32 mM) in $CDCl_3$ at 25 °C.

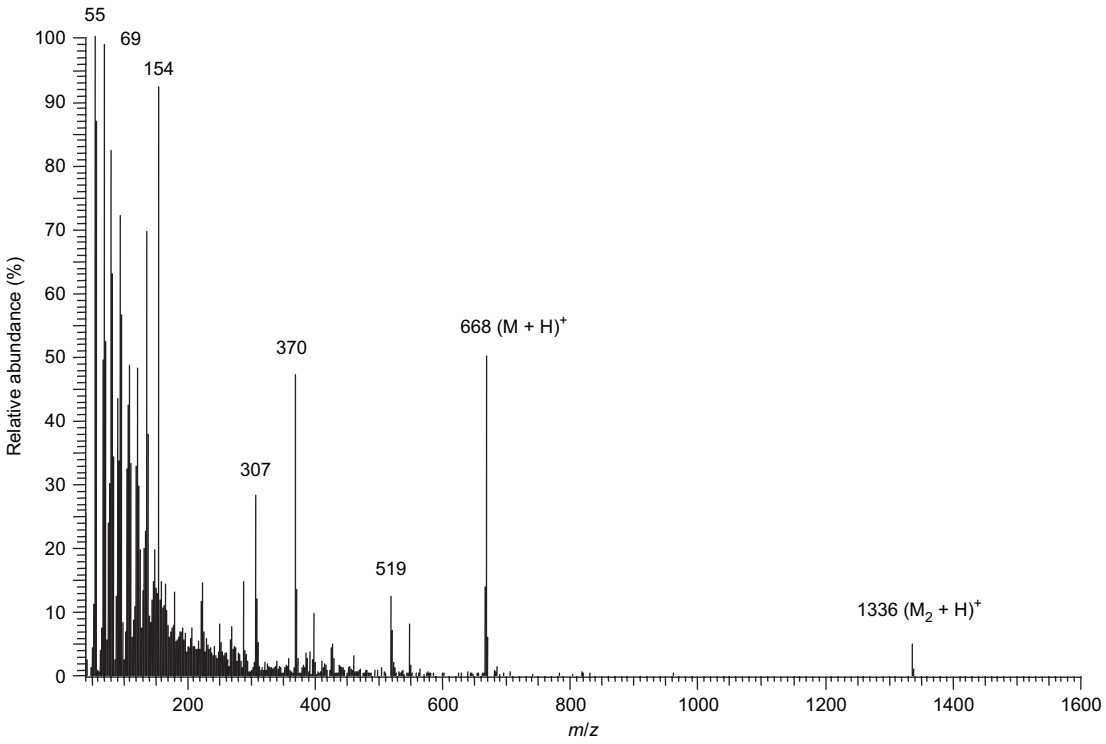


Figure 3. FAB mass spectrum of compound **1**-Phe.

Table 2. Gelation properties of organogelators in various solvents[a]

Solvent	**1**-Gly	**1**-Ala	**1**-Val	**1**-Leu	**1**-Phe	**1**-Asp β-benzyl ester	**1**-Tyr	**1**-Ser	**1**-Asn	**1**-Pro	**7**	**8**	**9**
Hexane	I	I	I	I	I	I	I	I	I	I	I	I	I
MeOH	P	P	P	P	P	P	P	I	I	P	P	P	P
EtOH	I	P	P	P	G (15)	G (4)	P	I	I	S	P	P	G (15)
i-PrOH	I	P	P	P	G (15)	G (8)	P	I	I	S	P	P	G (15)
CCl_4	I	P	P	P	G (10)	G (4)	P	I	I	P	P	P	G (10)
$CHCl_3$	P	P	S	P	S	S	I	I	I	S	P	P	S
Et_2O	I	I	I	I	I	I	I	I	I	I	I	I	I
THF	P	S	S	S	S	S	P	P	I	S	S	S	S
Acetone	I	S	S	P	S	S	P	I	I	S	S	P	S
Benzene	I	P	P	P	G (10)	G (10)	P	I	I	P	P	P	G (15)
Toluene	I	P	P	P	G (10)	G (10)	P	I	I	P	P	P	G (15)
m-Xylene	I	P	P	P	G (10)	G (10)	P	I	I	P	P	P	G (15)
p-Xylene	I	P	P	P	G (10)	G (10)	P	I	I	P	P	P	G (15)
Anisole	P	P	P	P	G (20)	G (20)	P	P	I	S	P	P	G (20)
o-DCB[b]	I	P	G (20)	P	G (20)	G (20)	P	P	I	S	P	P	G (20)
$C_6H_5NO_2$	P	P	P	P	P	P	P	P	P	S	P	S	P

[a] G=transparent gel; I=insoluble; P=precipitation; S=soluble. The values given in parentheses are the minimum concentration (mg/mL) to achieve gelation at 25 °C.
[b] *o*-Dichlorobenzene.

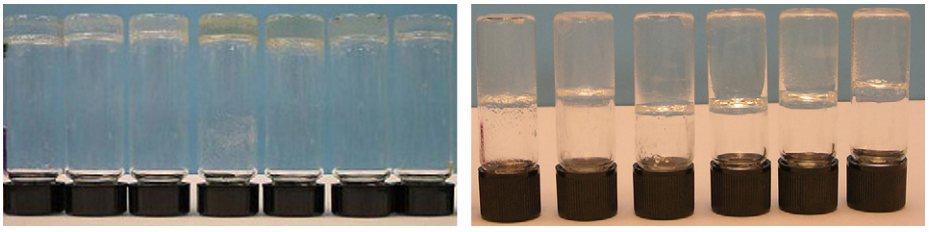


Figure 4. (Left) Transparent gels of **1**-Phe at 20 mg/mL in various solvents (from left to right): *p*-xylene, *m*-xylene, toluene, anisole, *o*-dichlorobenzene, ethanol, and 2-propanol. (Right) Transparent gels of **1**-Asp β-benzyl ester at 20 mg/mL in various solvents (from left to right): ethanol, 2-propanol, CCl_4, toluene, *m*-xylene, and *p*-xylene.

their mgc values were slightly inferior (~10–20 mg/mL) as compared to the 3,5-diaminobenzoic analogues, they exhibited a wider gelation solvent spectrum, as very strong gels (mgc=4–10 mg/mL) were also formed in CCl_4 and alcoholic solvents such as ethanol and 2-propanol.

It was interesting to note that, compound **7**, having the carboxamide linkages replaced by ester linkages, and compound **8**, having the pyridine ring replaced by a phenyl ring, were both poor organogelators. Both of these compounds still contained the phenylalanine side chain, but were devoid of gelating power. It was therefore concluded that the intra-molecular hydrogen bonds between the carboxamide N–Hs and the pyridine N were extremely important in conferring the gelation power. In other words, an increase in structural rigidity actually enhanced the gelation property of this class of bis(amino acid)-functionalized organogelators.

Table 3. FTIR data of **1**-Phe in $CHCl_3$ solution, *p*-xylene gels, and KBr disc[a]

Physical states	Absorption (cm^{-1})[b]			
	$\nu_{anilide\ N-H}$	$\nu_{carboxamide\ N-H}$	$\nu_{anilide\ C=O}$	$\nu_{carboxamide\ C=O}$
$CHCl_3$ solution (15 mM)	3412	3305	1686	1666
p-Xylene gel (20 mg/mL)	3406	3275	1669	
Solid (KBr disc)	3390	3308	1662	

[a] All spectra were recorded at 25 °C.
[b] Peak assignments were made based on the IR spectral data of compound **8** and *N*2,*N*6-dibenzylpyridine-2,6-dicarboxamide.

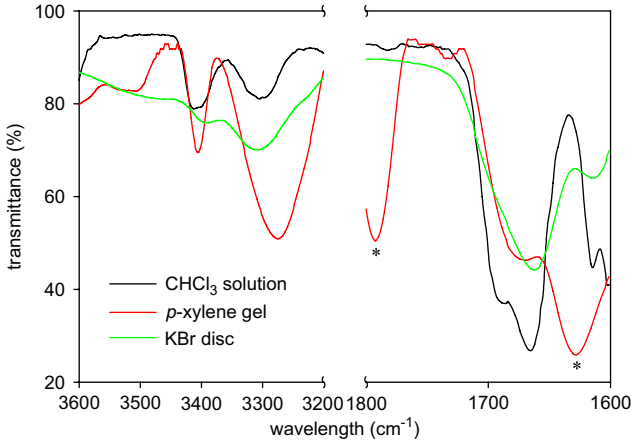


Figure 5. FTIR spectra of **1**-Phe in different physical states (peaks with an asterisk are due to *p*-xylene absorption).

Replacing the 3,5-dimethylanilide aromatic rings at the carboxyl termini, however, did not seem to have any apparent effect on the gelation behavior. Compound **9**, containing simple *N*-butyl pendant groups at the amino acid carboxyl ends, also formed transparent gels with comparable mgc values and similar solvent specificities. Apparently this is a structural motif where wider structural varieties could be accommodated without hampering the gelating ability.

2.4. Gelation mechanism

2.4.1. Infra-red spectroscopy. The gelation mechanism of the organogelators was investigated by infra-red (FTIR), NMR, and circular dichroism (CD) spectroscopy. The solution FTIR spectrum of **1**-Phe exhibited two N–H and two C=O peaks (Table 3 and Fig. 5). Upon gelation in *p*-xylene (20 mg/mL), the two N–H peaks were red-shifted by about 6 and 30 cm^{-1}. Incidentally, the two C=O peaks merged into one single broader peak at 1669 cm^{-1}. This value represented a red shift of 17 cm^{-1} with respect to the anilide C=O signal. Similar findings were also noted for the solid state KBr sample of compound **1**-Phe. Hence, there was strong evidence that hydrogen bonding was involved in gel formation.

2.4.2. NMR spectroscopy. Monitoring the change of chemical shift values by variation of the temperature could provide valuable information on the organization of the gelators in the gel network. Hence, the ^1H NMR spectra of **1**-Phe in toluene-d_8 (c=20 mg/mL) at different temperatures

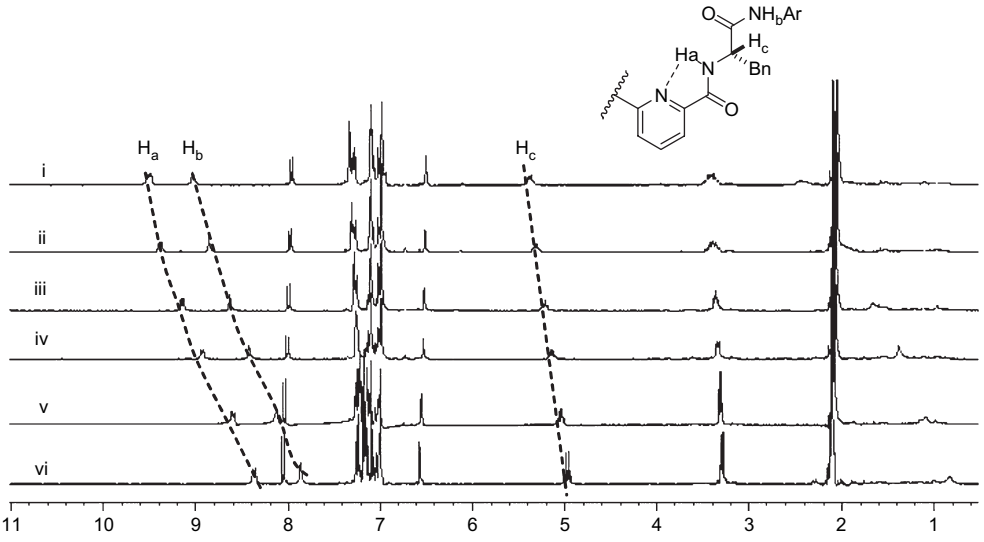


Figure 6. ^1H NMR (toluene-d_8) stacked spectra of **1**-Phe (c=20 mg/mL) at different temperature and physical states: (i) 25 °C, gel, (ii) 30 °C, gel, (iii) 40 °C, solution–gel, (iv) 50 °C, solution–gel, (v) 75 °C, solution–gel, (vi) 100 °C, solution state.

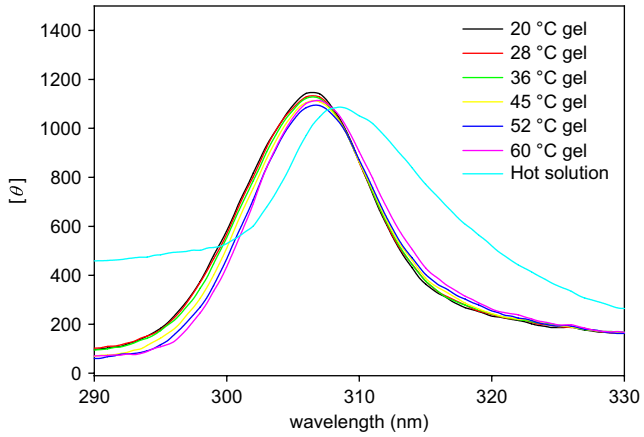


Figure 7. Temperature dependent CD spectra of **1**-Phe in *p*-xylene (15 mg/mL).

were recorded (Fig. 6). At 25 °C in the gel state, the chemical shift values of the carboxamide N–Hs (H_a) and anilide N–Hs (H_b) in toluene gel were located at δ∼9.6 and ∼9.1, respectively. At elevated temperatures (30–75 °C), these two N–H signals shifted upfield due to partial melting of the gel and hence a gradual breakdown of the inter-molecular hydrogen bonding network. Finally, at 100 °C where the gel turned into a solution, the chemical shift values of two relevant N–Hs appeared at δ∼8.4 and ∼7.9, respectively. These results also demonstrate that inter-molecular hydrogen bonding is the main driving force for gel formation.

2.4.3. CD spectroscopy. The CD spectrum of **1**-Phe in *p*-xylene gels (15 mg/mL) displayed one CD band at 306.5 nm at 20 °C (Fig. 7). Increasing the temperature of the gel sample did not lead to any noticeable changes of both the intensity and position of the CD band. Finally, when the gel sample was forced to dissolution by heating, the original CD band was slightly shifted to 308.5 nm. From these experiments, it could be concluded that the chiroptical properties of the organogelator in the gel state were similar to those in the solution state. In other words, there was little chiroptical amplification during gel formation and this also suggested that the chiral organogelators were not organized in a synergistic and orderly manner in the gel state. This also implied that the molecules had a high degree of orientational freedom and were possibly tumbling in the gel state, which was consistent with the results obtained from NMR study. The relatively small blue shift (2 nm) of the CD signal upon gelation also indicated that the energy gap of the electronic transition was widened upon gelation. This can be assigned to a change of π–π interactions between the organogelator and the aromatic solvent (i.e., *p*-xylene) on going from the solution to the gel state.

2.5. Electron microscopy

The morphology of the gel structure was examined by scanning electron microscopy (SEM). Figure 8 showed the electron micrographs of xerogels from **1**-Phe and **1**-Asp β-benzyl ester in different solvents. The micromorphology of the gels was found to be independent of the gelating solvent. The xerogels appeared as long thin fibers with a diameter range of 50–70 nm. This value was much larger than the figure expected from a single molecular chain and suggested that the xerogels were actually super-bundles resulting from

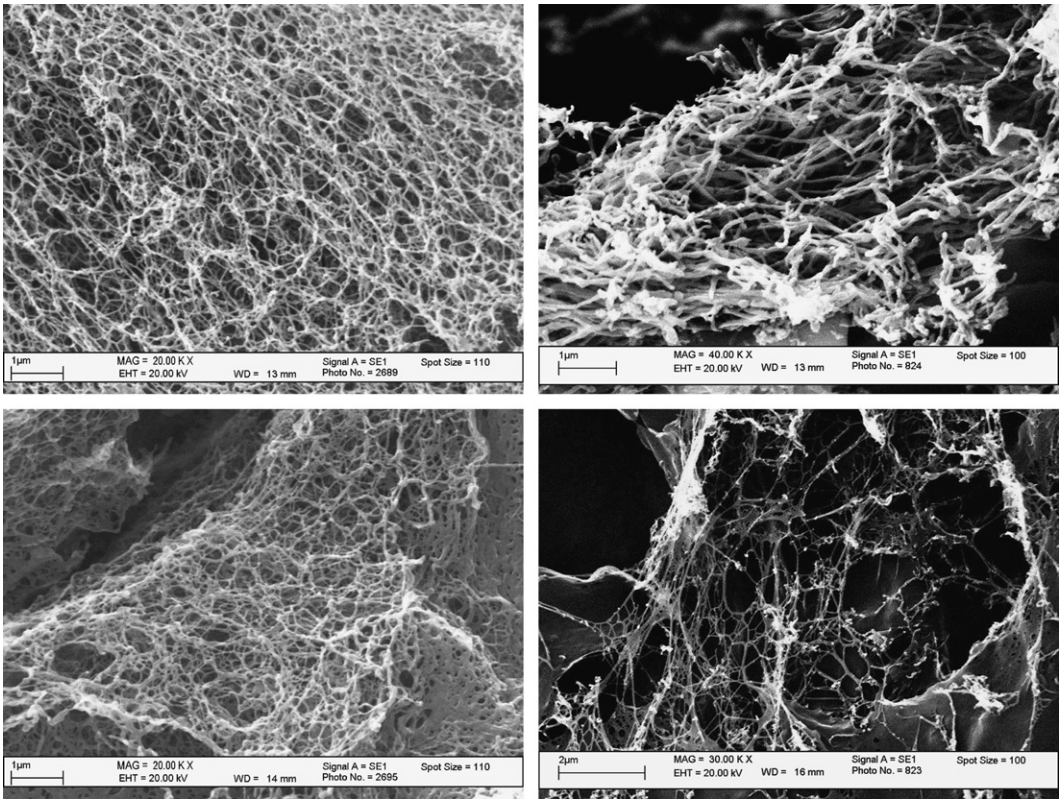


Figure 8. SEM images of xerogels of (top left) **1**-Phe in CCl_4, (top right) **1**-Phe in *p*-xylene, (bottom left) **1**-Asp β-benzyl ester in CCl_4, and (bottom right) **1**-Asp β-benzyl ester in *p*-xylene.

the intertwining of several molecular chains. Such superbundles were further extended to form a large three-dimensional fibrillar network. Although these bis(amino acid)-based pyridine-2,6-dicarboxamides were optically active, we were unable to identify any chiral microstructures such as helical architecture in their SEM images.

3. Conclusions

By replacing the central 3,5-diaminobenzoic acid ring with pyridine-2,6-dicarboxylic acid, a new series of bis(amino acid)-containing pyridine-2,6-dicarboxamide derivatives **1** was prepared. Three of the synthesized compounds (**1**-Phe, **1**-Asp β-benzyl ester, and **9**), all bearing aromatic amino acid side chains, were found to be excellent organogelators toward aromatic solvents (mgc∼10–20 mg/mL). In contrast to the 3,5-diaminobenzoic acid derived organogelators, the pyridine-2,6-dicarboxamide derivatives have an expanded range of gelating solvents. In addition to aromatic solvents, they are also efficient organogelators for alcohols (mgc∼4–15 mg/mL) and CCl_4 (mgc∼4–10 mg/mL). It was found that the intra-molecular hydrogen bonds between the carboxamide N–Hs and the pyridine N atom were the key structural elements for gel formation. This series of compounds thus represents one of the rare examples where both inter- and intra-molecular hydrogen bondings are needed for gel formation. FTIR, ^{1}H NMR, and CD spectroscopy revealed that both H-bonding and π–π aromatic stacking were the driving forces for gelation.

4. Experimental

4.1. General

THF was distilled from sodium benzophenone ketyl and CH_2Cl_2 from CaH_2 prior to use. Silica gel for flash chromatography is Macherey Nagel 60M (230–400 mesh) silica gel. Cbz-protected or Boc-protected L-amino acids and other reagents were used as supplied from Aldrich or Sigma. All reactions were conducted under dry N_2 unless otherwise stated. All NMR spectra were recorded in DMSO-d_6 (dried over molecular sieves 4 Å) on a Brüker DPX300 Spectrometer at 300 MHz for ^{1}H and 75.5 MHz for ^{13}C nucleus at 25 °C unless otherwise stated. The residual proton or carbon signals of DMSO-d_6 (δ_H=2.50; δ_C=39.52) were used as internal references. All chemical shifts are reported in ppm (δ) and coupling constants in Hz. FAB and L-SIMS spectra were carried out on a Thermo Finnigan MAT 95XL Mass Spectrometer. Melting points were measured on an Electrothermal IA9100 Digital Melting Point Apparatus and are uncorrected. IR spectra were recorded on a Brüker Vertex 70 FTIR Spectrophotometer. Optical rotations were taken on a Perkin Elmer 341 Polarimeter at 589 nm and at 20 °C. CD spectra were recorded on a JASCO J-715 Spectropolarimeter connected to a NESLAB RTE-211 Temperature Controller. All SEM images were taken on a Leo 1450 VP Scanning Electron Microscope. Elemental analyses were performed at MEDAC LTD, Brunel Science Center, Cooper's Hill Lane, Englefield Green, Egham, Surrey TW20 0JZ, UK.

4.2. General procedure for the synthesis of *N*-protected amino amides 5

A solution of the 3,5-dimethylaniline (1.1 equiv) and EEDQ (1.1 equiv) in THF was added to a solution of CbzNH- or BocNH-protected amino acid (1.0 equiv) at 20 °C. The mixture was stirred at 20 °C for 24 h. The solvent was removed under reduced pressure and the product was isolated according to the following procedure.

4.2.1. 5-Gly (P=Boc). Starting from Boc-alanine (3.85 g, 22.0 mmol), 3,5-dimethylaniline (2.93 g, 24.2 mol), and EEDQ (5.98 g, 24.2 mmol), the title compound (4.80 g, 78%) was obtained as a white solid by precipitation from acetone/Et_2O. Mp: 160–162 °C; ^{1}H NMR ($CDCl_3$): δ 8.30 (1H, br s), 7.14 (2H, s), 6.75 (1H, s), 5.47 (1H, br s), 3.93 (2H, d, J=5.4), 2.27 (6H, s), 1.47 (9H, s); ^{13}C NMR ($CDCl_3$): δ 167.7, 156.4, 138.7, 137.3, 126.2, 117.7, 80.5, 45.4, 28.3, 21.3; MS (FAB): m/z 279 [(M+H)$^+$, 80%]; HRMS (L-SIMS): calcd for $C_{15}H_{23}N_2O_3$ (M+H)$^+$: 279.1703, found 279.1698; Anal. Calcd for $C_{15}H_{22}N_2O_3$: C, 64.73, H, 7.97, N, 10.06. Found: C, 64.59, H, 8.02, N, 9.92.

4.2.2. 5-Ala (P=Boc). Starting from Boc-alanine (3.80 g, 20.1 mmol), 3,5-dimethylaniline (2.68 g, 22.1 mmol), and EEDQ (5.46 g, 22.1 mmol), the title compound (5.40 g, 92%) was obtained as a white solid by precipitation from acetone/Et_2O. Mp: 145–146 °C; $[\alpha]_D$ −91.5 (c 0.75, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 8.21 (1H, br s), 7.14 (2H, s), 6.74 (1H, s), 5.00 (1H, br s), 4.38–4.20 (1H, m), 2.28 (6H, s), 1.49 (9H, s), 1.42 (3H, d, J=6.0); ^{13}C NMR ($CDCl_3$): δ 171.1, 156.0, 138.4, 137.6, 125.9, 117.6, 80.4, 50.7, 28.3, 21.2, 18.1; MS (FAB): m/z 293 [(M+H)$^+$, 100%]; HRMS (L-SIMS): calcd for $C_{16}H_{25}N_2O_3$ (M+H)$^+$: 293.1860, found 293.1855; Anal. Calcd for $C_{16}H_{24}N_2O_3$: C, 65.73, H, 8.27, N, 9.58. Found: C, 65.79, H, 8.33, N, 9.55.

4.2.3. 5-Val (P=Boc). Starting from Boc-valine (4.35 g, 20.0 mmol), 3,5-dimethylaniline (2.67 g, 22.0 mmol), and EEDQ (5.45 g, 22.0 mmol), the target compound (4.90 g, 76%) was obtained as a white solid by precipitation from acetone/Et_2O. Mp: 140–141 °C; $[\alpha]_D$ −29.9 (c 0.55, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.84 (1H, br s), 7.14 (2H, s), 6.74 (1H, s), 5.10 (1H, br s), 3.99 (1H, dd, J=9 and 6), 2.27 (6H, s), 2.24–2.17 (1H, m), 1.46 (9H, s), 1.02 (3H, d, J=6.0), 0.98 (3H, d, J=6.0); ^{13}C NMR ($CDCl_3$): δ 169.9, 156.0, 138.7, 137.3, 126.2, 117.7, 61.0, 30.6, 28.3, 21.3, 19.4, 18.0; MS (FAB): m/z 321 [(M+H)$^+$, 80%]; HRMS (L-SIMS): calcd for $C_{18}H_{29}N_2O_3$ (M+H)$^+$: 321.2173, found 321.2171; Anal. Calcd for $C_{18}H_{28}N_2O_3$: C, 67.47, H, 8.81, N, 8.74. Found: C, 67.68, H, 9.35, N, 8.29.

4.2.4. 5-Leu (P=Cbz). Starting from Cbz-leucine (5.30 g, 20.0 mmol), 3,5-dimethylaniline (2.66 g, 22.0 mmol), and EEDQ (5.43 g, 22.0 mmol), the title compound (5.70 g, 77%) was obtained as a white solid by precipitation from acetone/Et_2O. Mp: 138–140 °C; $[\alpha]_D$ +8.0 (c 0.95, DMF); ^{1}H NMR ($CDCl_3$): δ 8.32 (1H, br s), 7.38–7.27 (5H, m), 7.12 (2H, s), 6.73 (1H, s), 5.46 (1H, br s), 5.12 (1H, d, J=12), 5.08 (1H, d, J=12), 4.42–4.30 (1H, m), 2.24 (6H, s), 1.77–1.68 (2H, m), 1.62–1.56 (1H, m), 0.95 (3H, d, J=6), 0.94 (3H, d, J=6); ^{13}C NMR ($CDCl_3$): δ 170.5, 156.6, 138.6, 137.4, 135.9, 128.5, 128.2, 128.0, 126.1, 117.7, 67.3, 54.3,

41.0, 24.7, 22.8, 22.1, 21.3; MS (FAB): *m/z* 369 [(M+H)$^+$, 94%]; HRMS (L-SIMS): calcd for $C_{22}H_{29}N_2O_3$ (M+H)$^+$: 369.2173, found 369.2178; Anal. Calcd for $C_{22}H_{28}N_2O_3$: C, 71.71, H, 7.66, N, 7.60. Found: C, 71.56, H, 7.72, N, 7.61.

4.2.5. 5-Phe (P=Boc). Starting from Boc-phenylalanine (26.5 g, 100 mmol), 3,5-dimethylaniline (13.3 g, 110 mmol), and EEDQ (27.2 g, 110 mmol), the title compound (31.3 g, 85%) was obtained as a white solid by precipitation from acetone/Et_2O. Mp: 143–144 °C. $[\alpha]_D$ −15.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.67 (1H, br s), 7.35–7.23 (5H, m), 7.00 (2H, s), 6.73 (1H, s), 5.16 (1H, br s), 4.46–4.35 (1H, m), 3.13 (2H, d, *J*=6.9), 2.26 (6H, s), 1.42 (9H, s); ^{13}C NMR ($CDCl_3$): δ 169.4, 155.7, 138.6, 137.1, 136.7, 129.3, 128.8, 127.0, 126.2, 117.8, 80.5, 56.7, 38.5, 28.3, 21.3; MS (FAB): *m/z* 369 [(M+H)$^+$, 30%]; HRMS (L-SIMS): calcd for $C_{22}H_{29}N_2O_3$ (M+H)$^+$: 369.2173, found 369.2179; Anal. Calcd for $C_{22}H_{28}N_2O_3$: C, 71.71, H, 7.66, N, 7.60. Found: C, 71.69, H, 7.71, N, 7.51.

4.2.6. 5-Asp β-benzyl ester (P=Boc). Starting from Boc-aspartic acid β-benzyl ester (16.2 g, 50.1 mmol), 3,5-dimethylaniline (6.68 g, 55.1 mmol), and EEDQ (13.6 g, 55.1 mmol), the target compound (16.1 g, 75%) was obtained as a white solid by precipitation from acetone/Et_2O. Mp: 133–135 °C; $[\alpha]_D$ −25.8 (*c* 0.55, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 8.42 (1H, br s), 7.32–7.28 (5H, m), 7.12 (2H, s), 6.75 (1H, s), 5.82 (1H, br s), 5.16 (1H, d, *J*=12.3), 5.13 (1H, d, *J*=12.3), 4.70–4.59 (1H, m), 3.06 (1H, dd, *J*=17.1 and 4.2), 2.79 (1H, dd, *J*=17.1 and 6.3), 2.28 (6H, s), 1.47 (9H, s); ^{13}C NMR ($CDCl_3$): δ 171.8, 168.7, 155.8, 138.6, 137.3, 135.2, 128.6, 128.4, 128.2, 126.2, 117.6, 80.8, 66.9, 51.3, 35.8, 28.2, 21.3; MS (FAB): *m/z* 427 [(M+H)$^+$, 57%); HRMS (L-SIMS): calcd for $C_{24}H_{31}N_2O_5$ (M+H)$^+$: 427.2227, found 427.2230; Anal. Calcd for $C_{24}H_{30}N_2O_5$: C, 67.59, H, 7.09, N, 6.57. Found: C, 67.59, H, 7.15, N, 6.52.

4.2.7. 5-Tyr (P=Cbz). Starting from Cbz-tyrosine (6.30 g, 20.0 mmol), 3,5-dimethylaniline (2.66 g, 22.0 mmol), and EEDQ (5.43 g, 22.0 mmol), the target compound (6.70 g, 80%) was obtained as a white solid by precipitation from acetone/Et_2O. Mp: 153–155 °C; $[\alpha]_D$ +38.3 (*c* 0.65, DMF); ^{1}H NMR: δ 9.94 (1H, s), 9.24 (1H, s), 7.63 (1H, d, *J*=8.1), 7.41–7.20 (7H, m), 7.15 (2H, d, *J*=8.1), 6.75–6.60 (3H, m), 5.01 (2H, s), 4.38–4.28 (1H, m), 2.93 (1H, dd, *J*=13.5 and 4.5), 2.75 (1H, dd, *J*=13.5 and 10.2), 2.27 (6H, s); ^{13}C NMR: δ 170.5, 155.8, 155.7, 138.6, 137.5, 136.9, 130.1, 128.2, 127.8, 127.6, 127.4, 124.8, 117.0, 114.8, 65.2, 57.2, 36.7, 21.0; MS (FAB): *m/z* 419 [(M+H)$^+$, 24%]; HRMS (L-SIMS): calcd for $C_{25}H_{26}N_2O_4$ (M+H)$^+$: 419.1965, found 419.1974; Anal. Calcd for $C_{25}H_{26}N_2O_4$: C, 71.75, H, 6.26, N, 6.69. Found: C, 71.67, H, 6.29, N, 6.53.

4.2.8. 5-Ser (P=Cbz). Starting from Cbz-serine (4.80 g, 20.1 mmol), 3,5-dimethylaniline (2.67 g, 22.1 mmol), and EEDQ (5.46 g, 22.1 mmol), the title compound (4.80 g, 70%) was obtained as a white solid by precipitation from acetone/Et_2O. Mp: 150–152 °C; $[\alpha]_D$ −10.7 (*c* 0.65, DMF); ^{1}H NMR ($CDCl_3$): δ 8.48 (1H, br s), 7.38–7.32 (5H, m), 7.10 (2H, s), 6.77 (1H, s), 5.95–5.88 (1H, m), 5.17 (2H, s), 4.34–4.20 (2H, m), 3.78–3.65 (1H, m), 3.00–2.90 (1H, m), 2.29 (6H, s); ^{13}C NMR ($CDCl_3$): δ 169.1, 157.2, 138.8, 137.0, 135.8, 128.6, 128.4, 128.1, 126.5, 117.9, 67.6, 62.5, 55.6, 21.3; MS (FAB): *m/z* 343 [(M+H)$^+$, 54%]; HRMS (L-SIMS): calcd for $C_{19}H_{23}N_2O_4$ (M+H)$^+$: 343.1652, found 343.1655; Anal. Calcd for $C_{19}H_{22}N_2O_4$: C, 66.65, H, 6.48, N, 8.18. Found: C, 66.34, H, 6.47, N, 8.03.

4.2.9. 5-Asn (P=Cbz). Starting from Cbz-asparagine (5.30 g, 19.9 mmol), 3,5-dimethylaniline (2.65 g, 21.9 mmol), and EEDQ (5.41 g, 21.9 mmol), the target product (5.00 g, 68%) was obtained as a white solid by precipitation from acetone/Et_2O. Mp: 156–158 °C; $[\alpha]_D$ −2.3 (*c* 0.90, DMF); ^{1}H NMR: δ 9.89 (1H, s), 7.58 (1H, d, *J*=7.8), 7.41–7.30 (6H, m), 7.27 (2H, s), 6.99 (1H, s), 6.73 (1H, s), 5.07 (2H, s), 4.51 (1H, q, *J*=7.8), 2.59–2.45 (2H, m), 2.26 (6H, s); ^{13}C NMR: δ 171.0, 169.9, 155.7, 138.7, 137.5, 136.8, 128.3, 127.7, 124.7, 117.0, 65.4, 52.3, 37.1, 21.0; MS (FAB): *m/z* 370 [(M+H)$^+$, 68%]; HRMS (L-SIMS): calcd for $C_{20}H_{23}N_3O_4$ (M+H)$^+$: 370.1761, found 370.1756; Anal. Calcd for $C_{20}H_{23}N_3O_4$: C, 65.03, H, 6.28, N, 11.37. Found: C, 65.01, H, 6.27, N, 11.35.

4.2.10. 5-Pro (P=Cbz). Starting from Cbz-proline (5.00 g, 20.1 mmol), 3,5-dimethylaniline (2.67 g, 22.1 mmol), and EEDQ (5.46 g, 22.1 mmol), the target compound (4.60 g, 65%) was obtained as a white solid by precipitation from acetone/Et_2O. Mp: 124–126 °C; $[\alpha]_D$ −129.1 (*c* 0.65, $CHCl_3$); ^{1}H NMR: δ 9.92 and 9.90 (total 1H, s), 7.45–7.35 (2H, m), 7.35–7.14 (5H, m), 6.74 (1H, s), 5.15–4.95 (2H, m), 4.42–4.32 (1H, m), 3.60–3.40 (2H, m), 2.27 (6H, s), 2.27–2.23 (1H, m), 2.00–1.82 (3H, m); ^{13}C NMR: δ 170.8, 170.5, 153.9, 153.6, 138.7, 138.6, 137.4, 136.9, 136.7, 128.3, 127.9, 127.7, 127.4, 126.8, 124.7, 124.6, 117.1, 116.9, 65.8, 65.7, 60.4, 59.8, 47.1, 46.5, 31.2, 30.1, 23.8, 23.0, 21.0; MS (FAB): *m/z* 353 [(M+H)$^+$, 93%]; HRMS (L-SIMS): calcd for $C_{21}H_{25}N_2O_3$ (M+H)$^+$: 353.1860, found 353.1861; Anal. Calcd for $C_{21}H_{24}N_2O_3$: C, 71.75, H, 6.86, N, 7.95. Found: C, 71.36, H, 6.83, N, 7.93.

4.3. (*S*)-*N*-Butyl-2-benzyloxycarbonylamino-3-phenylpropamide

A solution of Cbz-phenylalanine (6.00 g, 20.0 mmol), *n*-butylamine (1.61 g, 22.0 mmol), and EEDQ (5.45 g, 22.0 mmol) was stirred in THF at 20 °C for 24 h. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel (eluent: hexane/EtOAc=1/1) to give the target product (5.70 g, 80%) as a white solid. R_f: 0.66 (hexane/EtOAc=1/1); Mp: 127–130 °C; $[\alpha]_D$ +12.3 (*c* 0.50, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.29–7.05 (10H, m), 5.73 (1H, br s), 5.50–5.40 (1H, m), 4.98 (2H, s), 4.29 (1H, q, *J*=7.2), 3.15–2.90 (4H, m), 1.30–1.17 (2H, m), 1.17–1.03 (2H, m), 0.77 (3H, d, *J*=7.2); ^{13}C NMR ($CDCl_3$): δ 170.6, 155.9, 136.6, 136.1, 129.2, 128.6, 128.5, 128.1, 127.9, 126.9, 66.9, 56.4, 39.1, 38.9, 31.2, 19.8, 13.6; MS (FAB): *m/z* 355 [(M+H)$^+$, 28%]; HRMS (L-SIMS): calcd for $C_{21}H_{27}N_2O_3$ (M+H)$^+$: 355.2016, found 355.2019; Anal. Calcd for $C_{21}H_{26}N_2O_3$: C, 71.16, H, 7.39, N, 7.90. Found: C, 71.06, H, 7.51, N, 7.76.

4.4. (*S*)-*N*-(3,5-Dimethylphenyl)-2-hydroxy-3-phenylpropamide

A mixture of (*S*)-2-hydroxy-3-phenylpropionic acid[11] (3.30 g, 19.9 mmol), 3,5-dimethylaniline (2.65 g, 21.8 mmol), and

EEDQ (5.40 g, 21.8 mmol) was stirred in THF at 20 °C for 24 h. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel (eluent: hexane/EtOAc=2/1) to afford the target compound (4.00 g, 75%) as a white solid. R_f: 0.42 (hexane/EtOAc=2/1); Mp: 127–129 °C; $[\alpha]_D$ −150.7 (*c* 0.65, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 8.22 (1H, s), 7.38–7.24 (5H, m), 7.16 (2H, s), 6.78 (1H, s), 4.45–4.35 (1H, m), 3.33 (1H, dd, *J*=14.1 and 4.2), 2.96 (1H, dd, *J*=14.0 and 8.7), 2.61 (1H, d, *J*=4.5), 2.30 (6H, s); ^{13}C NMR ($CDCl_3$): δ 170.7, 138.7, 136.8, 136.7, 129.5, 128.8, 127.0, 126.3, 117.6, 73.1, 40.8, 21.3; MS (FAB): *m/z* 270 [$(M+H)^+$, 100%]; HRMS (L-SIMS): calcd for $C_{17}H_{20}NO_2$ $(M+H)^+$: 270.1489, found 270.1494; Anal. Calcd for $C_{17}H_{19}NO_2$: C, 75.81, H, 7.11, N, 5.20. Found: C, 75.68, H, 7.11, N, 5.15.

4.5. General procedure for the deprotection of the *N*-protecting groups

(a) *Deprotection of Cbz group*: A solution of Cbz-protected amino compound **5** (P=Cbz) and 10% Pd/C in THF/EtOH (v/v=1/1) was stirred under H_2 (1 atm) at 20 °C and the reaction was monitored by TLC until the starting material disappeared. The reaction mixture was filtered through Celite and washed with THF. The combined filtrates were concentrated under reduced pressure to give the crude product **6** that was directly used in the next reaction without characterization.

(b) *Deprotection of Boc group*: A solution of Boc-protected amino compound **5** (P=Boc) in TFA/CH_2Cl_2 (v/v=1/1) was stirred at 20 °C and the reaction was monitored by TLC until the starting material disappeared. The excess TFA was removed under reduced pressure and the residue neutralized with $NaHCO_3$ solution. The residue was then extracted with EtOAc and the combined extracts were washed with saturated NaCl solutions. The organic phase was dried ($MgSO_4$), filtered, and evaporated under reduced pressure to give the crude product **6** that was directly used in the next step without characterization.

4.6. General procedure for the bis(amino acid)-functionalized pyridine-2,6-dicarboxamides 1

A mixture of the deprotected, free amino carboxamide **6** (2.0 equiv), pyridine-2,6-dicarboxylic acid (1.0 equiv), and EEDQ (2.2 equiv) in THF was stirred at 20 °C for 24 h under N_2. The solvent was then removed under reduced pressure and the residue was purified according to the following methods.

4.6.1. 1-Gly. Starting from **6**-Gly [obtained from deprotection of **5**-Gly (P=Boc) (5.33 g, 19.2 mmol)], pyridine-2,6-dicarboxylic acid (1.60 g, 9.6 mmol), and EEDQ (5.21 g, 21.1 mmol), the target compound (2.70 g, 58%) was obtained as a white solid by precipitation from acetone/Et_2O. Mp: >300 °C (dec); ^1H NMR: δ 10.05 (2H, s), 9.81 (2H, t, *J*=6.0), 8.30–8.22 (3H, m), 7.28 (4H, s), 6.73 (2H, s), 4.21 (4H, d, *J*=9.0), 2.26 (12H, s); ^{13}C NMR: δ 167.3, 163.7, 148.4, 139.5, 138.7, 137.6, 124.8, 124.3, 116.9, 42.9, 21.0; MS (FAB): *m/z* 488 [$(M+H)^+$, 20%], 975 [$(M_2+H)^+$, 2%]; HRMS (L-SIMS): calcd for $C_{27}H_{30}N_5O_4$ $(M+H)^+$: 488.2292, found 488.2292.

4.6.2. 1-Ala. Starting from **6**-Ala [obtained from deprotection of **5**-Ala (P=Boc) (5.60 g, 19.2 mmol)], pyridine-2,6-dicarboxylic acid (1.60 g, 9.6 mmol), and EEDQ (5.21 g, 21.1 mmol), the titled compound (3.50 g, 71%) was obtained as a white solid by precipitation from acetone/Et_2O. Mp: 238–239 °C; $[\alpha]_D$ +206.9 (*c* 0.65, DMF); ^1H NMR: δ 10.02 (2H, s), 9.34 (2H, d, *J*=9.0), 8.29–8.18 (3H, m), 7.29 (4H, s), 6.74 (2H, s), 4.77–4.60 (2H, m), 2.27 (12H, s), 1.58 (6H, d, *J*=9.0); ^{13}C NMR: δ 170.9, 163.4, 148.8, 139.4, 138.8, 137.7, 124.9, 117.2, 49.8, 21.1, 17.9; MS (FAB): *m/z* 516 [$(M+H)^+$, 55%], 1031 [$(M_2+H)^+$, 8%]; HRMS (L-SIMS): calcd for $C_{29}H_{34}N_5O_4$ $(M+H)^+$: 516.2605, found 516.2609; Anal. Calcd for $C_{29}H_{33}N_5O_4$: C, 67.55, H, 6.45, N, 13.58. Found: C, 67.41, H, 6.66, N, 13.46.

4.6.3. 1-Val. Starting from **6**-Val [prepared from the deprotection of **5**-Val (P=Boc) (6.14, 19.1 mmol)], pyridine-2,6-dicarboxylic acid (1.60 g, 9.6 mol), and EEDQ (5.21 g, 21.1 mmol), the target product (4.30 g, 79%) was obtained as a white solid by precipitation from acetone/Et_2O. Mp: 231–232 °C; $[\alpha]_D$ +195.2 (*c* 0.50, DMF); ^1H NMR ($CDCl_3$): δ 8.70 (2H, d, *J*=8.7), 8.63 (2H, s), 8.37 (2H, d, *J*=7.5), 8.03 (1H, t, *J*=7.5), 7.19 (4H, s), 6.73 (2H, s), 4.73 (2H, dd, *J*=8.7 and 7.5), 2.49–2.40 (2H, m), 2.23 (12H, s), 1.17 (12H, d, *J*=6.9); ^{13}C NMR ($CDCl_3$): δ 169.3, 163.9, 148.6, 139.1, 138.6, 137.5, 126.1, 125.4, 117.8, 60.0, 31.2, 21.3, 19.5, 18.5; MS (FAB): *m/z* 572 [$(M+H)^+$, 93%], 1143 [$(M_2+H)^+$, 14%]; HRMS (L-SIMS): calcd for $C_{33}H_{42}N_5O_4$ $(M+H)^+$: 572.3231, found 572.3229; Anal. Calcd for $C_{33}H_{41}N_5O_4$: C, 69.33, H, 7.23, N, 12.25. Found: C, 69.14, H, 7.65, N, 12.18.

4.6.4. 1-Leu. Starting from **6**-Leu (prepared from **5**-Leu (P=Cbz) (7.06 g, 19.1 mmol), pyridine-2,6-dicarboxylic acid (1.60 g, 9.6 mmol), and EEDQ (5.21 g, 21.1 mmol), the target product (4.20 g, 73%) was obtained as a white solid by precipitation from acetone/Et_2O. Mp: 162–163 °C; $[\alpha]_D$ +151.9 (*c* 1.15, DMF); ^1H NMR ($CDCl_3$): δ 8.58 (2H, d, *J*=7.8), 8.41 (2H, s), 8.35 (2H, d, *J*=7.8), 8.02 (1H, t, *J*=7.8), 7.16 (4H, s), 6.72 (2H, s), 4.90–4.75 (2H, m), 2.23 (12H, s), 2.00–1.70 (6H, m), 1.01–0.88 (12H, m); ^{13}C NMR ($CDCl_3$): δ 169.8, 164.0, 148.4, 139.1, 138.7, 137.5, 126.2, 125.5, 117.7, 53.0, 40.2, 25.0, 22.9, 22.3, 21.3; MS (FAB): *m/z* 600 [$(M+H)^+$, 30%]; HRMS (L-SIMS): calcd for $C_{35}H_{46}N_5O_4$ $(M+H)^+$: 600.3544, found 600.3538.

4.6.5. 1-Phe. Starting from **6**-Phe (prepared from **5**-Phe (P=Boc) (7.06 g, 19.1 mmol), pyridine-2,6-dicarboxylic acid (1.60 g, 9.6 mol), and EEDQ (5.21 g, 21.1 mmol), the target compound (4.80 g, 75%) was obtained as a white solid by flash chromatography (eluent: hexane/acetone=1:1). R_f: 0.35 (hexane/acetone=2/1); Mp: 170–171 °C; $[\alpha]_D$ −13.7 (*c* 0.75, $CHCl_3$); ^1H NMR: δ 10.14 (2H, s), 9.31 (2H, d, *J*=7.8), 8.18 (3H, s), 7.48 (4H, d, *J*=6), 7.40–7.15 (10H, m), 6.75 (2H, s), 4.95 (2H, q, *J*=7), 3.35–3.21 (4H, m), 2.27 (12H, s); ^{13}C NMR: δ 169.4, 163.2, 148.4, 139.3, 138.5, 137.5, 129.2, 128.1, 126.3, 124.9, 124.7, 117.1, 55.7, 37.4, 21.0; MS (FAB): *m/z* 668 [$(M+H)^+$, 43%], 1335 [$(M_2+H)^+$, 7%]; HRMS (L-SIMS): calcd for $C_{41}H_{42}N_5O_4$ $(M+H)^+$: 668.3231, found 668.3231.

4.6.6. 1-Asp β-benzyl ester. Starting from **6**-Asp β-benzyl ester [prepared from **5**-Asp β-benzyl ester (P=Boc)

(8.17 g, 19.1 mol)], pyridine-2,6-dicarboxylic acid (1.60 g, 9.6 mmol), and EEDQ (5.21 g, 21.1 mmol), the target compound (5.28 g, 70%) was obtained as a white solid by precipitation from acetone/Et_2O. Mp: 175–176 °C; $[\alpha]_D$ +21.4 (*c* 0.80, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 9.47 (2H, d, *J*=8.1), 8.70 (2H, s), 8.34 (2H, d, *J*=7.8), 8.05 (1H, t, *J*=7.8), 7.30–7.22 (10H, m), 7.15 (4H, s), 6.71 (2H, s), 5.20–5.09 (6H, m), 3.15–3.00 (4H, m), 2.24 (12H, s); ^{13}C NMR ($CDCl_3$): δ 172.0, 167.8, 163.9, 147.6, 139.4, 138.6, 137.4, 135.2, 128.4, 128.2, 126.1, 125.2, 117.5, 67.2, 50.6, 34.4, 21.3; MS (FAB): *m/z* 784 [$(M+H)^+$, 6%]; HRMS (L-SIMS): calcd for $C_{45}H_{46}N_5O_8$ $(M+H)^+$: 784.3341, found 784.3347; Anal. Calcd for $C_{45}H_{45}N_5O_8$: C, 68.95, H, 5.79, N, 8.93. Found: C, 69.10, H, 5.92, N, 8.54.

4.6.7. 1-Tyr. Starting from **6**-Tyr [prepared from **5**-Tyr (P=Cbz) (8.01 g, 19.1 mmol)], pyridine-2,6-dicarboxylic acid (1.60 g, 9.6 mmol), and EEDQ (5.21 g, 21.1 mmol), the title compound (4.80 g, 72%) was obtained as a white solid by precipitation from acetone/Et_2O. Mp: 148–150 °C; $[\alpha]_D$ +63.5 (*c* 0.40, DMF); ^1H NMR ($CDCl_3$): δ 8.49 (2H, s), 8.27 (2H, d, *J*=7.8), 8.00–7.90 (3H, m), 7.17 (4H, s), 6.92 (4H, d, *J*=8.4), 6.76 (2H, s), 6.69 (4H, d, *J*=8.4), 6.61 (2H, br s), 5.05–4.93 (2H, m), 3.25 (2H, dd, *J*=14.1 and 6.6), 3.09 (2H, dd, *J*=14.1 and 6.0), 2.27 (12H, s); ^{13}C NMR ($CDCl_3$): δ 169.0, 163.8, 155.4, 147.8, 139.4, 139.3, 137.2, 131.0, 127.0, 126.6, 125.7, 117.8, 116.1, 54.4, 35.2, 21.3; MS (FAB): *m/z* 700 [$(M+H)^+$, 26%]; HRMS (L-SIMS): calcd for $C_{41}H_{42}N_5O_6$ $(M+H)^+$: 700.3130, found 700.3145.

4.6.8. 1-Ser. Starting from **6**-Ser [prepared from **5**-Ser (P=Cbz) (6.56 g, 19.1 mmol)], pyridine-2,6-dicarboxylic acid (1.60 g, 9.6 mmol), and EEDQ (5.21 g, 21.1 mmol), the title compound (3.42 g, 65%) was obtained as a white solid by precipitation from acetone/Et_2O. Mp: 250–251 °C; $[\alpha]_D$ +156.2 (*c* 0.60, DMF); ^1H NMR: δ 10.05 (2H, s), 9.01 (2H, d, *J*=7.8), 8.31–8.20 (3H, m), 7.31 (4H, s), 6.75 (2H, s), 5.25 (2H, br s), 4.80–4.70 (2H, m), 3.98–3.88 (4H, m), 2.27 (12H, s); ^{13}C NMR: δ 168.4, 163.4, 148.8, 139.5, 138.7, 137.6, 124.9, 117.2, 61.6, 56.4, 21.1; MS (FAB): *m/z* 548 [$(M+H)^+$, 36%], 1095 [$(M_2+H)^+$, 2%]; HRMS (L-SIMS): calcd for $C_{29}H_{33}N_5O_6$ $(M+H)^+$: 548.2504, found 548.2502.

4.6.9. 1-Asn. Starting from **6**-Asn [prepared from **5**-Asn (P=Cbz) (7.07 g, 19.1 mmol)], pyridine-2,6-dicarboxylic acid (1.60 g, 9.6 mmol), and EEDQ (5.21 g, 21.1 mmol), the target compound (3.51 g, 61%) was obtained as a white solid by precipitation from acetone/Et_2O. Mp: >243 °C (dec); $[\alpha]_D$ +122.8 (*c* 0.65, DMF); ^1H NMR: δ 10.03 (2H, s), 9.52 (2H, d, *J*=9.0), 8.30–8.27 (3H, m), 7.60 (2H, s), 7.29 (4H, s), 7.07 (2H, s), 6.74 (2H, s), 4.94 (2H, q, *J*=7.8), 2.82 (4H, d, *J*=7.8), 2.26 (12H, s); ^{13}C NMR: δ 171.8, 169.2, 163.0, 148.3, 139.8, 138.7, 137.6, 124.9, 124.5, 117.3, 51.2, 36.8, 21.1; MS (FAB): *m/z* 602 [$(M+H)^+$, 10%]; HRMS (L-SIMS): calcd for $C_{31}H_{36}N_7O_6$ $(M+H)^+$: 602.2722, found 602.2724.

4.6.10. 1-Pro. Starting from **6**-Pro [prepared from **5**-Pro (P=Cbz) (6.75 g, 19.1 mmol)], pyridine-2,6-dicarboxylic acid (1.60 g, 9.6 mmol), and EEDQ (5.21 g, 21.1 mmol), the target compound (3.28 g, 60%) was obtained as a white solid by precipitation from acetone/Et_2O. Mp: >200 °C (dec); $[\alpha]_D$ −185.8 (*c* 0.55, $CHCl_3$); ^1H NMR: δ 10.04, 9.91, 9.62, 9.60 (total 2H, 4 s), 8.15–7.50 (total 3H, m), 7.31, 7.27, 7.13, 6.97 (total 4H, 4 s), 6.73–6.63 (total 2H, m), 5.00–4.33 (total 2H, m), 3.90–3.40 (total 4H, m), 2.38–1.55 (total 20H, m); ^{13}C NMR: δ 170.7, 170.3, 170.0, 165.4, 165.2, 165.0, 152.3, 152.1, 152.0, 138.9, 138.7, 138.3, 138.1, 137.55, 137.48, 137.4, 124.7, 124.6, 124.4, 117.7, 117.1, 116.8, 62.1, 61.0, 60.9, 49.4, 48.9, 47.7, 32.2, 29.5, 29.3, 28.8, 25.0, 24.5, 21.7, 21.0, 20.9; MS (FAB): *m/z* 568 [$(M+H)^+$, 88%]; HRMS (L-SIMS): calcd for $C_{33}H_{38}N_5O_4$ $(M+H)^+$: 568.2918, found 568.2907.

4.7. Compound 7

A mixture of **6**-Phe [obtained from **5**-Phe (P=Boc) (7.10 g, 19.3 mmol)], benzene-1,3-dicarboxylic acid (1.60 g, 9.6 mmol), and EEDQ (5.24 g, 21.2 mmol) in THF was stirred at 20 °C for 24 h under N_2. The target compound **7** (4.50 g, 70%) was obtained as a white solid by precipitation from acetone/Et_2O. Mp: 255–256 °C; $[\alpha]_D$ +44.8 (*c* 0.85, DMF); ^1H NMR: δ 10.11 (2H, s), 8.89 (2H, d, *J*=9.0), 8.29 (1H, s), 7.98 (2H, dd, *J*=9.0 and 3.0), 7.58 (1H, t, *J*=9.0), 7.48–7.15 (14H, m), 6.74 (2H, s), 4.95–4.82 (2H, m), 3.20–3.05 (4H, m), 2.27 (12H, s); ^{13}C NMR: δ 170.1, 166.1, 138.7, 138.1, 137.7, 134.1, 130.1, 129.2, 128.1, 126.9, 126.3, 124.9, 117.1, 55.9, 37.2, 21.1; MS (FAB): *m/z* 667 [$(M+H)^+$, 38%], 1334 [$(M_2+H)^+$, 7%]; HRMS (ESI): calcd for $C_{42}H_{42}N_4O_4Na$ $(M+Na)^+$: 689.3098, found 689.3094.

4.8. Compound 8

A mixture of (*S*)-*N*-(3,5-dimethylphenyl)-2-hydroxy-3-phenylpropamide (5.43 g, 19.1 mmol), pyridine-2,6-dicarboxylic acid (1.60 g, 9.6 mmol), and EDCI (6.26 g, 21.1 mmol) in THF was stirred at 20 °C for 24 h. The target compound (4.83 g, 75%) was obtained as a white solid by precipitation from acetone/Et_2O. Mp: 140–141 °C; $[\alpha]_D$ +6.1 (*c* 0.50, DMF); ^1H NMR: δ 10.21 (2H, s), 8.32–8.21 (3H, m), 7.50 (4H, d, *J*=9.0), 7.35 (4H, t, *J*=9.0), 7.30–7.20 (6H, m), 6.77 (2H, s), 5.51 (2H, dd, *J*=6.0 and 3.3), 3.43–3.30 (4H, m), 2.27 (12H, s); ^{13}C NMR: δ 166.7, 163.1, 147.2, 139.4, 138.1, 137.7, 136.4, 129.5, 128.2, 126.6, 125.2, 117.3, 75.7, 37.3, 20.9; MS (FAB): *m/z* 670 [$(M+H)^+$, 26%]; HRMS (L-SIMS): calcd for $C_{41}H_{40}N_3O_6$ $(M+H)^+$: 670.2912, found 670.2921; Anal. Calcd for $C_{41}H_{39}N_3O_6$: C, 73.52, H, 5.87, N, 6.27. Found: C, 73.31, H, 5.93, N, 6.20.

4.9. Compound 9

The Cbz protecting group in (*S*)-*N*-butyl-2-benzyloxycarbonylamino-3-phenylpropamide (6.79 g, 19.1 mmol) was removed according to Section 4.5 to give the corresponding free amino compound. The crude product was stirred with pyridine-2,6-dicarboxylic acid (1.60 g, 9.6 mmol) and EEDQ (5.21 g, 21.1 mmol) in THF at 20 °C for 24 h. The solvent was evaporated under reduced pressure and the target compound (3.85 g, 70%) was obtained as a white solid by flash chromatography (eluent: hexane/acetone=1/1). R_f: 0.69 (hexane/acetone=1/1); Mp: 165–166 °C; $[\alpha]_D$ −35.8 (*c* 0.50, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 8.48 (2H, d, *J*=8.1),

8.29 (2H, d, J=7.8), 7.99 (1H, t, J=7.8), 7.34–7.20 (10H, m), 5.89 (2H, t, J=5.7), 4.79 (2H, q, J=7.8), 3.29–3.05 (8H, m), 1.40–1.25 (4H, m), 1.25–1.10 (4H, m), 0.85 (6H, t, J=7.2); ^{13}C NMR ($CDCl_3$): δ 170.3, 163.3, 148.4, 138.9, 136.8, 129.4, 128.8, 127.0, 125.3, 55.4, 39.3, 38.5, 31.3, 19.9, 13.7; MS (FAB): m/z 572 [$(M+H)^+$, 90%]; HRMS (L-SIMS): calcd for $C_{33}H_{42}N_5O_4$ $(M+H)^+$: 572.3231, found 572.3233.

4.10. CD experiments

1-Phe (45 mg) was dissolved in hot *p*-xylene (3 mL) and transferred to a quartz cell (1 cm path length). It was then cooled down to allow for gel formation. The temperature of the cell was then increased to the specified temperature via the temperature controller. The measurement was done from the gel state (20–60 °C) to the solution state (100 °C) at increasing temperature.

4.11. SEM experiments

1-Phe (15 mg) and **1**-Asp β-benzyl ester (15 mg) were dissolved in the specified solvent (*p*-xylene or CCl_4) (1 mL) separately. The samples were freeze-dried on a Labconco Freezone 6LT Freezer Dry System under 50×10^{-3} mbar at −47 °C for 7 days. The SEM images were taken by a Leo Scanning Electron Microscope as described previously.[6a]

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