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PREFERRED CONFORMATIONS OF DIASTEREOMERIC *N*-ACYL-1-NAPHTHYLALANYLPROLINAMIDES AND RELATED DIPEPTIDES AND THEIR FLUORESCENCE QUENCHING BY CHIRAL AMINES

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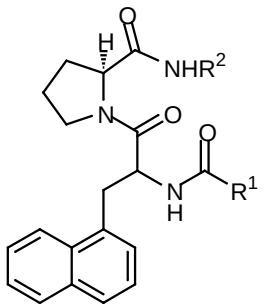
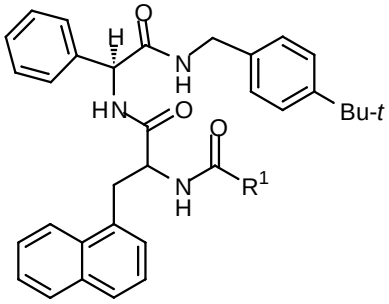
Abstract–Enantioselective fluorescence quenching was observed in the quenching processes of the 1-naphthylalanyl-(*S*)-phenylglycinamide-derived diastereomers by enantiomeric pyrrolidine-2-methanols in 1,4-dioxane at room temperature, whereas the (*S*)-prolinamide-derived ones exhibited only a much weaker enantioselective emission quenching under the same conditions. These findings were explained on the basis of substituent and conformational effects on the stability of a singlet exciplex formed between given diastereomer and chiral amine.

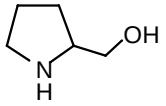
Excited-state chemistry has continued to contribute to the development of a variety of functional materials. In recent years much attention has been devoted to studies on the enantioselective emission quenching and enhancement of chiral luminescent organic materials in the presence of chiral substrates,[1] owing to the fact that emission-based molecular sensors make it possible to determine enantiomeric composition of these substrates in a high sensitivity. However, there is little study regarding the enantiodiscriminating fluorescence quenching of *N*-acyl dipeptide (bearing a fluorescent aromatic chromophore) that enables the facile determination of the absolute configuration and enantiomeric composition of chiral amines. In the course of our systematic studies toward the characterization of intramolecular fluorescence quenching in 1-naphthylalanine-based model compounds having a dialkylamino group at the carboxamide side chain, we found that charge transfer-type emission quenching takes place by a singlet exciplex mechanism even in polar solvents.[2] It is, thus, possible to develop a new type of fluorescent dipeptide sensor having the ability to differentiate the chirality of a given amine quencher in the excited state by incorporating (*S*)-proline with the rigid pyrrolidine ring or (*S*)-phenylglycine with the bulky benzene ring into *N*-acyl-1-naphthylalanine. Taking into account that it is also significant to obtain mechanistic information regarding the excited-state chiral discrimination, we synthesized diastereomeric *N*-acyl-1-naphthylalanylprolinamide and *N*-acyl-1-naphthylalanylphenylglycinamide derivatives (**1a**–**e**), and investigated substituent and conformational effects on the ratio of rate constants for the fluorescence quenching of these derivatives by chiral pyrrolidine-2-methanol (PMO) and *N*,*N*-dimethyl-1-phenylethylamine (PEA) quenchers.



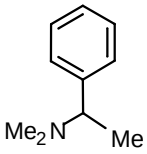
1a : R^1 = Me, R^2 = Bu
1b : R^1 = Ph, R^2 = Bu
1c : R^1 = Ph, R^2 = $CH_2C_6H_4Bu$-*t*-4



1d : R^1 = Me
1e : R^1 = Ph



PMO



PEA

The diastereomeric mixtures of **1a**–**e** were prepared by the condensation reactions of racemic *N*-acyl-1-naphthylalanines with (*S*)-*N*'-butylprolinamide, (*S*)-*N*'-(4-*tert*-butylbenzyl)prolinamide, or (*S*)-*N*'-(4-*tert*-butylbenzyl)phenylglycinamide under usual conditions in dimethylformamide.[2] The synthesis of the naphthylalanines was accomplished by the selective reduction of *N*-acyl-α-dehydronaphthylalanines[2,3] with nickel(II) chloride hexahydrate and sodium borohydride in ice-cold ethanol. Repeated preparative thin-layer chromatography over silica gel (eluent: EtOAc:hexane=1:1 or 3:1 v/v) allowed us to separate a given diastereomeric mixture into (*R*,*S*)-**1** and (*S*,*S*)-**1** of high purity.[4] Based on the finding that the proline *trans* amide bond is thermodynamically more stable than the *cis* amide bond,[5] ^{1}H NMR spectral analysis of proline-derived diastereomers confirmed that one diastereomer contains 70–80% the *trans* amide bond and 30–20% the *cis* amide bond while about 1–2% the *cis* amide bond is only included in the other. Sisido and his coworkers found that optically pure *N*-acetyl-1-naphthylalanine ethyl ester having the (*S*)-configuration exhibits a circular dichroism (CD) band of the positive sign around 280 nm.[6] Thus, the fact that the proline moiety gives no absorption in the 250–320 nm region allows us to unambiguously determine the absolute configuration of the 1-naphthylalanine moiety in each diastereomer by comparison of the CD spectrum of *N*-acetyl-(*S*)-1-naphthylalanine ethyl ester with that of the isolated diastereomer (**1a**). The diastereomer of **1a** ([**1a**]= 1.5×10^{-4} mol dm^{-3}) with the lower R_f value gave a positive CD band at 280 nm in methanol ($[\theta]_{280}$= +1000 deg cm^2 dmol^{-1}) whereas a negative CD band with equal intensities ($[\theta]_{280}$= –1000 deg cm^2 dmol^{-1}) was observed for **1a** of the higher R_f [the naphthylmethyl chromophore in **1a** gives its ^1L_a band at 283 nm in methanol; molar absorption coefficient at this wavelength is 7600 dm^3 mol^{-1} cm^{-1}]. This observation led us to conclude that the former diastereomer has (*S*,*S*)-configuration [(*S*,*S*)-**1a**] and the latter (*R*,*S*)-configuration [(*R*,*S*)-**1a**]. Because **1a**–**c**-derived diastereomers showed characteristic ^{1}H NMR signals at 4.85–5.10, 8.14–8.24 [*trans*-(*R*,*S*)-**1**, ≥98%]; 4.65–4.93, 8.05–8.16 [*cis*-(*R*,*S*)-**1**, ≤2%]; 5.19–5.39, 8.35–8.47 [*trans*-(*S*,*S*)-**1**, 70–80%]; 4.70–5.02, 8.26–8.36 ppm [*cis*-(*S*,*S*)-**1**, 30–20%], we were able to establish the configuration about the asymmetric carbon of the naphthylalanyl moiety based on the chemical shift values for a given diastereomer. On the other hand, there appeared no conformational isomerism in **1d**,**e**-derived diastereomers at room temperature. Thus, the finding that the

1-naphthylalanyl chromophore having the (*R*)-configuration exhibits these two characteristic signals at higher magnetic fields allowed us to determine the absolute configuration of a given 1-naphthylalanylphenylglycine diastereomer.

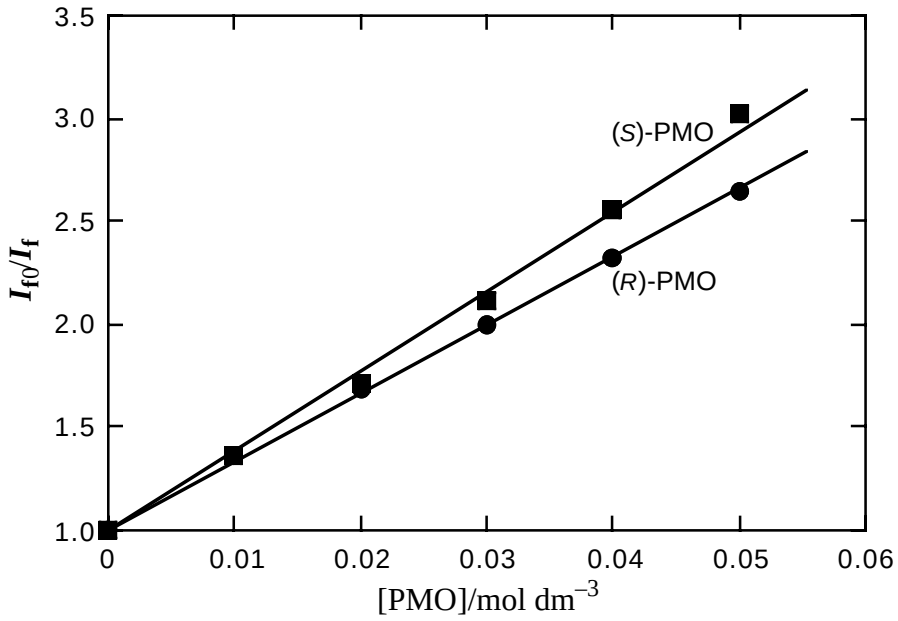


Figure 1. Stern-Volmer plots for the fluorescence quenching of (*R*,*S*)-**1b** (1.0×10^{-4} mol dm^{-3}) by (*R*)-PMO (●) and (*S*)-PMO (■) in nitrogen-saturated 1,4-dioxane at room temperature.

Table 1. Quenching constant (K_{SV}), fluorescence lifetime (τ_S), quenching rate constant (k_q), and k_q ratio [$k_q(S)/k_q(R)$] for the fluorescence quenching of (*R*,*S*)-**1** and (*S*,*S*)-**1** (1.0×10^{-4} mol dm^{-3}) by (*R*)-PMO and (*S*)-PMO in 1,4-dioxane under nitrogen at room temperature

Compound	K_{SV}/dm^3 mol^{-1}		τ_S/ns	$k_q/10^9$ dm^3 mol^{-1} s^{-1}		$k_q(S)/k_q(R)$
	(*R*)-PMO	(*S*)-PMO		(*R*)-PMO	(*S*)-PMO	
(*R*,*S*)-**1a**	73	69	33	2.2	2.1	1.0
(*S*,*S*)-**1a**	86	89	31	2.8	2.9	1.0
(*R*,*S*)-**1b**	32	38	25	1.3	1.5	1.2
(*S*,*S*)-**1b**	39	44	15	2.6	2.9	1.1
(*R*,*S*)-**1c**	31	38	26	1.2	1.5	1.2
(*S*,*S*)-**1c**	21	23	14	1.5	1.6	1.1
(*R*,*S*)-**1d**	48	63	32	1.5	2.0	1.3
(*S*,*S*)-**1d**	42	58	32	1.3	1.8	1.4
(*R*,*S*)-**1e**	24	43	16	1.5	2.7	1.8
(*S*,*S*)-**1e**	20	28	12	1.7	2.3	1.4

As typically shown in Figure 1, the fluorescence quenching of (*R*,*S*)-**1b** (1.0×10^{-4} mol dm^{-3}) by the enantiomeric isomers (*R*)-PMO and (*S*)-PMO took place according to the Stern-Volmer equation: $I_{f0}/I_f = 1$

+ K_{SV}[PMO], where I_f and I_{f0} refer to the emission intensities at 340 nm with and without PMO and K_{SV} the quenching constant. The finding that **1a**–**c** form singlet exciplexes with PMO to exhibit their fluorescences near 450–470 nm in some solvents substantiates the participation of an exciplex intermediate in the observed emission quenching process. Because more intensive exciplex fluorescence was observed in 1,4-dioxane than in other solvents examined (MeCN and THF), this nonpolar solvent was chosen for the exploration of enantiodifferentiating fluorescence quenching. Taking into account the result that (*R*,*S*)-**1** and (*S*,*S*)-**1** have different fluorescence lifetimes (τ_S) from each other in 1,4-dioxane [for example, τ_S for (*R*,*S*)-**1b** and (*S*,*S*)-**1b**= 25 and 15 ns, respectively],[7] quenching rate constants (k_q) were estimated from the slopes (K_{SV}= $k_q\tau_S$) of the linear Stern-Volmer plots and collected in Table 1. Intriguingly, while both the *N*-acetyl-(*S*)-prolinamide-derived diastereomers [(*R*,*S*)-**1a** and (*S*,*S*)-**1a**] gave almost the same quenching rate constant in any fluorescence quenching systems, quenching rate-constant ratios for the corresponding *N*-benzoyl-substituted diastereomers [(*R*,*S*)-**1b**,**c** and (*S*,*S*)-**1b**,**c**] have a tendency to become greater than unity to some extent. This tendency is more clearly recognized in the fluorescence quenching of (*R*,*S*)-**1d**,**e** and (*S*,*S*)-**1d**,**e** by PMO. In addition, a comparison of the ability of *N*-benzoyl-substituted (*R*,*S*)- and (*S*,*S*)-diastereomers to discriminate between enantiomeric PMO isomers confirms that the former diastereomer exhibits the higher discriminating ability to give a larger quenching rate-constant ratio. These findings demonstrate the benzoyl substituent to be involved in the stabilization of an exciplex intermediate in a more effective way, as compared to the acetyl one. A careful inspection of the quenching rate constant data summarized in Table 1 also reveals that the *N*-acyl-1-naphthylalanylphenylglycine-derived diastereomers (**1d**,**e**) have greater capabilities for differentiating given chiral quenchers than the proline-derived ones (**1a**–**c**), suggesting the participation of the benzene ring in the stabilization of the **1**-PMO exciplex system.

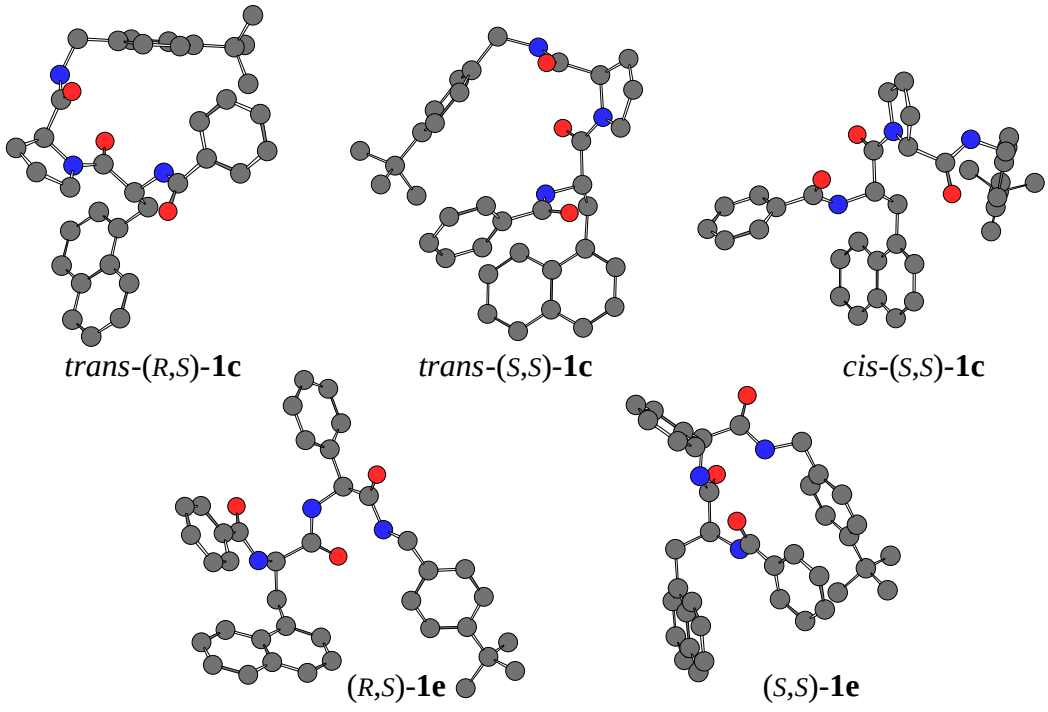


Figure 2. Energy-minimized conformations of diastereomeric **1c** and **1e**.

Table 2. Quenching constant (K_{SV}), quenching rate constant (k_q), and k_q ratio [$k_q(S)/k_q(R)$] for the fluorescence quenching of (*R*,*S*)-**1** and (*S*,*S*)-**1** (1.0×10^{-4} mol dm^{-3}) by (*R*)-PEA and (*S*)-PEA in 1,4-dioxane under nitrogen at room temperature

Compound	K_{SV}/dm^3 mol^{-1}		$k_q/10^9$ dm^3 mol^{-1} s^{-1}		$k_q(S)/k_q(R)$
	(*R*)-PEA	(*S*)-PEA	(*R*)-PEA	(*S*)-PEA	
(*R*,*S*)-**1a**	114	127	3.5	3.8	1.1
(*S*,*S*)-**1a**	97	99	3.1	3.2	1.0
(*R*,*S*)-**1b**	47	45	1.9	1.8	1.0
(*S*,*S*)-**1b**	41	44	1.6	1.8	1.1
(*R*,*S*)-**1c**	32	36	3.6	4.1	1.1
(*S*,*S*)-**1c**	22	22	1.6	1.6	1.0
(*R*,*S*)-**1d**	43	43	1.3	1.3	1.0
(*S*,*S*)-**1d**	40	45	1.3	1.4	1.1
(*R*,*S*)-**1e**	21	26	1.3	1.6	1.2
(*S*,*S*)-**1e**	16	17	1.3	1.4	1.1

Our attention is now given to a mechanism by which the PMO-derived enantiomers are discriminated in the presence of the singlet excited-state **1e**. Because attempts were not fruitful to analyze the ground-state conformations of (*R*,*S*)-**1** and (*S*,*S*)-**1** on the basis of these 2D NMR spectra in deuterated 1,4-dioxane, MM2 and PM5 calculations were applied to the searching of low-energy conformations for (*R*,*S*)-**1c**, (*S*,*S*)-**1c**, (*R*,*S*)-**1e**, and (*S*,*S*)-**1e**. First we generated all conformations of these two dipeptides by using MM2 calculations and then determined appropriate conformations [10 for (*R*,*S*)-**1c**, 13 for (*S*,*S*)-**1c**, 10 for (*R*,*S*)-**1e**, and 19 for (*S*,*S*)-**1e**] whose energies are close to those of the corresponding energy-minimized conformations depicted in Figure 2 ($\Delta E \leq 4.2$ kJ mol^{-1}), on the basis of their heats of formation (ΔH_f) estimated by PM5 calculations.[8] Our conformational analysis showed that the conformers obtained are classified into two groups: one group has the benzoyl substituent that is spatially located near the naphthalene ring and, hence, exerts its steric effect on the stability of an exciplex formed, and in the other group this acyl chromophore is relatively remote from the naphthalene ring. Valuable information obtained from this analysis is that while the proline-derived diastereomer (*R*,*S*)-**1c** (98% *trans*) has the conformers belonging to the former group in the proportion of 70% which is comparable to that (84%) of the conformers of (*S*,*S*)-**1c** (78% *trans*) classified into the former group, the phenylglycine-derived diastereomer (*R*,*S*)-**1e** possesses the former group in a much higher proportion (80%) than the diastereomer (*S*,*S*)-**1e** does (32%). These are consistent with the findings that (*R*,*S*)-**1e** shows the higher ability to discriminate between (*R*)-PMO and its enantiomer, as compared to the corresponding (*S*,*S*)-diastereomer, but there is only a small difference in its ability between the **1c**-derived diastereomers. It is likely that steric bulkiness around the naphthalene ring in diasetereomeric **1** works so as to enlarge the difference in stability between the diastereomeric **1**–amine exciplex intermediates. Next, we have to explain the reason why the **1e**-derived diastereomers display the enantiodifferentiating

ability superior to that of the **1c**-derived ones. As seen from conformers of low energies depicted in Figure 2, a benzene ring in the phenylglycine residue is spatially located on the average in the vicinity of a naphthalene ring in the naphthylalanine residue whereas a planar pyrrolidine ring in the proline residue is never able to approach the naphthalene ring and, hence, makes a negligible contribution to discriminating between diastereomeric singlet-exciplex intermediates formed. Interestingly, the use of chiral PEA as a quencher made it very difficult to observe enantiodifferentiating fluorescence quenching even for (*R*,*S*)-**1e**, as shown in Table 2. Taking into account the fact that this chiral tertiary amine quenches the given diastereomer fluorescence to a similar extent to PMO, we suggest that there are only small conformational changes of surrounding functional groups on forming a singlet exciplex between the more bulky amine, PEA, and the naphthalene ring in excited-state **1e** whereas the formation of the exciplex intermediate with the less bulky amine, PMO, is accompanied by relatively large conformational changes of this intermediate that play a pivotal role in showing the enantiodiscriminating ability in the singlet excited state.

In conclusion, it was found that among the 1-naphthylalanylphenylglycine and 1-naphthylalanylproline dipeptides examined, *N*-benzoyl-(*R*)-1-naphthylalanyl-(*S*)-phenylglycin-*N*'-(4-*tert*-butylbenzyl)amide [(*R*,*S*)-**1e**] has the highest ability to differentiate between (*R*)-PMO and (*S*)-PMO in the singlet excited state. Analysis of substituent, chiral amine, and conformational effects on the fluorescence quenching rate-constant ratios led us to propose that steric bulkiness of functional groups (spatially located near the naphthalene ring in a given dipeptide) as well as conformational changes (in this dipeptide) caused by formation of a singlet exciplex contributes to enhancing the estimated rate-constant ratio.

ACKNOWLEDGMENTS

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REFERENCES AND NOTES

1. T. Nishiyama, K. Mizuno, Y. Otsuji, and H. Inoue, *Chem. Lett*., 1994, 2227; F. Lahmani, K. Le Barbu, and A. Zehnacker-Rentien, *J. Phys. Chem. A*, 1999, **103**, 1991; L.-Z. Gong, Q.-S. Hu, and L. Pu, *J. Org. Chem*., 2001, **66**, 2358; M. T. Reetz and S. Sostmann, *Tetrahedron*, 2001, **57**, 2515; K. Jennings and D. Diamond, *Analyst*, 2001, **126**, 1063; V. J. Pugh, Q.-S. Hu, X. Zuo, F. D. Lewis, and L. Pu, *J. Org. Chem*., 2001, **66**, 6136; C. Lynam, K. Jennings, K. Nolan, P. Kane, M. A. McKervey, and D. Diamond, *Anal. Chem*., 2002, **74**, 59; J. Lin, H.-C. Zhang, and L. Pu, *Org. Lett*., 2002, **4**, 3297; L. Ma, P. S. White, and W. Lin, *J. Org. Chem*., 2002, **67**, 7577; W.-L. Wong, K.-H. Huang, P.-F. Teng, C.-S. Lee, and H.-L. Kwong, *Chem. Commun*., 2004, 384; X. Mei and C. Wolf, *J. Am. Chem. Soc*., 2004, **126**, 14736; J. Lin, A. R. Rajaram, and L. Pu, *Tetrahedron*, 2004, **60**, 11277; Z.-B. Li, J. Lin, and L. Pu, *Angew. Chem., Int. Ed*., 2005, **44**, 1690; Z.-B. Li, J. Lin, Y.-C. Qin, and L. Pu, *Org. Lett*., 2005, **7**, 3441.
2. T. Sakurai, K. Miyoshi, M. Obitsu, and H. Inoue, *Ber. Bunsenges. Phys. Chem*., 1996, **100**, 46; K. Miyoshi, K. Kubo, T. Sakurai, and H. Inoue, *Nippon Kagaku Kaishi*, 1999, 37; K. Ozawa, K. Miyoshi,

K. Kubo, T. Igarashi, and T. Sakurai, *Nippon Kagaku Kaishi*, 2000, 511.

3. K. Noda, Y. Shimohigashi, and N. Izumiya, 'The Peptides-Analysis, Synthesis, Biology,' Vol. 5 (Part B), ed. by E. Gross and J. Meienhofer, Academic Press, New York, 1983, pp. 305–308; K. Maekawa, T. Igarashi, K. Kubo, and T. Sakurai, *Tetrahedron*, 2001, **57**, 5515.
4. Selected data for (*R*,*S*)-**1a**: mp 104.0–105.0 °C (EtOAc-hexane); IR (KBr) ν/cm^{-1}= 3286, 2956, 1641, 1542; ^{1}H NMR (600 MHz, $CDCl_3$) δ= 0.89 (3H, t, *J*= 7.3 Hz), 1.08–1.19 (2H, m), 1.29 (2H, tq, *J*= 7.0, 7.3 Hz), 1.43 (2H, tt, *J*= 5.5, 7.0 Hz), 1.49–1.57 (1H, m), 1.81–1.86 (1H, m), 1.96–1.99 (1H, m), 2.04 (3H, s), 3.08–3.29 (3H, m), 3.45 (1H, dd, *J*= 10.7, 13.2 Hz), 3.60 (1H, dd, *J*= 4.9, 13.2 Hz), 4.21 (1H, d, *J*= 6.9 Hz), 4.63–4.67 (1H, m; *cis*-isomer), 4.85 (1H, ddd, *J*= 4.9, 6.4, 10.7 Hz), 6.57 (1H, d, *J*= 6.4 Hz), 6.73 (1H, t, *J*= 6.4 Hz), 7.35–7.40 (2H, m), 7.51 (1H, dd, *J*= 7.0, 7.1 Hz), 7.58 (1H, dd, *J*= 7.0, 7.1 Hz), 7.77 (1H, d, *J*= 8.0 Hz), 7.85 (1H, d, *J*= 8.0 Hz), 8.05 (1H, d, *J*= 8.5 Hz; *cis*), 8.14 (1H, d, *J*= 8.5 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ= 13.8, 20.0, 23.0, 23.7, 28.1, 31.4, 35.7, 39.3, 46.5, 52.9, 60.6, 123.3, 125.4, 126.1, 126.7, 127.7, 128.2, 128.9, 132.05, 132.10, 133.7, 170.6, 170.7, 171.4. Anal. Calcd for $C_{24}H_{31}N_3O_3$: C, 70.39; H, 7.63; N, 10.26. Found: C, 70.18; H, 7.55; N, 10.15.

   Selected data for (*S*,*S*)-**1a**: mp 108.0–110.0 °C (EtOAc-hexane); IR (KBr) ν/cm^{-1}= 3350, 3316, 2956, 1635, 1539; ^{1}H NMR (600 MHz, $CDCl_3$) δ= 0.87 (3H, t, *J*= 7.3 Hz; *cis*-isomer), 0.96 (3H, t, *J*= 7.3 Hz), 1.23 (2H, tq, *J*= 7.3, 7.5 Hz; *cis*), 1.34–1.43 (1H, m), 1.38 (2H, tq, *J*= 7.3, 7.5 Hz), 1.50 (2H, tt, *J*= 5.8, 7.5 Hz), 1.58–1.73 (2H, m), 2.01 (3H, s), 2.05 (3H, s; *cis*), 2.18–2.25 (2H, m), 2.63 (1H, dd, *J*= 2.1, 8.3 Hz; *cis*), 3.04 (2H, tt, *J*= 5.8, 7.3 Hz; *cis*), 3.10–3.40 (4H, m), 3.66 (1H, dd, *J*= 10.0, 13.7 Hz; *cis*), 3.70 (1H, dd, *J*= 4.9, 13.7 Hz), 4.46 (1H, dd, *J*= 2.1, 8.3 Hz), 4.70 (1H, ddd, *J*= 4.9, 8.4, 10.0 Hz; *cis*), 5.19 (1H, ddd, *J*= 4.9, 8.4, 10.0 Hz), 6.10 (1H, t, *J*= 6.7 Hz; *cis*), 6.41 (1H, d, *J*= 8.4 Hz; *cis*), 6.42 (1H, d, *J*= 8.4 Hz), 6.61 (1H, t, *J*= 6.7 Hz), 7.23 (1H, d, *J*= 7.0 Hz), 7.35 (1H, dd, *J*= 7.0, 8.2 Hz), 7.41 (1H, dd, *J*= 7.0, 8.2 Hz; *cis*), 7.50–7.55 (1H, m), 7.60–7.64 (1H, m), 7.77 (1H, d, *J*= 8.2 Hz), 7.80 (1H, d, *J*= 8.2 Hz; *cis*), 7.86 (1H, d, *J*= 8.2 Hz), 7.89 (1H, d, *J*= 8.2 Hz; *cis*), 8.26 (1H, d, *J*= 8.2 Hz; *cis*), 8.35 (1H, d, *J*= 8.2 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ= 13.9, 20.2, 21.9, 23.2, 24.7, 27.0, 30.4, 31.3, 31.7, 36.8, 37.1, 39.3, 39.4, 46.6, 47.2, 51.3, 52.9, 60.16, 60.19, 123.58, 123.63, 125.2, 125.7, 126.1, 126.3, 126.9, 127.6, 127.8, 128.2, 128.3, 128.9, 129.0, 131.9, 132.2, 133.7, 169.7, 170.0, 171.8. Anal. Calcd for $C_{24}H_{31}N_3O_3$: C, 70.39; H, 7.63; N, 10.26. Found: C, 70.10; H, 7.62; N, 10.51.

   Selected data for (*R*,*S*)-**1e**: mp 223.5–224.5 °C (EtOAc); IR (KBr) ν/cm^{-1}= 3299, 2965, 1625, 1546; ^{1}H NMR (600 MHz, $CDCl_3$) δ= 1.24 (9H, s), 3.38 (1H, ddd, *J*= 5.8, 8.2, 13.6 Hz), 3.74 (1H, ddd, *J*= 5.8, 8.2, 13.6 Hz), 4.27 (1H, dd, *J*= 5.8, 15.2 Hz), 4.38 (1H, dd, *J*= 5.8, 15.2 Hz), 4.99 (1H, ddd, *J*= 5.8, 5.8, 6.8 Hz), 5.33 (1H, d, *J*= 3.2, 6.5 Hz), 6.14 (1H, dd, *J*= 5.8, 5.8 Hz), 6.62 (1H, d, *J*= 6.5 Hz), 6.99 (1H, d, *J*= 6.8 Hz), 7.04 (2H, d, *J*= 7.2 Hz), 7.05 (1H, d, *J*= 6.9 Hz), 7.12 (1H, dd, *J*= 6.8, 8.2 Hz), 7.23 (1H, dd, *J*= 8.6, 8.6 Hz), 7.28-7.34 (7H, m), 7.39 (2H, dd, *J*= 7.2, 7.2 Hz), 7.55 (1H, dd, *J*= 7.2, 8.2 Hz), 7.64 (2H, d, *J*= 7.2 Hz), 7.66 (1H, dd, *J*= 7.2, 8.2 Hz), 7.81 (1H, d, *J*= 8.2 Hz), 8.32 (1H, d, *J*= 8.2 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ= 31.3 (3C), 34.5, 43.5 (2C), 54.8, 57.6, 123.7, 125.4, 125.5 (2C), 126.0, 126.8, 127.1 (2C), 127.3 (2C), 127.6 (2C), 127.9, 128.0, 128.5, 128.6 (3C), 128.9, 129.0 (2C), 131.8, 131.9, 133.9, 134.4 (2C), 136.9, 150.5, 167.3, 169.0, 170.4. Anal. Calcd for

$C_{39}H_{39}N_3O_3$: C, 78.36; H, 6.58; N, 7.03. Found: C, 78.23; H, 6.26; N, 6.96.

Selected data for (*S*,*S*)-**1e**: mp 248.5–249.5 °C (EtOAc); IR (KBr) ν/cm^{-1}= 3289, 2961, 1631, 1530; ^{1}H NMR (600 MHz, $CDCl_3$) δ= 1.29 (9H, s), 3.51 (1H, dd, *J*= 5.8, 8.2 Hz), 3.80 (1H, dd, *J*= 5.8, 8.2 Hz), 4.25 (1H, dd, *J*= 5.8, 8.9 Hz), 4.38 (1H, dd, *J*= 5.8, 8.9 Hz), 5.04 (1H, ddd, *J*= 5.8, 5.8, 6.5 Hz), 5.16 (1H, d, *J*= 7.9 Hz), 5.83 (1H, dd, *J*= 5.8, 5.8 Hz), 6.77 (1H, d, *J*= 6.8 Hz), 6.96 (1H, d, *J*= 6.5 Hz), 7.19–7.20 (2H, m), 7.26–7.27 (4H, m), 7.31–7.38 (5H, m), 7.48 (2H, dd, *J*= 6.8, 7.9 Hz), 7.57 (1H, dd, *J*= 6.8, 8.2 Hz), 7.65 (1H, d, *J*= 8.6 Hz), 7.77 (1H, d, *J*= 7.9 Hz), 7.86 (1H, d, *J*= 8.6 Hz), 8.35 (1H, d, *J*= 8.6 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ= 31.3 (3C), 34.5, 35.9, 43.4, 54.7, 57.8, 123.7, 125.4, 125.6 (2C), 125.9, 126.7, 127.1 (2C), 127.28 (2C), 127.34 (2C), 127.9, 128.2, 128.5 (4C), 129.0, 129.1 (2C), 131.8, 132.1, 132.5, 133.7, 134.0, 134.5, 150.7, 167.2, 168.6, 170.3. Anal. Calcd for $C_{39}H_{39}N_3O_3$: C, 78.36; H, 6.58; N, 7.03. Found: C, 78.45; H, 6.70; N, 6.79.

5. D. Q. McDonald and W. C. Still, *J. Org. Chem*., 1996, **61**, 1385; M. A. Fox and E. Galoppini, *J. Am. Chem. Soc*., 1997, **119**, 5277.
6. M. Sisido, S. Egusa, and Y. Imanishi, *J. Am. Chem. Soc*., 1983, **105**, 1041.
7. Fluorescence lifetimes were measured with a time-correlated single-photon counting apparatus (Edinburgh OB920), which was equipped with a flash lamp filled with hydrogen. For excitation, 283 nm light was isolated by means of a monochromator and then 339 nm fluorescence light was also separated in the same way.
8. MM2 and PM5 calculations were accomplished by using CAChe 5.0 for Windows available from Fujitsu Ltd (2002).