Synthesis of Donor–Acceptor Molecules Bridged by Turned Oligopeptides and their Photo-Induced Electron-Transfer Process

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Electron donor–acceptor molecules bridged by a β-turned dipeptide were synthesized; donor = *p*-(dimethylamino)phenyl, acceptor = 9-anthryl, and β-turned dipeptide = Pro-Xaa.† ^{1}H NMR data indicated that freedom of the molecule in solution was moderately restricted by intramolecular hydrogen bonding; the order of the rigidity follows the sequence: *trans*-form (in the CO–Pro amido bond) of the molecule **1** with D-Pro-L-Xaa > *cis*-form of **1**, *trans*-form of the diastereoisomeric **2** with L-Pro-L-Xaa > *cis*-form of **2**. Fluorescence data showed that intramolecular photo-induced electron transfer occurred in an acetonitrile solution of the molecule. In the process, the electron should move more slowly in the more conformationally restricted conformer, *trans*-**1**, than in *cis*-**1** and *trans*-**2**.

Electron-transfer processes are one of the current major topics in organic, physical, and biochemistry.[1] A variety of bridged donor–acceptor molecules have been synthesized to allow investigation of intramolecular electron-transfer mechanisms.[2] Recently, donor–acceptor molecules linked with rigid spacers have been needed to elucidate the electron-transfer mechanisms.[3] Cyclic hydrocarbons, *e.g.* cycloalkanes,[4] aromatic compounds,[5,6] *etc.*, have been used as the rigid spacer. On the other hand, proteins are important mediators of biological electron transfer and some peptides have been studied as the spacer in these molecules.[7,8] However, only macromolecules have been available as the rigid peptide-spacer: well defined α-helix[9] and globular proteins.[10] We report here the preparation of small electron donor–acceptor molecules bridged by a fairly rigid β-turned dipeptide and the intramolecular photo-induced electron transfer in a solution of the molecule; in the process, the electron moves more slowly in the more conformationally restricted molecule.

Results and Discussion

As shown in Scheme 1, two diastereoisomeric electron donor–acceptor molecules D,L-**1** and L,L-**2** were synthesized by classical procedures using a water-soluble carbodiimide (EDC) as the coupling reagent; the *N,N*-dimethylaniline moiety acts as the donor and the photo-excited anthracene moiety is the acceptor. In deuteriochloroform at 25 °C, D,L-**1** as well as the reference compounds **3**, **4** showed the presence of only the *trans*-form for the CO–Pro amido bond by their ^{1}H NMR spectra. The chemical shifts δ of the C-terminal amido and methyl protons in **1** were 6.75 and 1.80, respectively (see Table 1). The δ-values for the reference compound **3** (absence of the dimethylamino group) were 6.77 and 1.79 ppm and almost the same as those in compound **1**. However, the values of δ in the reference compound **4** (absence of anthryl group) were 7.32 and 2.74 ppm and larger than those of **1** and **3**. The upfield shift Δδ in **1** and **3** might be ascribed to the ring-current effect[11] of the *N*-terminal anthryl group. The N-terminal of compound **1** was situated close to the C-terminal in the molecule.

Fig. 1 shows that the δ-value of the NH of the (*p*-dimethylamino)phenylalanyl group of compound **1** was much more affected by addition of [$^2H_6$]dimethyl sulfoxide than was that of the C-terminal NH. Moreover, the former proton was exchanged with deuterium more rapidly than was the latter proton when a sodium carbonate–deuterium oxide solution was added to a [^{2}H]chloroform solution of compound **1**. Both the solvent effect and the H–D exchange study indicated that the

Table 1 ^{1}H NMR chemical shifts (δ) in deuteriochloroform[a]

	1	2	3	4
NH (phenylalanyl)	5.96 (−0.01)	6.11	5.95 (−0.02)	5.97
NMe_2	2.84 (−0.08)	2.80 (−0.12)		2.92
NH (C-terminal)	6.75 (−0.57)	6.30	6.77 (−0.55)	7.32
Me (C-terminal)	1.80 (−0.94)	2.35 (−0.39)	1.79 (−0.95)	2.74

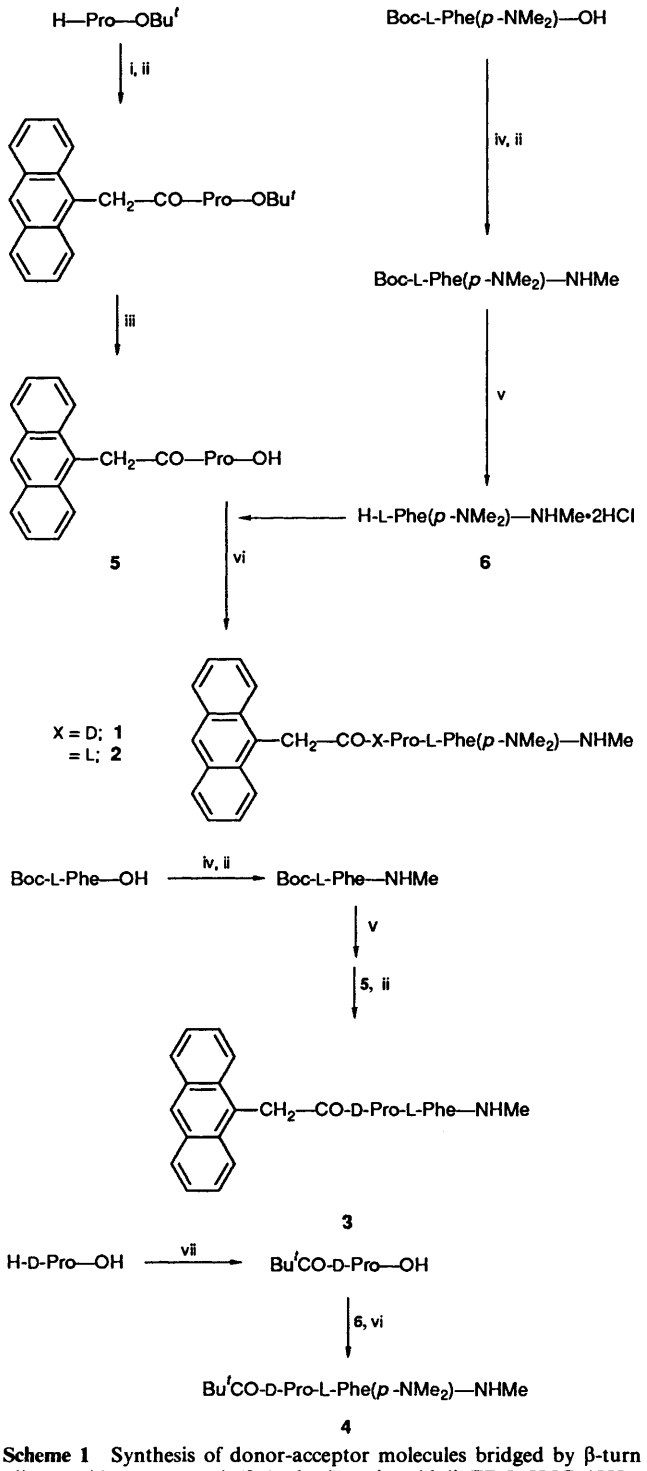
[a] 10^{-3} Mol dm^{-3}, at 25 °C. Parentheses indicate $\Delta\delta = \delta(\mathbf{1}\text{–}\mathbf{3}) - \delta(\mathbf{4})$.

C-terminal amido proton was shielded from solvent and was hydrogen-bonded to a carbonyl group in the molecule. Since it is well known that a rigid type-II′ β-turn occurs in D-Pro-L-Xaa sequence (Fig. 2A),[12] the N-terminal C=O was intramolecularly hydrogen bonded to the C-terminal NH in the solution of compound **1**.

The crystal structure of *N,N*-dimethyl(9-anthryl)acetamide, (9-anthryl)CH_2CONMe_2, has shown the following;[13] (i) two planes of an anthracene π-system and an *N,N*-dimethylacetamido moiety were nearly perpendicular because of steric repulsion between the H-atoms at C(1) and C(8) and the *N,N*-dimethylcarbamoylmethyl group, the dihedral angle being 82.1°, (ii) another steric repulsion between the 9-anthryl and dimethylamino groups might give rise to the conformer in which these groups are on opposite sides of the CH_2–CO bond axis. Such a situation might hold for the conformation of compound **1** in solution. From conformational analysis based on the above results, the most favourable conformation of compound **1** in [^{2}H]chloroform solution was proposed, as shown in Fig. 2A.

On the other hand, the δ-value of the C-terminal methyl group in L,L-**2** was 2.35 in deuteriochloroform and 0.39 ppm upfield from that in compound **4**. The upfield shift Δδ in L,L-**2** was less than half that in D,L-**1**. The C-terminal NHMe group of dipeptide **2** was situated further from the *N*-terminal anthryl group than was that of the diastereoisomeric dipeptide **1**. Since L-Pro-L-Xaa favours a weak type-I β-turn conformation (Fig. 2B),[12] the mean distance between the N-terminal and C-

† The following abbreviations are used in this paper; Xaa = amino acid, Pro = proline, Phe = phenylalanine, Phe(*p*-NMe_2) = [*p*-(dimethylamino)phenyl]alanine, Boc = *tert*-butoxycarbonyl, EDC = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, HONSu = *N*-hydroxysuccinimide, HOBt = 1-hydroxybenzotriazole, TFA = trifluoroacetic acid, I_f = fluorescence intensity, τ = fluorescence lifetime, k_{et} = electron-transfer rate.



Scheme 1 Synthesis of donor-acceptor molecules bridged by β-turn oligopeptide. *Reagents:* i, (9-Anthryl)acetic acid; ii, EDC, HOBt/CH_2Cl_2; iii, TFA; iv, $MeNH_2$•HCl, NEt_3; v, 4 mol dm^{-3} HCl/dioxane; vi, NEt_3, EDC, HONSu/CH_2Cl_2; vii, Bu^{t}COCl, aq. NaOH.

terminal of L,L-**2** in deuteriochloroform was greater than that in D,L-**1**.

In [$^2H_3$]acetonitrile at 25 °C, compound **4** showed only the *trans*-form for the CO–Pro amido bond but compound **1** showed two forms (*cis*:*trans* ≈ 1:9). In the *trans*-form of compound **1** in [$^2H_3$]acetonitrile, similar upfield shifts of the NHMe group due to an anthracene ring current were observed, as in deuteriochloroform (Table 2). In [$^2H_3$]acetonitrile, the *trans*-form of **1** favoured a rigid type-II′ β-turn conformer as well as in deuteriochloroform. A small upfield shift (0.11 ppm) of C-terminal methyl protons in the *cis*-form of compound **1** might indicate random conformation.

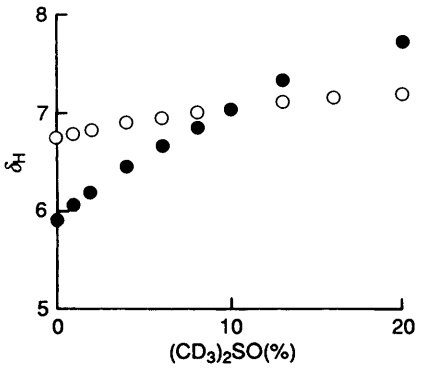


Fig. 1 Chemical shifts (δ) of amido protons of compound **1** in $CDCl_3$ and $(CD_3)_2SO$, 10^{-3} mol dm^{-3}, at 25 °C. ●: *p*-(dimethylamino)phenylalanyl NH, ○: C-terminal NH

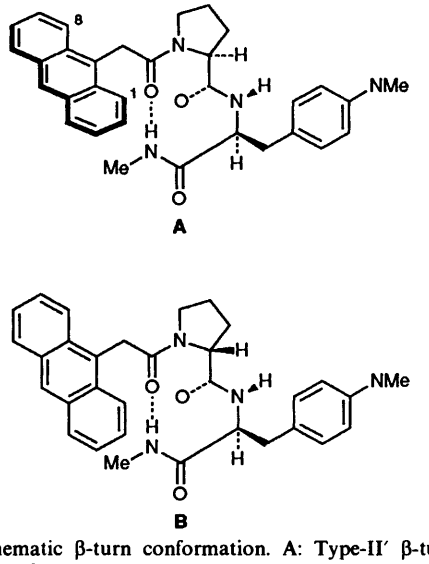


Fig. 2 Schematic β-turn conformation. A: Type-II′ β-turn (**1**). B: Type-I β-turn (**2**).

Dipeptide **2** also showed two forms (*cis*:*trans* ≈ 2:8) in [$^2H_3$]acetonitrile. The smaller value of Δδ of the *trans*-form of compound **2** in [$^2H_3$]acetonitrile was observed as well as in deuteriochloroform, and indicated a relatively weak turn conformer. The above results indicated the order of conformational rigidity (strength of hydrogen bonding, stability of folding conformer, *trans*-**1** > *cis*-**1**, *trans*-**2** > *cis*-**2**.

The absorption spectrum of compound **1** in acetonitrile could be analysed as a summation of the absorptions of the reference compounds **3** and **4**. Ground-state interactions between the 9-anthryl and *p*-(dimethylamino)phenyl groups were not observed.

In an acetonitrile solution of compound **1** under argon at 25 °C (≈1 × 10^{-5} mol dm^{-3}), the fluorescence intensity I_f was quenched to about 38% of that of compound **3** (Fig. 3). The I_f of compound **1** was unchanged upon addition of equimolar *N*,*N*-dimethyl-*p*-toluidine, but addition of a small amount of TFA induced recovery of the I_f of compound **1** to the value which was the same as the I_f of compound **3**. As well as in many other anthracene–amine molecules reported so far,[5,14] the quenching in an acetonitrile solution of compound **1** should be capable of being induced by intramolecular electron transfer. The fluorescence lifetimes τ of compounds **1** and **3** in acetonitrile under the same conditions were measured by a HORIBA NAES-1100 time-resolved spectrofluorometer. The anthryl group was selectively excited at 348 ± 10 nm and fluorescence (400–500 nm) was observed. The fluorescence decay of compounds **1** and

Table 2 ^{1}H NMR chemical shifts (δ) in [$^2H_3$]acetonitrile[a]

	1		2		
	cis	*trans*	*cis*	*trans*	4
NH (phenylalanyl)	7.1	6.76 (−0.04)	7.0	6.64	6.72
NMe_2	2.77 (−0.11)	2.82 (−0.06)	2.84 (−0.04)	2.84 (−0.04)	2.88
NH (C-terminal)	6.6	6.85 (−0.59)	6.6	6.46	7.44
Me (C-terminal)	2.51 (−0.14)	1.79 (−0.86)	2.73 (+0.08)	1.96 (−0.69)	2.65

[a] 10^{-3} Mol dm^{-3}, at 25 °C. Parentheses indicates $\Delta\delta = \delta(1,2) - \delta(4)$.

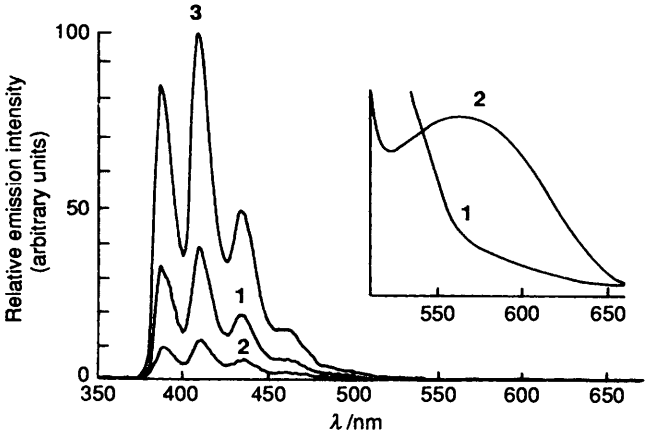


Fig. 3 Fluorescence spectra in acetonitrile. 10^{-5} Mol dm^{-3}, at 25 °C, under argon, 348 ± 4 nm excitation. The insert shows spectra on an expanded scale (348 ± 25 nm excitation).

3 followed a single exponential curve and their τ-values were 2.0 ± 0.1 and 4.7 ± 0.1 ns, respectively. The quenching value estimated from these τ was 57 ± 2% [$=1 - \tau(\mathbf{1})/\tau(\mathbf{3})$], 5% smaller than the value estimated from static fluorescence intensities, 62 ± 2% [$=1 - I_f(\mathbf{1})/I_f(\mathbf{3})$]. The 5% difference might be ascribed to the presence of *cis*-form in solution. The *cis–trans* isomerization was much slower compared with the time-scale of ^{1}H NMR measurements,[15] because each form was separately and sharply detected in the ^{1}H NMR spectrum. Within the fluorescence lifetime, the isomerization between the *cis*- and *trans*-form could not have occurred. The mean τ-value of the *cis*-form might be shorter than the instrument-limited rate ($\approx$0.1 ns) because the flexible *cis*-form changed quickly to the conformation where the excited anthracene chromophore was easily quenched in the molecule. Therefore, the mean τ of *cis*-**1** might be $\leq$0.1 ns and the τ of *trans*-**1** might be 2.0 ns. The average fluorescence lifetime τ_{ave} of stereoisomers **1** was calculated to be 1.8 ns from equation (1) where (A_i; the

$$\tau_{ave} = A_{cis}\,\tau_{cis} + A_{trans}\,\tau_{trans} \quad (1)$$

fractional proportion of the *i*th-conformer). The corrected quenching value of compound **1** in acetonitrile estimated from τ_{ave} was about 62% and identical with the value from the I_f.

As a result, the electron-transfer rate k_{et} of *trans*-**1** in acetonitrile at 25 °C is calculated to be 3 × 10^8 s^{-1} from equation (2).

$$k_{et} = 1/\tau(\textit{trans}\text{-}\mathbf{1}) - /\tau(\mathbf{3}) \quad (2)$$

On the other hand, the I_f of compound **2** in acetonitrile decreased to 10% of the value of I_f (**3**) (see Fig. 3). A new emission, moreover, was observed in the longer wavelength region, $\lambda_{max} \approx$ 570 nm, but it was very weak and broad band (probably caused by an exciplex emission). As described above, the *trans*-form of compound **2** was more flexible than that of compound **1** and the ratio of the random *cis*-form to the restricted *trans*-form in compound **2** was larger than that in compound **1**. The photo-excited anthracene group of compound **2** might be quickly quenched *via* exciplex (probably by *cis*-**2**) and other conformations (mainly by *trans*-**2**) where the ground state of the *p*-(dimethylamino)phenyl group was situated close to the singlet excited state of the 9-anthryl group in the molecule, as in *cis*-**1** (*vide supra*). The fluorescence decay of compound **2** did not obey a single-exponential curve (more than two components). The finding also suggested that compound **2** should be more conformationally free.

While in D,L-**1** and L,L-**2** the number of covalent σ-bonds between the donor and acceptor groups was the same (nine), the fluorescence quenching in the two diastereoisomers was very different.* In the photo-induced electron-transfer process of restricted β-turned *trans*-**1**, the electron should move more slowly (3 × 10^8 s^{-1}) than in flexible *cis*-**1** and *trans*-**2**. This means that relatively rigid *trans*-**1** has difficulty in taking the conformation favourable to electron-transfer whereas the other, flexible, conformers can acquire it more easily.

Experimental

General.—All apparatus and solvents used were the same as in our previous report.[8] IR spectra were measured in KBr disks, ^{1}H NMR spectra (400 MHz) were measured in $CDCl_3$ [using $CHCl_3$ (δ 7.26) as reference] and mass spectra were measured by fast atomic bombardment. (9-Anthryl)acetic acid,[8,17] Boc-L-Phe(*p*-NMe_2)-OH[18] and H-Pro-OBu^t[19] were synthesized according to the literature procedure. Other reagents were commercially available and were used as received.

(9-*Anthryl*)CH_2CO-D-*Pro*-OBu^t.—To an ice-chilled CH_2Cl_2 solution (20 cm^3, alcohol free) of H-D-Pro-OBu^t (171 mg, 1 mmol), (9-anthryl)acetic acid (260 mg, 1.1 mmol) and HOBt·H_2O (184 mg, 1.2 mmol), were added EDC·HCl (211 mg, 1.1 mmol) and NEt_3 (153 mm^3, 1.1 mmol) under nitrogen in the dark. After being stirred overnight, the solution was washed successively with aq. 2% HCl, aq. 4% $NaHCO_3$, and brine, and dried over Na_2SO_4. Purification by column chromatography on alumina with CH_2Cl_2 as eluent and recrystallization from CH_2Cl_2–hexane gave the title amide (354 mg, 91%) as pale yellow needles, m.p. 138–140 °C; ν_{max}/cm^{-1} 1738 and 1653 (C=O); δ_H(*cis*/*trans* 3/7) *cis*-form: 1.40 (9 H, s), 2.22–2.29 (2 H, m), 2.36–2.46 (2 H, m), 3.62–3.77 (2 H, m), 4.43 (1 H, d, *J* 17), 4.57 (1 H, d, *J* 17), 4.66 [1 H, m (dd)], 7.42–7.52 (4 H, m), 8.00 (2 H, d, *J* 8), 8.08 (2 H, d, *J* 8.5) and 8.41 (1 H, s), *trans*-form: 1.55 (9 H, s), 1.92–2.05 (2 H, m), 2.10–2.20 (2 H, m), 3.56–3.63 (1 H, m), 3.82–3.88 (1 H, m), 4.45 (1 H, dd, *J* 3 and 8), 4.62 (1 H, d, *J* 17), 4.68 (1 H, d, *J* 17), 7.42–7.52 (4 H, m), 8.00 (2 H, d, *J* 8), 8.16 (2 H, d, *J* 8) and 8.41 (1 H, s); *m/z* 389 (M^+, 98%), 334 (M − Bu^t + 2 H, 76) and 191 (M − CO-Pro-OBu^t, 100).

(9-*Anthryl*)CH_2CO-D-*Pro*-OH D-**5**.—An ice-chilled TFA

* Some fluorescence behaviour of the diastereoisomers has been reported (see ref. 16).

solution (10 cm^3) of (9-anthryl)CH_2CO-D-Pro-OBu^t (120 mg, 0.31 mmol) was stirred for 2 h with exclusion of moisture and then condensed under reduced pressure. To the residue was added benzene and the mixture was evaporated to give the crude acid as a yellow solid in quantitative yield. The crude acid was washed with a small amount of benzene to afford pure acid D-**5** (89 mg, 86%) as a powder, m.p. 237–241 °C; ν_{max}/cm^{-1} 1739 and 1608 (C=O); δ_H 1.96–2.25 (3 H, m), 2.58 (1 H, ddt, *J* 6, 13 and 3), 3.68 (1 H, dt, *J* 7 and 10), 3.84 (1 H, ddd, *J* 3, 8 and 10), 4.69 (1 H, d, *J* 17), 4.70 (1 H, dd, *J* 2 and 8), 4.74 (1 H, d, *J* 17), 7.48 (2 H, ddd, *J* 1, 7 and 8), 7.55 (2 H, ddd, *J* 1, 7 and 9), 8.05 (4 H, d, *J* 9) and 8.48 (1 H, s); *m/z* 334 (MH^+, 100%) and 191 (M − CO-Pro-OH, 71).

Boc-L-*Phe*(p-NMe_2)-*NHMe*.—Similarly to the synthesis of (9-anthryl)CH_2CO-D-Pro-OBu^t, EDC–HOBt coupling of Boc-L-Phe(*p*-NMe_2)-OH with $MeNH_2$·HCl gave a reaction mixture. The CH_2Cl_2 solution was washed successively with aq. 4% $NaHCO_3$ and brine, and was dried over Na_2SO_4. Flash column chromatography on silica gel with 1% MeOH–CH_2Cl_2 as eluent gave the title amide (81%) as crystals (from CH_2Cl_2–hexane), m.p. 135–138 °C; ν_{max}/cm^{-1} 3334 (NH), 1685, 1654 and 1617 (C=O); δ_H 1.42 (9 H, s), 2.72 (3 H, d, *J* 5), 2.87 (1 H, dd, *J* 7.5 and 13.5), 2.92 (6 H, s), 3.02 (1 H, dd, *J* 5 and 13), 4.20 (1 H, q, *J* 7), 5.05 (1 H, br), 5.65 (1 H, br), 6.67 (2 H, d, *J* 9) and 7.05 (2 H, d, *J* 9); *m/z* 322 (MH^+, 20%), 266 (M − Bu^t + 2 H, 16), 222 (M − Boc + 2 H, 8), 204 (M − BocNH − H, 23), 134 ($CH_2C_6H_4NMe_2^+$, 100) and 58 ($CONHMe^+$, 15).

(9-*Anthryl*)CH_2CO-D-*Pro*-L-*Phe*(p-NMe_2)-*NHMe* **1**.—An ice-chilled 4 mol dm^{-3} HCl–1,4-dioxane solution (10 cm^3) of Boc-L-Phe(*p*-NMe_2)-NHMe (1 mmol) was stirred for 2 h with exclusion of moisture and then condensed under reduced pressure to give, quantitatively, H-L-Phe(*p*-NMe_2)-NHMe·2HCl **6** as a deliquescent residue. The salt was used for the following coupling without further purification.

Similarly to the synthesis of Boc-L-Phe(*p*-NMe_2)-NHMe, EDC coupling of D-**5** with **6** by using HONSu as a coupling-promotion reagent instead of HOBt gave the *title amide* **1** (63%). Recrystallization from CH_2Cl_2–hexane gave an analytical pure sample as pale yellow crystals, m.p. 259–260 °C (Found: C, 73.7; H, 6.7; N, 10.4. $C_{33}H_{36}N_4O_3$ requires C, 73.9; H, 6.8; N, 10.4%); ν_{max}/cm^{-1} 3294 (NH) and 1649 (C=O); δ_H 1.80 (3 H, d, *J* 5), 2.02–2.11 (3 H, m), 2.34–2.43 (1 H, m), 2.82 (1 H, dd, *J* 5 and 14), 2.84 (6 H, s), 3.06 (1 H, dd, *J* 6 and 14), 3.84 (1 H, dt, *J* 10 and 7), 3.96–4.02 (1 H, m), 4.12 (1 H, t, *J* 6), 4.553 (1 H, d, *J* 17), 4.555 (1 H, dt, *J* 9 and 6), 4.64 (1 H, d, *J* 17), 5.96 (1 H, d, *J* 9), 6.54 (2 H, d, *J* 9), 6.75 (1 H, q, *J* 5), 6.88 (2 H, d, *J* 9), 7.44 (2 H, dd, *J* 7 and 8), 7.49 (2 H, dd, *J* 7 and 8), 8.00 (4 H, t, *J* 8) and 8.42 (1 H, s); *m/z* 537 (MH^+, 45%), 316 [M − Phe(*p*-NMe_2)-NHMe, 11], 219 [M − Pro-Phe(*p*-NMe_2)-NHMe, 32], 204 [M − (anthryl)CH_2CO-Pro-NH − H, 31], 191 [M − CO-Pro-Phe(*p*-NMe_2)-NHMe, 48] and 134 ($CH_2C_6H_4NMe_2^+$, 100).

(9-*Anthryl*)CH_2CO-L-*Pro*-*OBu*^{t}.—Similarly to the synthesis of (9-anthryl)CH_2CO-D-Pro-OBu^t, EDC–HOBt coupling of (9-anthryl)acetic acid with H-L-Pro-OBu^t gave the title amide (89%) [(9-anthryl)CH_2CO-L-Pro-OH (L-**5**) and (9-anthryl)-CH_2CO-L-Pro-L-Phe(*p*-NMe_2)-NHMe (**2**) were also prepared by a similar procedure to the synthesis of D-**5** and **1**, respectively] as pale yellow needles, m.p. 135–138 °C; ν_{max}/cm^{-1} 1739, 1653 and 1645 (C=O); δ_H(*cis*/*trans* 1/2) *cis*-form: 1.57 (9 H, s), 2.22–2.29 (2 H, m), 2.36–2.46 (2 H, m), 3.64–3.77 (2 H, m), 4.43 (1 H, d, *J* 17), 4.57 (1 H, d, *J* 17), 4.67 (1 H, dd, *J* 3 and 9), 7.42–7.67 (4 H, m), 8.00 (2 H, d, *J* 8), 8.09 (2 H, d, *J* 9) and 8.41 (1 H, s); *trans*-form: 1.40 (9 H, s), 1.94–2.05 (2 H, m), 2.10–2.20 (2 H, m), 3.56–3.62 (1 H, m), 3.82–3.87 (1 H, m), 4.46 (1 H, dd, *J* 3 and 8), 4.62 (1 H, d, *J* 17), 4.67 (1 H, d, *J* 17), 7.42–7.67 (4 H, m), 8.00 (2 H, d, *J* 8), 8.16 (2 H, d, *J* 9) and 8.41 (1 H, s); *m/z* 389 (M^+, 62%), 334 (M − Bu^t + 2 H, 62) and 191 (M − CO-Pro-OBu^t, 100).

(9-*Anthryl*)CH_2CO-L-*Pro*-*OH* L-**5** 85%, white powder, m.p. 236–239 °C; ν_{max}/cm^{-1} 1739 and 1608 (C=O); δ_H 1.96–2.24 (4 H, m), 2.54–2.62 (1 H, m), 3.68 (1 H, dt, *J* 7 and 10), 3.84 (1 H, ddd, *J* 3, 7 and 10), 4.69 (1 H, d, *J* 17.5), 4.70 (1 H, m), 4.75 (1 H, d, *J* 17.5), 7.48 (2 H, dd, *J* 7 and 8.5), 7.55 (2 H, ddd, *J* 1, 7 and 9), 8.05 (4 H, d, *J* 10) and 8.48 (1 H, s); *m/z* 334 (MH^+, 100%), 246 [(anthryl)CH_2CONCH^+, 92], 219 (M − Pro-OH, 34) and 191 (M − CO-Pro-OH, 70).

(9-*Anthryl*)CH_2CO-L-*Pro*-L-*Phe*(p-NMe_2)-*NHMe* **2**. 60%, pale yellow crystals, m.p. 217–219 °C (Found: C, 73.6; H, 6.7; N, 10.4. $C_{33}H_{36}N_4O_3$ requires C, 73.9; H, 6.8; N, 10.4%); ν_{max}/cm^{-1} 3290–3300 (NH) and 1651 (C=O); δ_H 1.75–1.87 (1 H, m), 1.96–2.1 (3 H, m), 2.35 (3 H, d, *J* 5), 2.80 (6 H, s), 2.87 (1 H, dd, *J* 7 and 14), 2.92 (1 H, dd, *J* 6 and 14), 3.52–3.57 [1 H, m (ddd)], 3.69 [1 H, q, (dt), *J* 8], 4.45 (1 H, d, *J* 17), 4.44–4.52 (2 H, m), 4.61 (1 H, d, *J* 17), 6.11 (1 H, d, *J* 9), 6.30 (1 H, br q, *J* 5), 6.59 (2 H, br d, *J* 8), 6.81 (2 H, d, *J* 9), 7.46–7.51 [4 H, m (quintet)], 7.94 (2 H, d, *J* 9), 8.03–8.05 [2 H, m (d)] and 8.47 (1 H, s); *m/z* 537 (MH^+, 28%), 316 [M − Phe(*p*-NMe_2)-NHMe, 13], 204 [M − (anthryl)-CH_2CO-Pro-NH − H, 60], 191 [M − CO-Pro-Phe(*p*-NMe_2)-NHMe, 64] and 134 ($CH_2C_6H_4NMe_2^+$, 100).

Boc-L-*Phe*-*NHMe*.—Similarly to the synthesis of (9-anthryl)-CH_2CO-L-Pro-OBu^t, EDC–HOBt coupling of Boc-L-Phe-OH with $MeNH_2$·HCl gave the pure title amide (91%), without the need for column chromatography, as needles, m.p. 136–139 °C; ν_{max}/cm^{-1} 3342 (NH), 1682 and 1657 (C=O); δ_H 1.40 (9 H, s), 2.72 (3 H, d, *J* 5), 3.03 (1 H, dd, *J* 7 and 13.5), 3.08 (1 H, dd, *J* 6 and 13.5), 4.27 (1 H, q, *J* 7), 5.02 (1 H, br), 5.68 (1 H, br) and 7.19–7.32 (5 H, m); *m/z* 279 (MH^+, 84%), 223 (M − Bu^t + 2 H, 100), 179 (M − Boc + 2 H, 61) and 58 ($CONHMe^+$, 49).

(9-*Anthryl*)CH_2CO-D-*Pro*-L-*Phe*-*NHMe* **3**.—An ice-chilled 4 mol dm^{-3} HCl–1,4-dioxane solution of Boc-L-Phe-NHMe was stirred for 2 h with exclusion of moisture and was then concentrated under reduced pressure. To the residue was added Et_2O and the white precipitate was removed by filtration and dried *in vacuo* to give H-L-Phe-NHMe·HCl (89%).

Similarly to the synthesis of (9-anthryl)CH_2CO-D-Pro-OBu^t, EDC–HOBt coupling of D-**5** with H-L-Phe-NHMe·HCl and flash column chromatography on silica gel with 1% MeOH–CH_2Cl_2 as eluent gave the pure *title amide* **3** (79%) as pale yellow needles (from CH_2Cl_2–hexane), m.p. 276–277 °C (Found: C, 75.25; H, 6.3; N, 8.4. $C_{31}H_{31}N_3O_3$ requires C, 75.4; H, 6.3; N, 8.5%); ν_{max}/cm^{-1} 3310 (NH) and 1653 (C=O); δ_H 1.79 (3 H, d, *J* 5), 2.05–2.15 (3 H, m), 2.37–2.46 (1 H, m), 3.01 (1 H, dd, *J* 5 and 14), 3.14 (1 H, dd, *J* 7 and 14), 3.86 (1 H, dt, *J* 10 and 7), 3.95 (1 H, ddd, *J* 6, 7 and 10), 4.13 (1 H, dd, *J* 5 and 8), 4.58 (1 H, d, *J* 8), 4.65 (1 H, dt, *J* 4 and 3), 4.66 (1 H, d, *J* 8), 5.95 (1 H, d, *J* 9), 6.77 (1 H, br q), 7.05–7.06 (2 H, m), 7.12–7.20 (3 H, m), 7.45 (2 H, ddd, *J* 1, 7 and 8), 7.50 (2 H, ddd, *J* 1, 7 and 9), 8.00 (4 H, t, *J* 9) and 8.43 (1 H, s); *m/z* 494 (MH^+, 50%), 316 (M − Phe-NHMe, 24), 218 (M − Pro-Phe-NHMe − H, 78) and 191 (M − CO-Pro-Phe-NHMe, 100).

Bu^t*CO*-D-*Pro*-L-*Phe*(p-NMe_2)-*NHMe* **4**.—To aq. NaOH and D-proline (1 mmol) was added pivaloyl chloride (1.5 mmol) to give quantitatively Bu^{t}CO-D-Pro-OH,[20] m.p. 126–129 °C; δ_H 1.28 (9 H, s), 1.95–2.20 (4 H, m), 3.68–3.76 (2 H, m) and 4.59 (1 H, dd, *J* 4 and 9).

Similarly to the synthesis of compound **1**, EDC–HONSu coupling of Bu^{t}CO-D-Pro-OH with compound **6** gave the pure *title amide* **4** (77%) as needles, m.p. 210–212 °C (Found: C, 65.65; H, 8.6; N, 13.95. $C_{22}H_{34}N_4O_3$ requires C, 65.6; H, 8.5; N, 13.9%); ν_{max}/cm^{-1} 3338, 3274 (NH), 1684 and 1651 (C=O); δ_H

1.22 (9 H, s), 1.81–2.03 (3 H, m), 2.13–2.23 (1 H, m), 2.74 (3 H, d, *J* 5), 2.916 (6 H, s), 2.92 (1 H, dd, *J* 5.5 and 14), 3.27 (1 H, dd, *J* 6 and 14), 3.72 (2 H, t, *J* 7), 4.07 (1 H, dd, *J* 6 and 7), 4.63 (1 H, dt, *J* 9 and 6), 5.97 (1 H, d, *J* 9), 6.65 (2 H, d, *J* 9), 7.03 (2 H, d, *J* 9) and 7.32 (1 H, br); *m/z* 403 (MH^+).

(9-Anthryl)CH$_2$*CONMe*$_2$.—Similarly to the synthesis of compound **3**, EDC–HOBt coupling of (9-anthryl)acetic acid with Me_2NH·HCl gave the pure title amide[13] (67%) as yellow plates, m.p. 187.5–188.5 °C (Found: C, 82.4; H, 6.4; N, 5.3. Calc. for $C_{18}H_{17}NO$: C, 82.1; H, 6.5; N, 5.3%); ν_{max}/cm^{-1} 1651 (C=O); δ_H 3.03 (3 H, s), 3.25 (3 H, s), 4.64 (2 H, s), 7.45 (2 H, ddd, *J* 1, 7 and 8), 7.50 (2 H, ddd, *J* 1, 7 and 9), 8.01 (2 H, d, *J* 8), 8.10 (2 H, d, *J* 8) and 8.42 (1 H, s); *m/z* 264 (MH^+, 100%), 191 (M − $CONMe_2$, 66) and 72 ($CONMe_2^+$, 37).

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