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ENANTIOSELECTIVE FLUORESCENCE RECOGNITION OF CHIRAL AMINES BY *N*-ACYL-(*S*)-1-NAPHTHYLALANYL-(*S*)-PHENYLGLYCINE AND *N*-ACYL-(*S*)-1-NAPHTHYLALANYL-(*S*)-1-NAPHTHYLALANINE DIPEPTIDES BRIDGED BY A 1,2-PHENYLENE OR AN ETHYLENE SPACER CHAIN

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Abstract – This study sought to support the development of enantioselective dipeptide fluorescence sensors by examining the ability of the *N*-acyl-(*S*)-1-naphthylalanyl-(*S*)-phenylglycine and *N*-acyl-(*S*)-1-naphthylalanyl-(*S*)-1-naphthylalanine dipeptides (bridged by the 1,2-phenylene or ethylene spacer chain) to discriminate between aliphatic amine-derived (*S*)- and (*R*)-enantiomers. The results indicated that both hydrogen-bonding interactions in the ground state and charge-transfer interactions in the excited state are involved in the fluorescence quenching of these bridged dipeptides by chiral amines to produce the upward curving Stern–Volmer plots. In addition, the numerical analysis of these plots led to the conclusion that the bridged naphthylalanylphenylglycine dipeptide shows the highest ability to differentiate the (*S*)-enantiomer from (*R*)-enantiomer when the emission of this dipeptide is quenched by chiral alaninols.

INTRODUCTION

The intramolecular and intermolecular interactions of fluorescent host molecules (fluorophores) with guest molecules in the ground and excited states are directly reflected in the emission intensities of the former. Therefore, photophysical studies of these interactions have continued to contribute to the development of various photofunctional host molecules.[1] Recently, significant attention has been directed toward the enantioselective recognition of chiral biomolecules by a wide variety of fluorophores.[1b] A survey of recent literature published showed that in order to enhance the ability of these fluorophores to discriminate enantiomers of chiral guests, a number of molecules including 1,1´-binaphthols and related derivatives,[2] cyclohexane-based thioureas,[3] various chromophore-substituted macrocycles,[4] 1,8-diacridyl naphthalene derivatives,[5] α-amino acid-substituted calix[4]arenes,[6] and ingeniously-designed supramolecules[7] have been developed as rigid and sophisticated chiral fluorophores. However, only a few studies have been conducted into the enantioselective recognition of chiral amines (guests) by fluorophore-substituted peptides (hosts).[1b,4e]

In a previous study we discovered that the fluorescence quenching of a (*R*,*S*)-*N*-benzoyl-1-naphthylalanylphenylglycinamide derivative by chiral pyrrolidine-2-methanol (PMO) in 1,4-dioxane proceeds via a singlet exciplex intermediate and proceeds enantioselectively.[8] Despite the simple acyclic structure of this dipeptide fluorophore, it showed a relatively large enantioselectivity in the emission quenching by PMO (quenching constant ratio: K_{SV} [(*S*)-PMO]/K_{SV} [(*R*)-PMO] = 1.8). The effects of the *N*-acyl substituent and peptide conformation on the stability of the exciplex are believed to play major roles in discriminating the PMO-derived enantiomers. An inspection of the enantiomer recognition mechanisms proposed so far reveals the importance of the charge-transfer and hydrogen-bonding interactions and conformational rigidity in host–guest complexes as major factors controlling the enantioselectivity for chiral guest molecules.[2–7,9] Thus, it is expected that the enhancement of this interaction and rigidity contributes to the increased difference in stability between the (*R*)- and (*S*)-enantiomer-derived host–guest complexes.

The above considerations led us to assume that the connection between the two dipeptides previously examined results in an enhanced conformational rigidity and creates a site of interaction with chiral amines. To develop such a bridged dipeptide fluorophore and increase the enantioselectivity of this dipeptide, we chose ethylene and 1,2-phenylene groups as bridging spacer chains and synthesized the bridged dipeptides **1a**, **1b**, and **1c** (Chart 1). For comparison, we synthesized **1d** and **1e** as reference dipeptides containing no bridging spacer. In this paper, we report the bridging effects on the enantioselective fluorescence quenching of (*S*)-1-naphthylalanine-derived dipeptides by the acyclic chiral amines, *N*,*N*-dimethyl-1-phenylethylamine (PEA) and alaninol (ALO), and heterocyclic chiral amines, PMO and 2-methylpiperazine (MPZ).

RESULTS AND DISCUSSION

(*S*)-3-(1-Naphthyl)alanyl-(*S*)-2-phenylglycine *tert*-butyl ester as a precursor of the bridged dipeptides **1a** and **1b** and reference dipeptide **1d** was prepared according to the following reaction pathway: the benzyloxycarbonylation of the amino group in (*S*)-3-(1-naphthyl)alanine hydrochloride in sodium hydroxide solution, the condensation reaction of *N*-benzyloxycarbonyl-(*S*)-3-(1-naphthyl)alanine

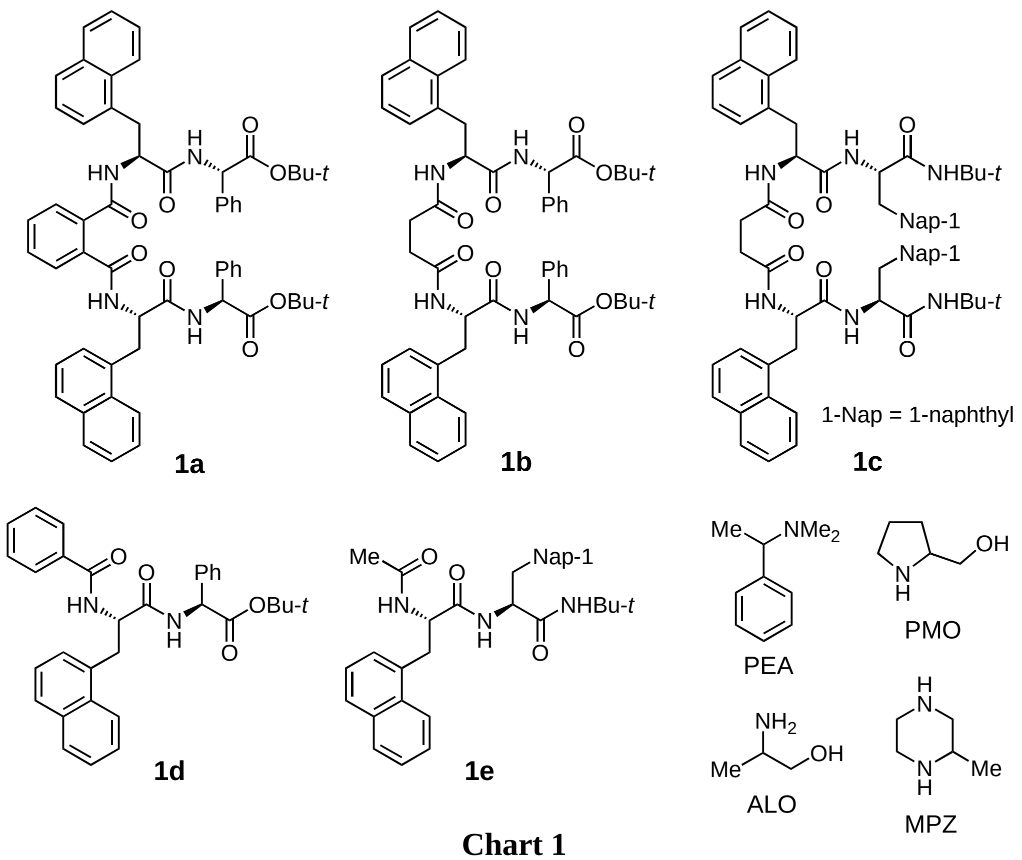


Chart 1

with (*S*)-2-phenylglycine *tert*-butyl ester in 1,4-dioxane containing *N*-hydroxysuccinimide and water-soluble carbodiimide, and the removal of the benzyloxycarbonyl group from *N*-acyl-(*S*)-3-(1-naphthyl)alanyl-(*S*)-2-phenylglycine dipeptide by catalytic hydrogenation in methanol-dimethylformamide. The acylation of the deprotected 3-(1-naphthyl)alanyl-2-phenylglycine dipeptide with phthaloyl chloride, succinyl chloride, and benzoyl chloride in 1,4-dioxane containing pyridine led to the successful formation of **1a**, **1b**, and **1d**, respectively.

On the other hand, (*S*)-3-(1-naphthyl)alanyl-(*S*)-3-(1-naphthyl)alanine *tert*-butylamide as a precursor of the bridged dipeptide **1c** and reference dipeptide **1e** was prepared by a condensation reaction between (*S*)-3-(1-naphthyl)alanine *tert*-butylamide and *N*-(*tert*-butoxycarbonyl)-(*S*)-3-(1-naphthyl)alanine in 1,4-dioxane containing water-soluble carbodiimide, followed by the deprotection of the resulting dipeptide in acidic methanol solution. The former deprotected 3-(1-naphthyl)alaninamide was synthesized by the amidation of *N*-benzyloxycarbonyl-(*S*)-3-(1-naphthyl)alanine with *tert*-butylamine and the subsequent catalytic hydrogenation of the resulting 1-naphthylalaninamide derivative. In addition, the latter *N*-protected (*S*)-3-(1-naphthyl)alanine was obtained from the reaction of (*S*)-3-(1-naphthyl)alanine with *tert*-butoxycarbonyl chloride in aqueous sodium hydroxide. The above precursor was acylated under weakly basic conditions by using succinyl chloride and acetyl chloride to afford the bridged dipeptide **1c** and reference dipeptide **1e**, respectively. The ^{1}H NMR spectral analysis of **1a**–**c** revealed that these bridged dipeptides contain only a single diastereomer and that no epimerization at the chiral methine carbon takes place during the protection, deprotection, and peptide bond-forming reactions described above.

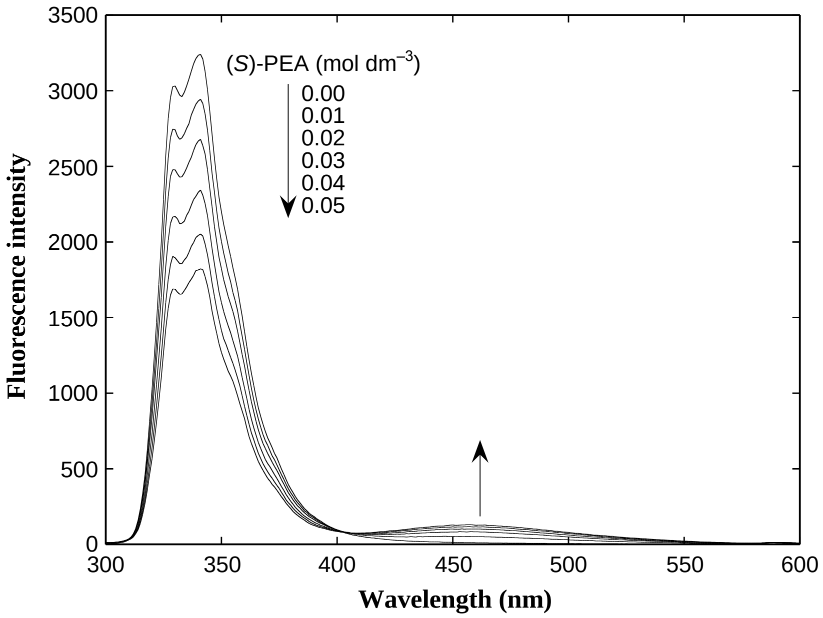


Figure 1. Fluorescence spectra of **1a** (1.25×10^{-4} mol dm^{-3}) in argon-saturated 1,4-dioxane containing various amounts of (*S*)-PEA at room temperature. The excitation wavelength was 295 nm.

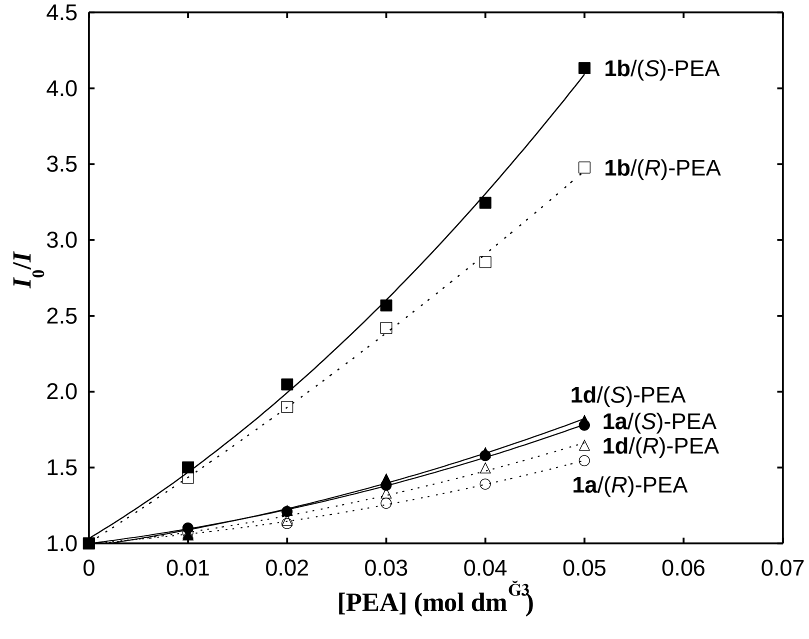


Figure 2. Stern–Volmer plots for the fluorescence quenching of **1a** (1.25×10^{-4} mol dm^{-3};●, ○), **1b** (1.25×10^{-4} mol dm^{-3};■, □), and **1d** (2.5×10^{-4} mol dm^{-3};▲, △) by (*S*)-PEA (●, ■, ▲) and (*R*)-PEA (○, □, △) in argon-saturated 1,4-dioxane. The excitation wavelength was 295 nm.

As typically shown in Figure 1, the 340-nm fluorescence of **1a** was relatively efficiently quenched in the presence of PEA in argon-saturated 1,4-dioxane with the appearance of a new fluorescence band at approximately 460 nm. Because tertiary alkylamines are well known to form singlet exciplexes with many naphthalene derivatives[10] and also an isoemissive point was observed when the 460-nm emission appeared, this new emission in the nonpolar solvent, 1,4-dioxane, can be attributed to singlet exciplex fluorescence. Interestingly, the Stern–Volmer plots for the above fluorescence quenching are upward curving, as shown in Figure 2, and can be approximated by the equation: $I_0/I = 1 + K_1[\mathrm{PEA}] + K_2[\mathrm{PEA}]^2$ (where K_1 and K_2 are constants, and I and I_0 represent the fluorescence intensities of **1** with and without PEA, respectively), suggesting the contribution of both dynamic and static quenching processes.[5a,5b,11] While a charge-transfer interaction between the excited-state **1a** and ground-state PEA is responsible for the former quenching, the latter quenching may be caused by an intermolecular hydrogen-bonding interaction between the fluorophore and quencher in the ground state. In addition, we previously revealed that tertiary alkylamine forms a hydrogen bond with the amide proton in *N*-acetyl-1-naphthylalaninamide derivative to catalyze the hydrogen–deuterium exchange of this derivative.[12] Thus, the hydrogen bond is considered to be formed between the PEA nitrogen and amide proton existing on the amino side of the 1-naphthylalanine moiety. Almost the same upward curving Stern–Volmer plots as those for **1a** were obtained for the bridged dipeptide **1b** and reference dipeptide **1d** (Figure 2).

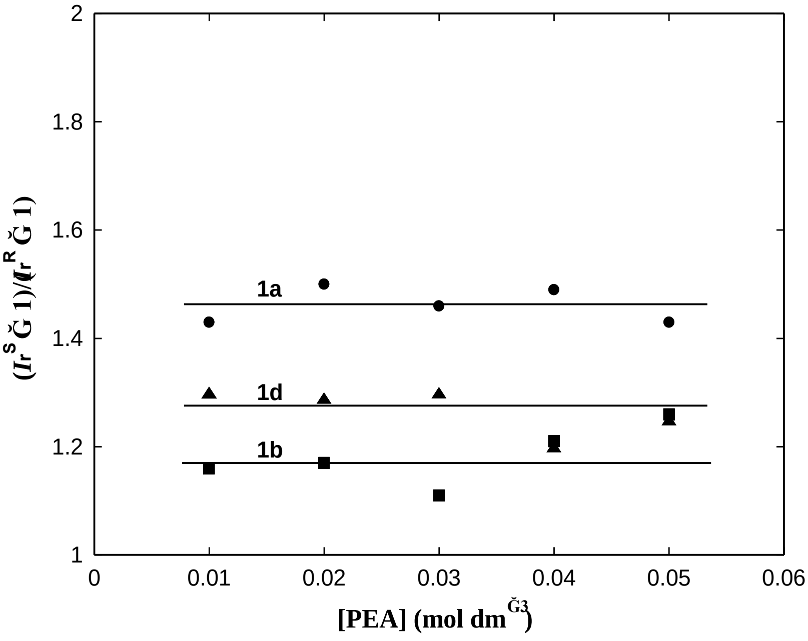
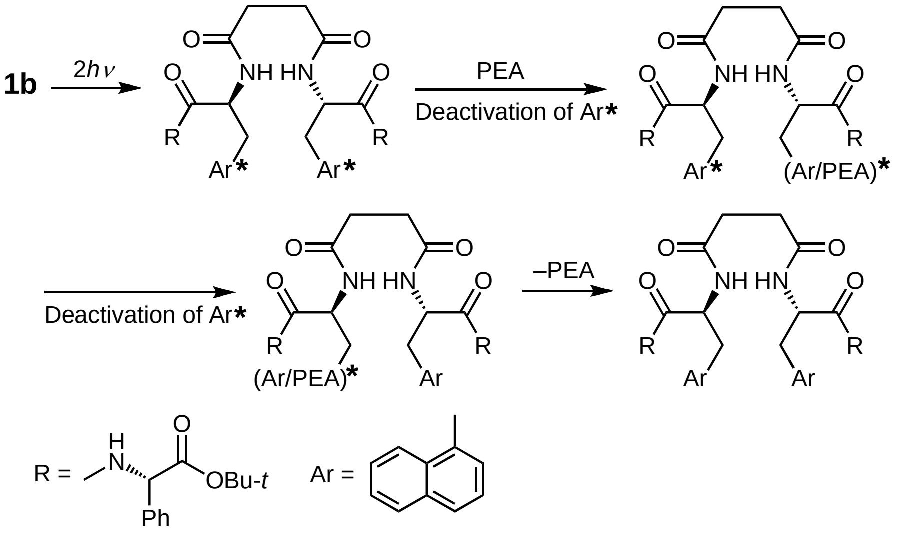


Figure 3. Plots of the $(I_\mathrm{r}^\mathrm{S} - 1)/(I_\mathrm{r}^\mathrm{R} - 1)$ ratios against PEA concentration for the fluorescence quenching of **1a** (1.25×10^{-4} mol dm^{-3}), **1b** (1.25×10^{-4} mol dm^{-3}), and **1d** (2.5×10^{-4} mol dm^{-3}) by (*S*)-PEA and (*R*)-PEA in argon-saturated 1,4-dioxane at room temperature. The excitation wavelength was 295 nm.

To estimate and compare the ability of **1a**, **1b**, and **1d** to discriminate between the (*S*)- and (*R*)-

enantiomers of chiral PEA, the ratio of (I_r^S – 1) for the (*S*)-enantiomer to (I_r^R – 1) for the (*R*)-enantiomer, (I_r^S – 1)/(I_r^R – 1), was used as a measure of this ability, where $I_r = I_0/I$. If the dynamic quenching is predominant under given conditions, this ratio is estimated to be equal to the ratio of quenching constants, K_{SV}^S/K_{SV}^R, on the basis of the equations, $I_r^S = 1 + K_{SV}^S$[(*S*)-PEA] and $I_r^R = 1 + K_{SV}^R$[(*R*)-PEA]. An inspection of the plots of (I_r^S – 1)/(I_r^R – 1) against [PEA], depicted in Figure 3, revealed that these ratios can be regarded as approximately constant in any plots irrespective of the PEA concentration and give a greater value for the **1a**/PEA system (1.5) than for the **1d**/PEA system (1.3). If the static quenching takes place in competition with the dynamic quenching, the former result indicates these two quenching processes to have an enantiodifferentiating ability comparable with each other. In addition, the latter result that the ability to differentiate (*S*)-PEA and (*R*)-PEA is somewhat enhanced by bridging the two 1-naphthylalanylphenylglycine dipeptides with the rigid 1,2-phenylene group led us to propose that owing to the rigid bridging group, the charge-transfer and hydrogen-bonding interactions between the (*R*)-enantiomer and naphthylalanine chromophore are subject to greater steric hindrance by the other naphthylalanine. This interpretation is supported by the finding that the introduction of the flexible ethylene spacer instead of the rigid 1,2-phenylene spacer lowers the enantiodiscriminating ability; in other words, the (I_r^S – 1)/(I_r^R – 1) ratio from 1.5 (**1a**) to 1.2 (**1b**) in the fluorescence quenching by chiral PEA.



Scheme 1

Interestingly, a contrasting bridging effect was observed between the (I_r^S – 1)/(I_r^R – 1) ratio and I_0/I ratio, as can be seen from comparison of the Stern–Volmer plots for the fluorescence quenching of **1a**, **1b**, and **1d** by PEA (Figure 2). For example, the magnitude of the latter emission intensity ratio for **1d** (1.8 at [(*S*)-PEA] = 0.05 mol dm^{-3}) was almost uninfluenced by bridging the naphthylalanylphenylglycine dipeptide with the 1,2-phenylene group (**1a**, I_0/I = 1.8), whereas the ethylene bridge (**1b**) enhanced this intensity ratio by a factor of approximately 2 (I_0/I = 4.1). If it is possible for one PEA molecule in the ground state to deactivate the two naphthylalanine chromophores of **1** in the excited state, the I_0/I ratio is expected to be increased by a factor of 2. Thus, the latter observation is consistent with the quenching mechanism illustrated in Scheme 1, in which the deactivation of the exciplex formed between PEA and one of the two naphthalene rings in the excited-state **1b** is accompanied by the generation of the exciplex derived from the other excited-state naphthalene ring and the chiral amine released by this deactivation. The flexible ethylene bridge in **1b** is considered to play a decisive role in the above quenching mechanism.

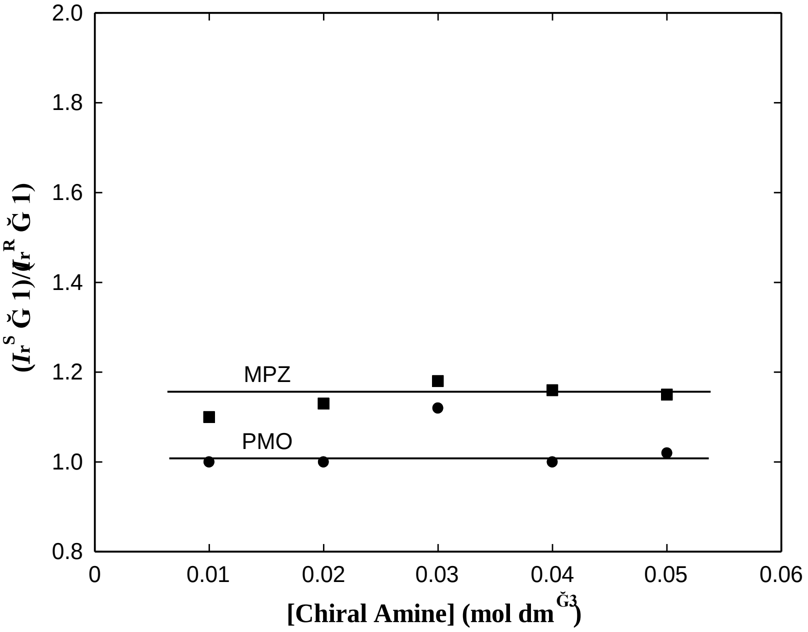
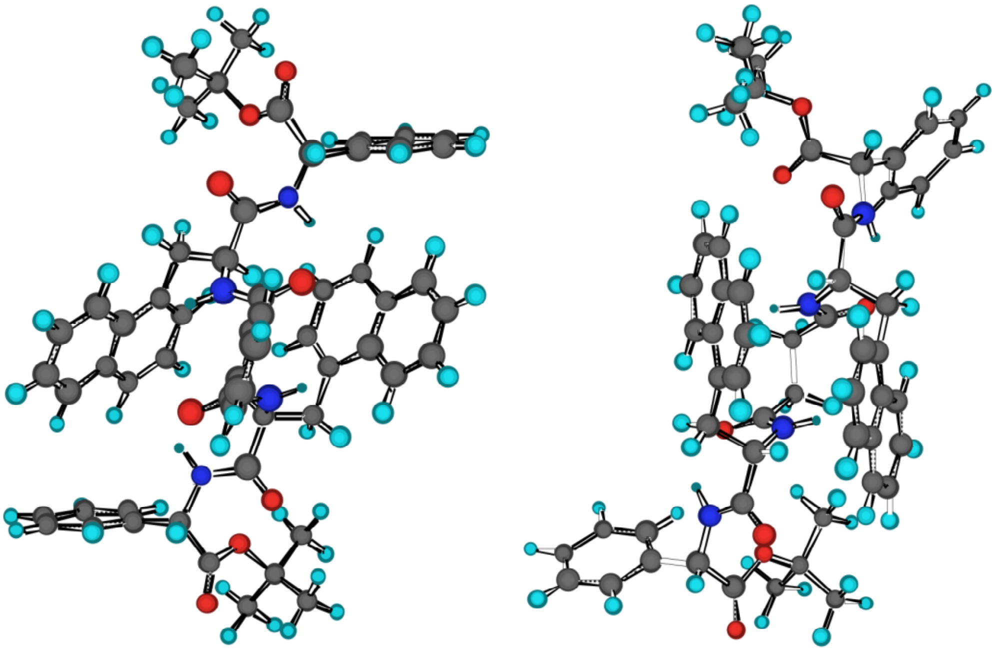


Figure 4. Plots of the $(I_r^S - 1)/(I_r^R - 1)$ ratios against chiral amine concentration for the fluorescence quenching of **1a** (1.25×10^{-4} mol dm^{-3}) by (*S*)-PMO and (*R*)-PMO or (*S*)-MPZ and (*R*)-MPZ in argon-saturated 1,4-dioxane at room temperature. The excitation wavelengths were 284 nm for PMO and 295 nm for MPZ.

On the other hand, from an analysis of the upward curving Stern–Volmer plots for the fluorescence quenching of **1a** by chiral PMO and MPZ, we estimated the $(I_r^S - 1)/(I_r^R - 1)$ ratio at 1.0 and 1.2 for the **1a**/PMO and **1a**/MPZ systems, respectively, as shown in Figure 4. These results confirmed that the bridged dipeptide **1a** has a lower enantiodiscriminating ability for these heterocyclic chiral amines than for the acyclic chiral amine PEA. The less upward curving Stern-Volmer plots for the quenching of **1a** by chiral PMO in particular reflect that this secondary amine is a weaker base than the tertiary amine PEA and hence contributes to the static quenching of **1a** to a much lesser extent through the hydrogen-bonding interaction (data not shown). Because MPZ forms a singlet exciplex with **1a** to exhibit fluorescence at around 405 nm, a charge-transfer interaction between the excited-state **1** and ground-state chiral amine should also be involved in the emission quenching by chiral PMO. Thus, it is likely that there is a very small difference in the stabilities of the hydrogen-bonding complexes and singlet exciplexes, formed between **1a** and each enantiomer of PMO having considerably less steric bulk than PEA. The negligible effect of the 1,2-phenylene bridge on the ability to differentiate between (*S*)-PMO and (*R*)-PMO may be attributed to the minor steric effect of one naphthylalanine chromophore in **1a** on the hydrogen-bonding and charge-transfer interactions between the chiral PMO and other naphthylalanine chromophore. We already demonstrated that the flexible ethylene bridge increased the fluorescence intensity ratio I_0/I (which can be utilized as a measure of the quenching efficiency of **1**) for the reference dipeptide **1d** by a factor of approximately 2. The same bridging effect as noted in **1a** was observed for the fluorescence quenching of **1b** by PMO (I_0/I = 1.9 for **1d** and 3.2 for **1b** at [(*S*)-PMO] = 0.05 mol dm^{-3}) and MPZ (I_0/I = 3.1 for **1d** and 7.2 for **1b** at [(*S*)-MPZ] = 0.05 mol dm^{-3}). To confirm whether the two naphthalene rings in **1a** and **1b** are able to interact with each other in their excited states, the conformational energies of these two bridged dipeptides were minimized by MM2 and PM5 calculations (Figure 5). Clearly, the two naphthalene rings in **1b** carrying the flexible ethylene group are present in mutual proximity in the ground state, and hence may easily interact with each other in the excited state, although the rigid 1,2-phenylene group in **1a** inhibits the close approach of these two naphthalene rings.



1a **1b**

Figure 5. Energy-minimized conformations of the bridged dipeptides **1a** and **1b**.

On the basis of the ability of **1a** and **1b** to discriminate the (*S*)- and (*R*)-enantiomers of PEA (tertiary amine) and PMO (secondary amine), we predict that these two bridged dipeptides will display a poor enantiodiscriminating ability for chiral ALO (primary amine) owing to the weaker charge-transfer

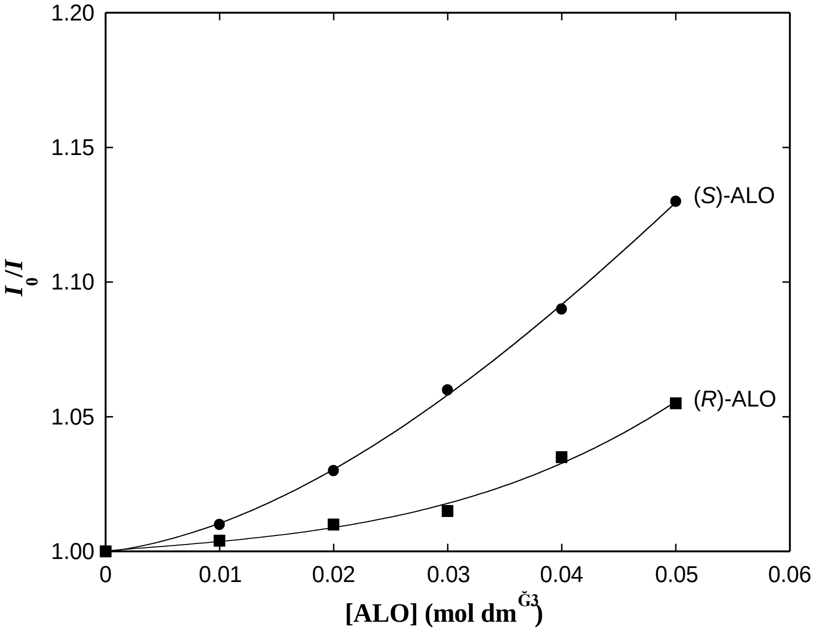


Figure 6. Stern–Volmer plots for the fluorescence quenching of **1a** (1.25×10^{-4} mol dm^{-3}) by (*S*)-ALO and (*R*)-ALO in argon-saturated 1,4-dioxane at room temperature. The excitation wavelength was 284 nm.

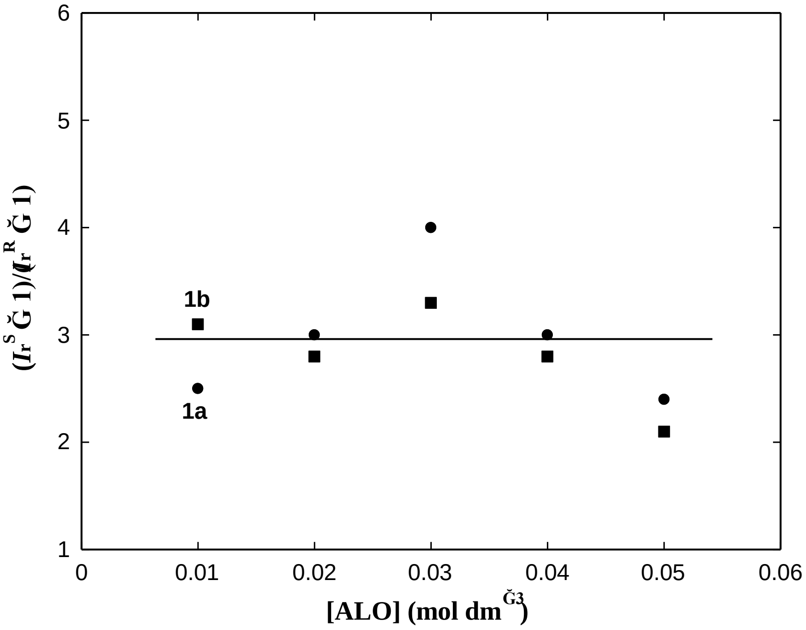


Figure 7. Plots of the $(I_r^S - 1)/(I_r^R - 1)$ ratios against ALO concentration for the fluorescence quenching of **1a** and **1b** (1.25×10^{-4} mol dm^{-3}) by (*S*)-ALO and (*R*)-ALO in argon-saturated 1,4-dioxane at room temperature. The excitation wavelengths were 284 nm.

interactions with this primary chiral amine than those with chiral PEA and PMO. Figure 6 illustrates the Stern–Volmer plots for the fluorescence quenching of **1a** by chiral ALO, and the $(I_r^S - 1)/(I_r^R - 1)$ ratio (used as a measure of the enantiodiscriminating ability of **1**) is shown in Figure 7 as a function of the

ALO concentration. The small I_0/I ratios (for example, 1.12 for **1a**, 1.25 for **1b**, and 1.17 for **1d** at [(*S*)-ALO] = 0.05 mol dm^{-3}) reflect the inefficiency of the emission quenching by chiral ALO and are consistent with the weaker charge-transfer interactions of **1** with chiral ALO that we predicted. In addition, the unexpected observation of the relatively large $(I_r^S - 1)/(I_r^R - 1)$ ratio of 3.0 for the **1a**/ALO and **1b**/ALO systems demonstrates that these systems display the highest enantiodiscriminating ability among the **1**/chiral amine systems examined (Figure 7). This observation also reveals that the ability to discriminate (*S*)-ALO and (*R*)-ALO is independent of the flexibility or rigidity of the spacer chain connecting the two naphthylalanylphenylglycine dipeptides. On the other hand, the pronouncedly curved Stern–Volmer plots (depicted in Figure 6) indicate an increased contribution of the static quenching to the total excited-state deactivation of **1** by chiral ALO. If we consider that the $(I_r^S - 1)/(I_r^R - 1)$ ratio of 1.3 for the reference dipeptide **1d** is not so large and the Stern–Volmer plots for this dipeptide is only weakly upward curving, the hydrogen-bonding interaction (that is responsible for the observed static quenching) between **1a** or **1b** and a chiral ALO molecule should occur in the two naphthylalanine chromophores bridged by the 1,2-phenylene or ethylene spacer chain. It is likely that in addition to the amino hydrogen in ALO, the hydroxy hydrogen is also involved in the above interaction, as schematically illustrated in Figure 8. A large difference in the $(I_r^S - 1)/(I_r^R - 1)$ ratio between the **1a**/ALO and **1d**/ALO systems strongly suggests that a chiral ALO molecule (which is hydrogen bonded to the amide carbonyl oxygen atoms in the naphthylalanine chromophores) plays a major role in differentiating between (*S*)-ALO and (*R*)-ALO; hence, the former enantiomer forms a more stabilized hydrogen-bonded complex than the latter enantiomer. Unfortunately, it was difficult to estimate the equilibrium constant for the formation of these hydrogen-bonded complexes because of very minor changes in the ultraviolet (UV) absorption spectra of **1a** and **1b** (measured in the presence of chiral ALO), in the wavelength range where the absorption of this amine is negligible.

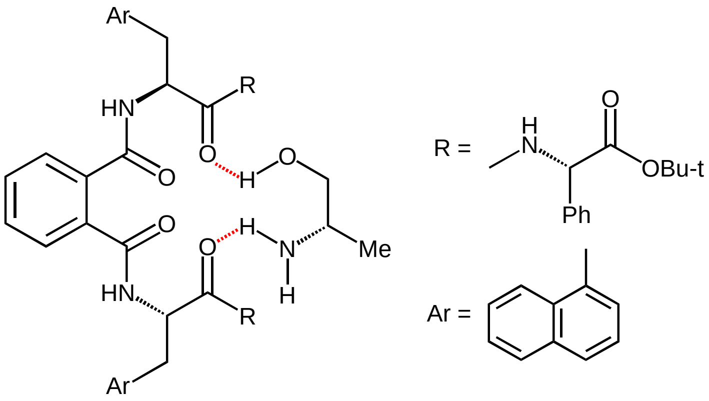


Figure 8. Schematic illustration for the hydrogen-bonding interaction between the amide carbonyl oxygen atoms in **1a** and the hydroxy and amino hydrogen atoms in (*S*)-ALO.

On the basis of the considerations described above, we predicted that the ability of the bridged dipeptide **1** to discriminate (*S*)-ALO from (*R*)-ALO is enhanced with increasing number of the 1-naphthylalanine residue in this dipeptide. To verify whether our prediction is correct, the $(I_r^S - 1)/(I_r^R - 1)$ ratios for the bridged (*S*)-1-naphthylalanyl-(*S*)-1-naphthylalanine dipeptide **1c** and its reference dipeptide **1e** were evaluated from the analysis of the Stern–Volmer plots for the fluorescence quenching of these dipeptides by chiral ALO and compared with that for **1b**. As shown in Figure 9, the Stern–Volmer plots obtained were much more weakly upward curved as compared with those for **1b**. This finding indicates a decreased contribution of the static quenching of **1c** by ALO and compatibility with the minor participation of the hydrogen bonds (between an ALO molecule and the amide carbonyl oxygen atoms of the naphthylalanine chromophores) depicted in Figure 8. The presence of the four bulky naphthylalanine chromophores in **1c** is assumed to inhibit the formation of such hydrogen bonds, as can be inferred from the energy-minimized conformation of this bridged dipeptide (Figure 10). This assumption is supported by the fact that the ability of the bridged naphthylalanylnaphthylalanine dipeptide **1c** to discriminate the ALO enantiomers [$(I_r^S - 1)/(I_r^R - 1) = 2.0$, see Figure 11] is comparable with that of the reference dipeptide **1e** [$(I_r^S - 1)/(I_r^R - 1) = 2.0$, see Figure 11]. In addition, a comparison of the $(I_r^S - 1)/(I_r^R - 1)$ ratio for **1c** (2.0) with that for **1b** (3.0) confirms that contrary to our prediction, an increase in the number of the naphthylalanine chromophore (2 → 4) lowers the enantiodiscriminating

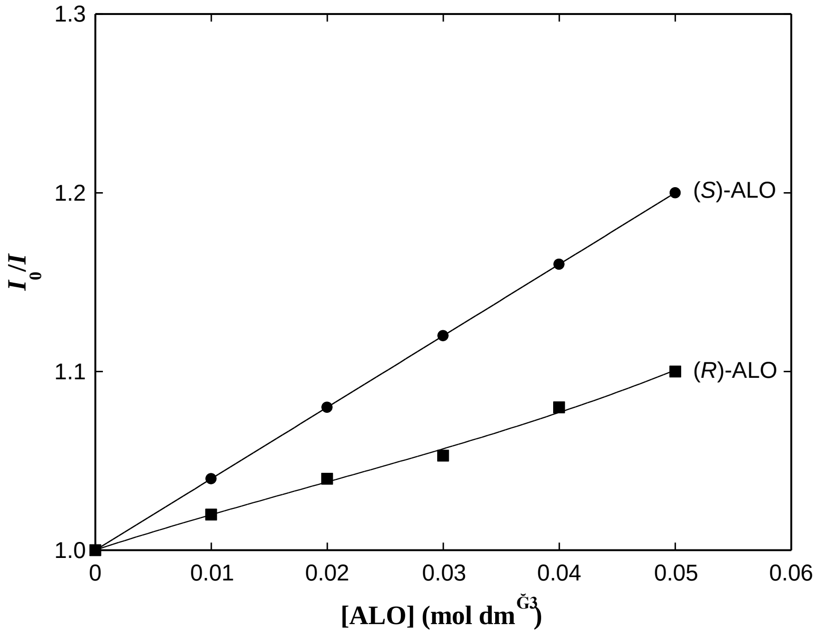
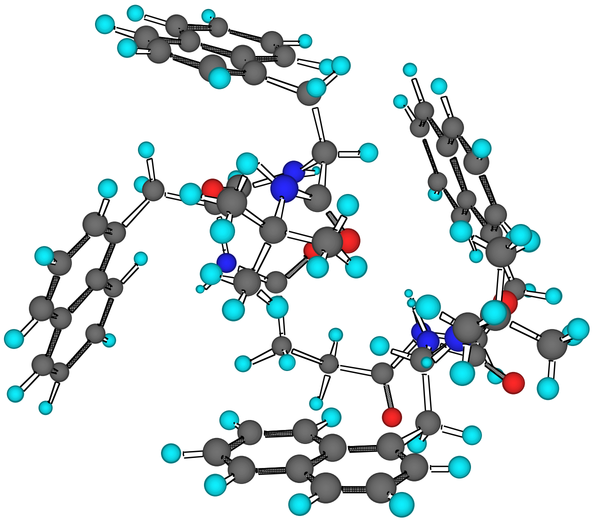


Figure 9. Stern–Volmer plots for the fluorescence quenching of **1c** (1.25×10^{-4} mol dm^{-3}) by (*S*)-ALO and (*R*)-ALO in argon-saturated 1,4-dioxane at room temperature. The excitation wavelength was 284 nm.



1c

Figure 10. Energy-minimized conformations of the bridged dipeptide **1c**.

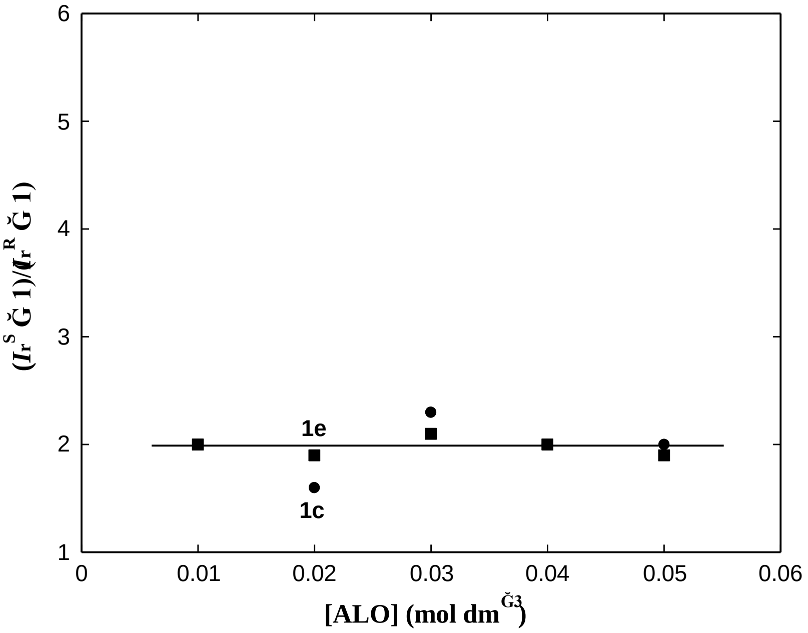


Figure 11. Plots of the $(I_r^S - 1)/(I_r^R - 1)$ ratios against ALO concentration for the fluorescence quenching of **1c** (1.25×10^{-4} mol dm^{-3}) and **1e** (2.5×10^{-4} mol dm^{-3}) by (*S*)-ALO and (*R*)-ALO in argon-saturated 1,4-dioxane at room temperature. The excitation wavelengths were 284 nm.

ability. Therefore, these considerations led to the conclusion that the bridged dipeptide **1** bearing the two naphthylalanine chromophores displays the highest ability to differentiate (*S*)-ALO from (*R*)-ALO.

EXPERIMENTAL

General methods

UV absorption and fluorescence spectra were recorded at room temperature on a Shimadzu UV-3150 spectrophotometer and Hitachi F-4500 spectrofluorometer, respectively. A cell with a 10-mm pathlength was used. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL JNM-ECA500 spectrometer. Chemical shifts were determined using tetramethylsilane as an internal standard. Electrospray ionization time-of-flight (ESI-TOF) mass spectra were recorded using a JEOL JMS-T100LC AccuTOF mass spectrometer. Matrix-assisted laser desorption/ionization (MALDI)-TOF mass spectra were recorded on a Shimadzu/Kratos TOF mass spectrometer. Elemental analyses were performed on a Perkin-Elmer PE2400 series II CHNS/O analyzer. MM2 and PM5 calculations were accomplished using CAChe 5.0 for Windows available from Fujitsu Ltd (2002). Spectrophotometric grade 1,4-dioxane was used without further purification. All other chemicals were obtained from commercial sources at the highest grade available.

N-Benzyloxycarbonyl-(*S*)-3-(1-naphthyl)alanine

(*S*)-3-(1-Naphthyl)alanine hydrochloride (2.01 g, 8.0 mmol) was dissolved in 2 mol dm^{-3} aqueous sodium hydroxide (8.0 mL, 16 mmol) and the resulting solution was cooled on ice. Benzyloxycarbonyl chloride (2.05 g, 12 mmol) and 2 mol dm^{-3} aqueous sodium hydroxide (4.0 mL, 8.0 mmol) were successively added to this solution. The reaction mixture was stirred for 1 h at room temperature and its pH was adjusted to 2 with 2 mol dm^{-3} hydrochloric acid. The resulting precipitates were collected by suction filtration and recrystallized from aqueous EtOH to afford the title compound as a colorless crystal (2.71 g, 97%). ^{1}H NMR (500 MHz, DMSO-d_6) δ = 3.22 (1H, dd, *J* = 10.3, 14.3 Hz), 3.64 (1H, dd, *J* = 4.0, 14.3 Hz), 4.31 (1H, ddd, *J* = 4.0, 8.6, 10.3 Hz), 4.91 (1H, d, *J* = 12.6 Hz), 4.95 (1H, d, *J* = 12.6 Hz), 7.23 (2H, d, *J* = 6.9 Hz), 7.29 (1H, dd, *J* = 6.9, 7.4 Hz), 7.33 (2H, dd, *J* = 7.4, 7.4 Hz), 7.40–7.44 (2H, m), 7.53 (1H, dd, *J* = 6.9, 8.0 Hz), 7.60 (1H, dd, *J* = 6.9, 8.6 Hz), 7.78 (1H, d, *J* = 8.6 Hz), 7.82 (1H, d, *J* = 7.4 Hz), 7.94 (1H, d, *J* = 8.0 Hz), 8.12 (1H, d, *J* = 8.6 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ = 33.9, 54.8, 65.2, 123.1, 125.3, 125.6, 126.3, 127.2, 127.4 (2C), 127.5, 127.7, 128.3 (2C), 128.8, 131.3, 133.4, 133.7, 136.9, 156.0, 173.4.

N-Benzyloxycarbonyl-(*S*)-3-(1-naphthyl)alanyl-(*S*)-2-phenylglycine *tert*-butyl ester

N-Benzyloxycarbonyl-(*S*)-3-(1-naphthyl)alanine (2.01 g, 5.7 mmol) and *N*-hydroxysuccinimide (0.79 g, 6.9 mmol) were dissolved in 1,4-dioxane (20 mL). *N*-Ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide hydrochloride (1.65 g, 8.6 mmol) was added to this dioxane solution with stirring at 0 °C. The reaction mixture was stirred for 2 h at room temperature and (*S*)-2-phenylglycine *tert*-butyl ester (1.42 g, 6.9 mmol) was added. The resulting mixture was stirred for an additional 1 h at room temperature. After the evaporation of the solvent, the residual solid was dissolved in EtOAc (30 mL). The EtOAc solution was washed with 10% aqueous citric acid and water and dried over magnesium sulfate. The removal of the solvent gave a crystalline solid, which was purified by column chromatography on silica gel (70–230 mesh, EtOAc/hexane = 2/1 v/v) to afford the title compound (2.32 g, 75%). ^{1}H NMR (500 MHz, DMSO-d_6) δ = 1.36 (9H, s), 3.21 (1H, dd, J = 10.9, 14.3 Hz), 3.54 (1H, dd, J = 4.0, 14.3 Hz), 4.60 (1H, ddd, J = 4.0, 9.2, 10.9 Hz), 4.87 (1H, d, J = 12.6 Hz), 4.91 (1H, d, J = 12.6 Hz), 5.31 (1H, d, J = 6.9 Hz), 7.18 (2H, d, J = 6.3 Hz), 7.30 (2H, dd, J = 6.3, 9.2 Hz), 7.31 (1H, dd, J = 9.2, 9.2 Hz), 7.36–7.43 (6H, m), 7.48 (1H, d, J = 6.9 Hz), 7.52 (1H, dd, J = 6.9, 7.4 Hz), 7.56 (1H, dd, J = 6.9, 8.0 Hz), 7.64 (1H, d, J = 9.2 Hz), 7.81 (1H, d, J = 8.0 Hz), 7.93 (1H, d, J = 7.4 Hz), 8.24 (1H, d, J = 8.6 Hz), 8.83 (1H, d, J = 6.9 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ = 27.5 (3C), 34.8, 54.8, 57.2, 65.2, 81.2, 123.8, 125.3, 125.5, 126.0, 127.0, 127.3 (2C), 127.5, 127.6, 127.7 (2C), 128.2, 128.3 (2C), 128.5, 128.6 (2C), 131.6, 133.3, 133.5, 136.4, 136.9, 155.8, 169.3, 171.5.

(*S*)-3-(1-Naphthyl)alanyl-(*S*)-2-phenylglycine *tert*-butyl ester

To a solution of *N*-benzyloxycarbonyl-(*S*)-3-(1-naphthyl)alanyl-(*S*)-2-phenylglycine *tert*-butyl ester (1.08 g, 2.0 mmol) in argon-saturated MeOH/DMF (3/1 v/v, 8 mL), 10% palladium on carbon (0.10 g) was added. The mixture was stirred for 48 h under hydrogen atmosphere at room temperature. After the catalyst had been removed by filtration, the filtrate was evaporated to dryness under reduced pressure. The resulting crystalline solid was subjected to column chromatography on silica gel (70–230 mesh, EtOAc/hexane = 2/1 v/v) to afford the title compound (0.73 g, 90%). ^{1}H NMR (500 MHz, DMSO-d_6) δ = 1.35 (9H, s), 1.85 (2H, s), 2.92 (1H, dd, J = 8.6, 13.7 Hz), 3.56 (1H, dd, J = 4.6, 13.7 Hz), 3.62 (1H, dd, J = 4.6, 8.6 Hz), 5.30 (1H, d, J = 6.9 Hz), 7.35–7.42 (7H, m), 7.51 (1H, dd, J = 6.9, 8.0 Hz), 7.54 (1H, dd, J = 6.9, 8.0 Hz), 7.79 (1H, d, J = 6.9 Hz), 7.92 (1H, d, J = 8.0 Hz), 8.16 (1H, d, J = 8.6 Hz), 8.67 (1H, d, J = 6.9 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ = 27.5 (3C), 38.1, 55.4, 56.6, 81.4, 123.8, 125.4, 125.5, 125.9, 126.8, 127.2 (2C), 127.6, 128.1, 128.5, 128.6 (2C), 131.7, 133.5, 134.8, 137.0, 168.5, 174.3.

N,*N*′-(1,2-Phenylenedicarbonyl)-bis[(*S*)-3-(1-naphthyl)alanyl-(*S*)-2-phenylglycine *tert*-butyl ester] (1a)

To a solution of (*S*)-3-(1-naphthyl)alanyl-(*S*)-2-phenylglycine *tert*-butyl ester (0.67 g, 1.7 mmol) and pyridine (0.11 g, 1.3 mmol) in 1,4-dioxane (10 mL), phthaloyl chloride (0.14 g, 0.66 mmol) was slowly added with stirring at 0 °C. The reaction mixture was stirred for 72 h at room temperature. After the solvent had been removed in vacuo, the residual solid was dissolved in EtOAc (20 mL). The EtOAc solution was washed with water and dried over magnesium sulfate. The removal of EtOAc afforded a crystalline solid, which was purified by column chromatography on silica gel (70–230 mesh, EtOAc/hexane = 2/1 v/v) to yield the title compound as a colorless crystal (0.45 g, 72%). ^{1}H NMR (500 MHz, DMSO-d_6) δ = 1.31 (18H, s), 3.34 (2H, dd, *J* = 9.2, 14.3 Hz), 3.74 (2H, dd, *J* = 4.6, 14.3 Hz), 4.90 (2H, ddd, *J* = 4.6, 9.2, 8.6 Hz), 5.28 (2H, d, *J* = 6.9 Hz), 7.13 (2H, dd, *J* = 3.4, 6.0 Hz), 7.24 (4H, d, *J* = 4.0 Hz), 7.26 (2H, dd, *J* = 5.1, 5.1 Hz), 7.35 (4H, dd, *J* = 4.0, 5.1 Hz), 7.38 (2H, dd, *J* = 3.4, 5.7 Hz), 7.40 (2H, d, *J* = 8.0 Hz), 7.44 (2H, d, *J* = 6.0 Hz), 7.48–7.51 (4H, m), 7.76 (2H, d, *J* = 8.0 Hz), 7.89 (2H, d, *J* = 7.4 Hz), 8.18 (2H, d, *J* = 6.9 Hz), 8.40 (2H, d, *J* = 6.9 Hz), 8.52 (2H, d, *J* = 8.6 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ = 27.5 (6C), 53.4 (2C), 57.3 (2C), 66.3 (2C), 81.0 (2C), 123.6 (2C), 125.3 (2C), 125.5 (2C), 126.1 (2C), 127.0 (2C), 127.3 (2C), 127.5 (2C), 127.7 (4C), 127.9 (2C), 128.4 (4C), 128.6 (2C), 129.4 (2C), 131.6 (2C), 133.4 (2C), 134.1 (2C), 135.6 (2C), 136.5 (2C), 167.7 (2C), 169.0 (2C), 170.6 (2C); ESI-TOF-MS: *m/z* calcd for $C_{58}H_{58}N_4NaO_8$ [M + Na]$^+$, 961.413; Found: 961.415. Anal. Calcd for $C_{58}H_{58}N_4O_8$: C, 74.18; H, 6.23; N, 5.97; Found: C, 74.18; H, 6.02; N, 5.94.

***N,N*´-Ethylenedicarbonyl-bis[(*S*)-3-(1-naphthyl)alanyl-(*S*)-2-phenylglycine *tert*-butyl ester] (1b)**

Following the above protocol, (*S*)-3-(1-naphthyl)alanyl-(*S*)-2-phenylglycine *tert*-butyl ester (0.32 g, 0.79 mmol), pyridine (0.056 g, 0.71 mmol), and succinyl chloride (0.055 g, 0.36 mmol) in 1,4-dioxane (4 mL) yielded the title compound as a colorless crystal (0.22 g, 70%). ^{1}H NMR (500 MHz, DMSO-d_6) δ = 1.34 (18H, s), 1.97–2.02 (2H, m), 2.09–2.15 (2H, m), 3.16 (2H, dd, *J* = 9.2, 14.3 Hz), 3.52 (2H, dd, *J* = 4.6, 14.3 Hz), 4.80 (2H, ddd, *J* = 4.6, 8.6, 9.2 Hz), 5.27 (2H, d, *J* = 6.9 Hz), 7.32–7.41 (14H, m), 7.50 (2H, dd, *J* = 6.9, 8.6 Hz), 7.54 (2H, dd, *J* = 6.9, 8.0 Hz), 7.77 (2H, d, *J* = 8.6 Hz), 7.90 (2H, d, *J* = 8.0 Hz), 8.16 (2H, d, *J* = 8.6 Hz), 8.22 (2H, d, *J* = 8.6 Hz), 8.79 (2H, d, *J* = 6.9 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ = 27.5 (6C), 30.5 (2C), 34.8 (2C), 52.7 (2C), 57.1 (2C), 81.2 (2C), 123.9 (2C), 125.2 (2C), 125.5 (2C), 125.9 (2C), 127.0 (2C), 127.4 (2C), 127.7 (4C), 128.1 (2C), 128.4 (2C), 128.5 (4C), 131.7 (2C), 133.3 (2C), 133.5 (2C), 136.4 (2C), 169.2 (2C), 171.1 (2C), 171.2 (2C); ESI-TOF-MS: *m/z* calcd for $C_{54}H_{58}N_4NaO_8$ [M + Na]$^+$, 913.413; Found, 913.415. Anal. Calcd for $C_{54}H_{58}N_4O_8$: C, 72.79; H, 6.56; N, 6.29; Found: C, 72.80; H, 6.28; N, 6.16.

***N*-Benzoyl-(*S*)-3-(1-naphthyl)alanyl-(*S*)-2-phenylglycine *tert*-butyl ester (1d)**

Following the above protocol, (*S*)-3-(1-naphthyl)alanyl-(*S*)-2-phenylglycine *tert*-butyl ester (0.25 g, 0.61 mmol), pyridine (0.050 g, 0.67 mmol), and benzoyl chloride (0.090 g, 0.67 mmol) in 1,4-dioxane (3 mL) yielded the title compound as a colorless crystal (0.30 g, 97%). ^{1}H NMR (500 MHz, DMSO-d_6) δ = 1.36 (9H, s), 3.45 (1H, dd, *J* = 10.9, 14.3 Hz), 3.66 (1H, dd, *J* = 4.0, 14.3 Hz), 5.05 (1H, ddd, *J* = 4.0, 8.6, 10.9 Hz), 5.33 (1H, d, *J* = 6.9 Hz), 7.37–7.45 (8H, m), 7.49 (1H, dd, *J* = 7.4, 8.0 Hz), 7.53 (1H, d, *J* = 8.0 Hz), 7.59 (2H, dd, *J* = 6.9, 8.6 Hz), 7.72 (2H, d, *J* = 8.6 Hz), 7.77 (1H, d, *J* = 8.0 Hz), 7.90 (1H, d, *J* = 7.4

Hz), 8.34 (1H, d, J = 8.6 Hz), 8.69 (1H, d, J = 8.6 Hz), 8.94 (1H, d, J = 6.9 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ = 27.5 (3C), 34.4, 53.4, 57.2, 81.2, 123.9, 125.3, 125.6, 126.1, 127.1, 127.3 (2C), 127.5, 127.8 (2C), 128.2 (3C), 128.5, 128.6 (2C), 131.3, 131.6, 133.3, 133.8, 133.9, 136.4, 166.3, 169.4, 171.4. Anal. Calcd for $C_{32}H_{32}N_2O_4$: C, 75.57; H, 6.34; N, 5.51; Found: C, 75.18; H, 6.21; N, 5.42.

N-Benzyloxycarbonyl-(*S*)-3-(1-naphthyl)alanine *tert*-butylamide

N-Benzyloxycarbonyl-(*S*)-3-(1-naphthyl)alanine (1.39 g, 4.0 mmol) and *N*-hydroxysuccinimide (0.69 g, 6.0 mmol) were dissolved in 1,4-dioxane (20 mL). To this dioxane solution, a solution of *N*-ethyl-*N′*-(3-dimethylaminopropyl)carbodiimide hydrochloride (1.15 g, 6.0 mmol) in DMF (5 mL) was added dropwise with stirring at 0 °C. The reaction mixture was stirred for 2 h at room temperature and *tert*-butylamine (0.58 g, 8.0 mmol) was added. After the resulting solution had been stirred for an additional 3 h at the same temperature, it was poured into water (100 mL). The resulting precipitate was collected by suction filtration and recrystallized from aqueous EtOH to afford the title compound as a colorless crystal (1.38 g, 86%). ^{1}H NMR (500 MHz, DMSO-d_6) δ = 1.20 (9H, s), 3.20 (1H, dd, J = 8.5, 13.7 Hz), 3.41 (1H, dd, J = 5.7, 13.7 Hz), 4.36 (1H, ddd, J = 5.7, 7.4, 8.5 Hz), 4.94 (2H, s), 7.22 (2H, d, J = 6.8 Hz), 7.27–7.33 (3H, m), 7.36–7.43 (2H, m), 7.36–7.43 (2H, m), 7.51 (1H, dd, J = 6.8, 8.0 Hz), 7.56 (1H, dd, J = 7.4, 8.0 Hz), 7.80 (1H, dd, J = 5.7, 6.8 Hz), 7.92 (1H, d, J = 8.0 Hz), 8.20 (1H, d, J = 8.5 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ = 28.3 (3C), 35.2, 50.2, 55.7, 65.1, 122.8 (2C), 123.9, 125.2, 125.4, 125.9, 126.9, 127.3 (2C), 127.5, 127.6, 128.4, 131.7, 133.3, 133.7, 137.0, 155.6, 170.4.

(*S*)-3-(1-Naphthyl)alanine *tert*-butylamide

To a solution of *N*-benzyloxycarbonyl-(*S*)-3-(1-naphthyl)alanine *tert*-butylamide (0.49 g, 1.2 mmol) in argon-saturated MeOH (20 mL), 10% palladium on carbon (0.10 g) was added. The mixture was stirred for 24 h under a hydrogen atmosphere at room temperature. After the catalyst had been removed by filtration, the filtrate was evaporated to dryness under reduced pressure. The crude product was purified by column chromatography on silica gel (70–230 mesh, $CHCl_3$/MeOH = 15/1 v/v) to yield the title compound (0.29 g, 89%). ^{1}H NMR (500 MHz, DMSO-d_6) δ = 1.23 (9H, s), 1.78 (2H, s), 2.92 (1H, dd, J = 8.5, 13.7 Hz), 3.43 (1H, dd, J = 5.1, 8.5 Hz), 3.55 (1H, dd, J = 5.1, 13.7 Hz), 7.39–7.56 (5H, m), 7.78 (1H, d, J = 6.8 Hz), 7.90 (1H, d, J = 8.0 Hz), 8.19 (1H, d, J = 8.5 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ = 28.4 (3C), 39.0, 49.6, 56.1, 123.9, 125.3, 125.5, 125.9, 126.8, 127.5, 128.5, 131.7, 133.5, 135.1, 173.8.

N-(*tert*-Butoxycarbonyl)-(*S*)-3-(1-naphthyl)alanine

(*S*)-3-(1-Naphthyl)alanine hydrochloride (1.07 g, 4.3 mmol) was dissolved in 2 mol dm^{-3} aqueous sodium hydroxide (4.2 mL, 8.4 mmol) and the resulting solution was cooled on ice. *tert*-

Butoxycarbonyl chloride (1.12 g, 5.1 mmol) and 2 mol dm^{-3} aqueous sodium hydroxide (2.1 mL, 4.2 mmol) were successively added to the above solution. The reaction mixture was stirred for 1 h at room temperature and its pH was adjusted to 2 with 2 mol dm^{-3} hydrochloric acid. The oily product was extracted several times with EtOAc and the combined EtOAc extracts were washed with water and dried over magnesium sulfate. The removal of the solvent yielded the title compound as an oily liquid (1.28 g, 95%). ^{1}H NMR (500 MHz, DMSO-d_6) δ = 1.28 (9H, s), 3.20 (1H, dd, J = 10.3, 13.7 Hz), 3.58 (1H, dd, J = 3.4, 13.7 Hz), 4.21 (1H, ddd, J = 3.4, 8.0, 10.3 Hz), 7.23 (1H, d, J = 8.0 Hz), 7.41 (1H, dd, J = 6.9, 6.9 Hz), 7.43 (1H, d, J = 6.9 Hz), 7.52 (1H, dd, J = 7.4, 8.0 Hz), 7.58 (1H, dd, J = 7.4, 8.5 Hz), 7.79 (1H, d, J = 6.9 Hz), 7.92 (1H, d, J = 8.0 Hz), 8.11 (1H, d, J = 8.5 Hz); ^{13}C NMR (500 MHz, DMSO-d_6) δ = 28.1 (3C), 33.9, 54.5, 78.1, 123.2, 125.4, 125.6, 126.3, 127.1, 127.5, 128.8, 131.4, 133.5, 134.0, 155.5, 173.8.

***N*-(*tert*-Butoxycarbonyl)-(*S*)-3-(1-naphthyl)alanyl-(*S*)-3-(1-naphthyl)alanine *tert*-butylamide**

N-(*tert*-Butoxycarbonyl)-(*S*)-3-(1-naphthyl)alanine (1.12 g, 4.2 mmol) and *N*-hydroxysuccinimide (0.72 g, 6.2 mmol) were dissolved in 1,4-dioxane (20 mL). To this dioxane solution, a solution of *N*-ethyl-*N*'-(3-dimethylaminopropyl)carbodiimide (0.72 g, 6.2 mmol) in DMF (5 mL) was added with stirring at 0 °C. The reaction mixture was stirred for 2h at room temperature and (*S*)-3-(1-naphthyl)alanine *tert*-butylamide (1.57 g, 5.0 mmol) was added to this mixture. After the resulting solution had been stirred for an additional 3 h at the same temperature, it was poured into water (100 mL). The resulting crystalline solid was collected by suction filtration and subjected to column chromatography on silica gel (70–230 mesh, EtOAc/hexane = 2/1 v/v) to yield the title compound as a colorless crystal (1.98 g, 84%). ^{1}H NMR (500 MHz, DMSO-d_6) δ = 1.15 (9H, s), 1.26 (9H, s), 3.06 (1H, dd, J = 10.3, 14.3 Hz), 3.27–3.40 (3H, m), 4.20 (1H, ddd, J = 7.4, 9.7, 14.3 Hz), 4.65 (1H, dd, J = 7.4, 14.3 Hz), 7.22–7.24 (2H, m), 7.33 (1H, dd, J = 7.4, 8.0 Hz), 7.41 (1H, d, J = 7.4 Hz), 7.41 (1H, d, J = 7.4 Hz), 7.52–7.59 (5H, m), 7.76–7.81 (2H, m), 7.88–7.93 (3H, m), 8.07 (1H, d, J = 8.5 Hz), 8.31 (1H, d, J = 8.5 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ = 28.0 (3C), 28.2 (3C), 30.7, 34.6, 35.6, 50.2, 53.6, 78.4, 123.4, 124.2, 125.2, 125.3, 125.5 (2C), 126.0, 126.1, 126.9, 127.0, 127.2, 127.8, 128.4, 128.6, 131.5, 131.9, 133.3 (2C), 133.5, 133.8, 155.1, 169.7, 171.1.

(*S*)-3-(1-Naphthyl)alanyl-(*S*)-3-(1-naphthyl)alanine *tert*-butylamide

To a solution of *N*-(*tert*-butoxycarbonyl)-(*S*)-3-(1-naphthyl)alanyl-(*S*)-3-(1-naphthyl)alanine *tert*-butylamide (0.41 g, 0.72 mmol) in MeOH (20 mL), 4 mol dm^{-3} hydrochloric acid (2 mL) was added with stirring at room temperature. The reaction mixture was allowed to stand for 3 h at this temperature. After the pH of the mixture had been adjusted to 10 with sodium carbonate, the product was extracted several times with EtOAc. The combined EtOAc extracts were washed with saturated aqueous sodium chloride and dried over magnesium sulfate. The removal of the solvent in vacuo yielded the title compound as a colorless crystal (0.30 g, 90%). ^{1}H NMR (500 MHz, DMSO-d_6) δ = 1.14 (9H, s), 1.84 (2H, s), 2.63 (1H, dd, J = 9.1, 14.8 Hz), 3.32–3.34 (3H, m), 3.45 (1H, dd, J = 4.0, 9.1 Hz), 4.67 (1H, dd, J = 7.4, 14.8 Hz), 7.23 (1H, d, J = 7.0 Hz), 7.33–7.41 (3H, m), 7.49–7.59 (5H, m), 7.76–7.80 (2H, m), 7.89–7.91 (2H, m), 8.06 (1H, d, J = 8.0 Hz), 8.21 (1H, d, J = 8.5 Hz), 8.31 (1H, d, J = 8.5 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ = 28.3 (3C), 35.9, 37.8, 50.2, 55.6, 59.7, 123.6, 124.3, 125.1, 125.3, 125.4, 125.5, 125.9 (2C), 126.8, 127.0, 127.3, 127.9, 128.4, 128.5, 131.5, 132.0, 133.3, 133.4, 133.6, 134.7, 169.9, 173.8.

***N*,*N*´-Ethylenedicarbonyl-bis[(*S*)-3-(1-naphthyl)alanyl-(*S*)-3-(1-naphthyl)alanine *tert*-butylamide] (1c)**

To a solution of (*S*)-3-(1-naphthyl)alanyl-(*S*)-3-(1-naphthyl)alanine *tert*-butylamide (0.81 g, 1.7 mmol) and pyridine (0.096 g, 1.2 mmol) in 1,4-dioxane (15 mL), succinyl chloride (0.094 g, 0.61 mmol) was slowly added with stirring at 0 °C. The reaction mixture was stirred for 24 h at room temperature. After the mixture had been concentrated to dryness under reduced pressure, the residual solid was dissolved in EtOAc (25 mL). The EtOAc solution was washed with 10% aqueous citric acid and water and dried over magnesium sulfate. The removal of the solvent afforded a crystalline solid, which was purified by column chromatography on silica gel (70–230 mesh, EtOAc/hexane = 2/1 v/v) to yield the title compound as a colorless crystal (0.36 g, 21%). ^{1}H NMR (500 MHz, DMSO-d_6) δ = 1.14 (18H, s), 2.17 (1H, d, J = 9.1 Hz), 2.32 (1H, d, J = 9.1 Hz), 2.64 (1H, d, J = 14.8 Hz), 2.74 (1H, d, J = 14.8 Hz), 3.06 (2H, dd, J = 9.1, 13.7 Hz), 3.29–3.34 (4H, m), 3.50 (2H, dd, J = 5.7, 13.7 Hz), 4.54 (4H, ddd, J = 7.4, 8.0, 14.8 Hz), 7.10 (2H, br s), 7.20 (2H, d, J = 6.8 Hz), 7.27 (2H, dd, J = 7.4, 8.0 Hz), 7.33–7.42 (4H, m), 7.44–7.47 (4H, m), 7.51 (2H, dd, J = 6.8, 7.4 Hz), 7.56 (2H, dd, J = 7.4, 8.0 Hz), 7.73 (2H, d, J = 8.5 Hz), 7.79 (2H, d, J = 8.0 Hz), 7.85–7.88 (2H, m), 7.91 (2H, d, J = 8.0 Hz), 8.05–8.07 (2H, m), 8.15 (1H, d, J = 8.0 Hz), 8.15 (1H, d, J = 8.0 Hz), 8.27 (2H, d, J = 8.0 Hz), 8.35 (2H, d, J = 6.8 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ = 28.3 (6C), 34.5 (2C), 34.9 (2C), 42.8 (2C), 50.2 (3C), 54.0 (3C), 123.5 (2C), 123.9 (2C), 125.2 (4C), 125.4 (2C), 125.5 (2C), 126.0 (2C), 126.1 (2C), 127.0 (4C), 127.2 (2C), 127.5 (2C), 128.5 (2C), 128.6 (2C), 131.5 (2C), 131.7 (2C), 133.3 (2C), 133.4 (2C), 133.5 (2C), 133.8 (2C), 169.8 (2C), 170.6 (2C), 171.2, 172.1; MALDI-TOF-MS: *m/z* calcd for $C_{64}H_{68}N_6NaO_6$ [M + Na]$^+$, 1017.26; Found, 1017.11.

***N*-Acetyl-(*S*)-3-(1-naphthyl)alanyl-(*S*)-3-(1-naphthyl)alanine *tert*-butylamide (1e)**

Following the above protocol, (*S*)-3-(1-naphthyl)alanyl-(*S*)-3-(1-naphthyl)alanine *tert*-butylamide (0.28 g, 0.60 mmol), pyridine (0.057 g, 0.72 mmol), and acetyl chloride (0.056 g, 0.71 mmol) in 1,4-dioxane (20 mL) afforded the title compound as a colorless crystal (0.30 g, 98%). ^{1}H NMR (500 MHz, DMSO-d_6) δ = 1.15 (9H, s), 1.76 (3H, s), 3.12 (1H, dd, J = 8.5, 13.7 Hz), 3.25–3.34 (2H, m), 3.46 (1H, dd, J = 6.3, 13.7 Hz), 4.58 (2H, dd, J = 7.4, 8.0 Hz), 7.21–7.24 (2H, m), 7.31 (1H, dd, J = 7.4, 7.4 Hz), 7.36 (1H, d, J = 6.3 Hz), 7.41 (1H, dd, J = 7.4, 8.0 Hz), 7.49–7.60 (4H, m), 7.75 (1H, d, J = 8.0 Hz), 7.80 (1H, d, J = 8.0 Hz), 7.89–7.94 (2H, m), 8.09–8.12 (2H, m), 8.22–8.27 (2H, m); ^{13}C NMR (125 MHz, DMSO-d_6) δ = 22.4, 28.3 (3C), 34.5, 35.0, 50.2, 53.6, 53.9, 123.6, 123.9, 125.2, 125.3, 125.5 (2C), 126.0 (2C), 126.9, 127.0, 127.1, 127.6, 128.5, 128.6, 131.5, 131.8, 133.3, 133.4, 133.6, 133.7, 169.3, 169.7, 170.8; MALDI-TOF-MS: *m/z* calcd for $C_{32}H_{35}N_3NaO_3$ [M + Na]$^+$, 509.64; Found, 509.81.

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