Synthesis and Electron-Transfer Efficiency of Oligopeptide-Bridged Donor–Acceptor Molecules

Hitoshi Tamiaki and Kazuhiro Maruyama*
Department of Chemistry, Faculty of Science, Kyoto University, Kyoto 606, Japan

The synthesis of anthracene–oligopeptide–*N*,*N*-dimethylaniline molecules is described. As the oligopeptide link, sequential oligomers, -(Gly-Aib)$_n$- (n = 0–11),† were used because they were easily prepared and highly soluble. A photoinduced intramolecular electron-transfer process in the oligopeptide bridged donor–acceptor molecules is described. The dependency of the estimated electron-transfer rate on the oligomerization number n supported the possible mediation of amido and/or hydrogen in the electron-transfer process.

Protein-mediated electron transfer is biologically important. Naturally occurring globular protein-bridged donor–acceptor systems have been investigated.[1,2] Natural proteins, however, are so complex and structurally unidentified, and have such subtle binding propensities that a desired modification of their molecular structure is difficult to achieve. In contrast, synthetic donor–acceptor molecules with a linkage of known structure will provide decisive means for elucidating electron-transfer mechanisms.[1,3] The synthetic donor–oligopeptide–acceptor systems investigated so far[3] have a limited length of oligopeptide between the donor and the acceptor (at most, five residues). They have, however, two inevitable disadvantages; their problematic synthesis and their poor solubility. Here, we report an efficient synthesis of highly soluble oligopeptides (0–22 residues) protected with donor and acceptor molecules at the two ends. Possible correlation between the number of oligomerized amino acids and the electron-transfer process was investigated. The study led to the interesting findings that (i) electrons moved through amido and hydrogen bonds and/or (ii) the synthetic molecules had some special structures.

Results and Discussion

In the oligopeptide-bridged donor–acceptor molecules, a dimethylaminophenyl group was used as the donor and a photoexcited 9-anthryl group as the acceptor. To avoid conjugation of the chromophores with the amide in the oligopeptide spacer, a methylene group was introduced between the chromophores and the amido groups. The above requirements led to synthesis of the oligopeptides protected with a 9-anthrylmethylcarbonyl group (A-CH_2CO-) at the *N*-terminal and 4-(dimethylamino)benzylamino group (-$NHCH_2$-D) at the *C*-terminal. Next, attempts were made to prepare an oligopeptide link which would be easily synthesized and highly soluble. It is well known that the oligopeptides containing many Aib residues are highly soluble,[4] but homo-oligomers of Aib are not so easy to synthesize because of the steric hindrance.[5] Although Gly has high reactivity, homo-oligomers of Gly are rather too insoluble and bend to form some intermolecular β-structures.[6] It was hoped that both problems could be solved by using sequential oligomers of Gly-Aib. In the present case, there was no chiral centre and it was unnecessary to suppress racemization. However, mild conditions were used for synthesis of the oligopeptides so that the method might be adopted for an optically active oligopeptide system: use of DCC or a water-soluble carbodiimide (EDC) as a coupling reagent in dichloromethane.

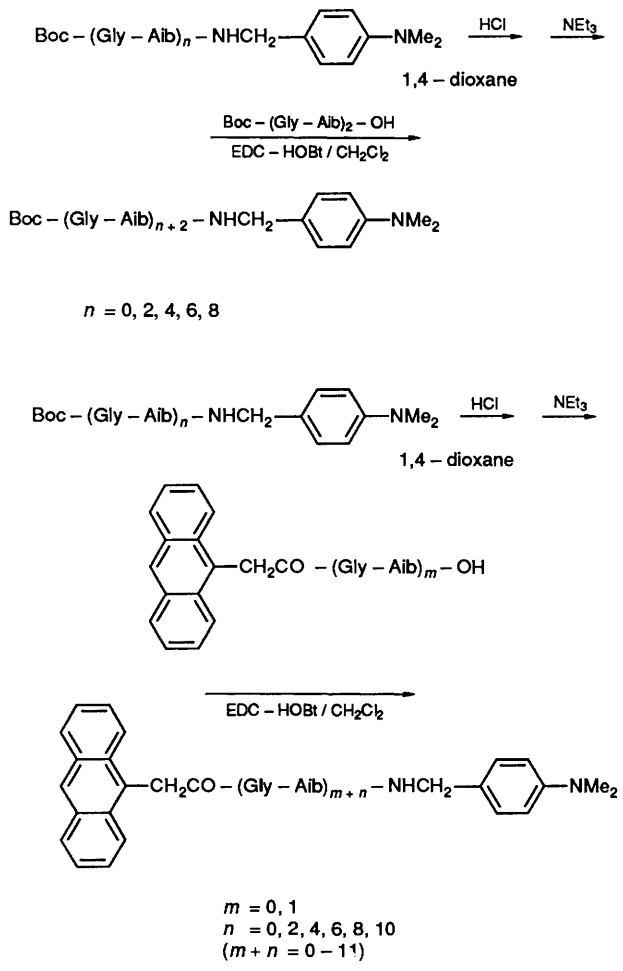
Using only EDC (or DCC) the yield of oligopeptides tended to be lower with increasing size of oligomer. Addition of HONSu as a coupling promoter improved the yield, but undesired by-products (not determined) were obtained when longer coupling components were used. Furthermore, in the coupling of 9-anthrylacetic acid (A-CH_2CO_2H) with an amino component, the active ester, A-CH_2CO_2NSu was too stable to react with the amino component.‡ Addition of HOBt gave a good yield in the synthesis of longer oligopeptides; the yields in the synthesis of Boc-(Gly-Aib)$_8$-$NHCH_2$-D from Boc-(Gly-Aib)$_2$-OH and H-(Gly-Aib)$_6$-$NHCH_2$-D with EDC–HONSu and EDC–HOBt were 26 and 72% respectively; also, the yields of A-CH_2CO-(Gly-Aib)$_{10}$-$NHCH_2$-D from A-CH_2CO-(Gly-Aib)$_2$-OH and H-(Gly-Aib)$_8$-$NHCH_2$-D with EDC–HONSu and EDC–HOBt were 35 and 59%, respectively.

Which carboxy and amino components were coupled in the synthesis of longer oligopeptides was also of importance. In the synthesis of Boc-(Gly-Aib)$_8$-$NHCH_2$-D, for example, the coupling of Boc-(Gly-Aib)$_4$-OH with H-(Gly-Aib)$_4$-$NHCH_2$-D by EDC–HOBt gave the product in 16% yield, and the yield from Boc-(Gly-Aib)$_2$-OH and H-(Gly-Aib)$_6$-$NHCH_2$-D was increased 4.5 times (to 72%). This showed that the reactivity of the intermediate formed by preliminary reaction of the acid with the dehydrating reagent (carbodiimide) could affect the overall yield. The acid should be as small as possible; Boc-Gly-Aib-OH and Boc-(Gly-Aib)$_2$-OH were used for the coupling reaction. As shown in Scheme 1, all the donor–acceptor molecules (n = 0–11) were synthesized in a reasonably high yield by stepwise elongation with EDC–HOBt.

All the above donor–acceptor molecules were soluble in typical organic solvents, as expected because of the presence of Aib residues in the molecules. In acetonitrile, they showed absorbance at wavelengths below *ca.* 400 nm. All their spectra (>280 nm) in donor–acceptor molecules were similar to the absorption of a mixture of A-CH_2CO-(Gly-Aib)$_2$-NHBzl and *N*,*N*-dimethyl-*p*-toluidine (Me-D) (see Fig. 1A). On irradiation at 366 nm in acetonitrile under argon (selective excitation of the anthracene moiety), the donor–acceptor molecules showed

† The following abbreviations are used in this paper; Gly = glycine, Aib = α-aminoisobutyric acid, Boc = *tert*-butoxycarbonyl, Z = benzyloxycarbonyl, Bzl = benzyl, PTSA = toluene-*p*-sulphonic acid, DCC = dicyclohexylcarbodiimide, EDC = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, HONSu = *N*-hydroxysucciniimide, HOBt = 1-hydroxybenzotriazole, A = 9-anthryl, D = 4-(dimethylamino)phenyl.

‡ The coupling of A-CH_2CO_2H with H-(Gly-Aib)$_8$-$NHCH_2$-D by EDC–HONSu gave A-CH_2CO-(Gly-Aib)$_8$-$NHCH_2$-D in 14% yield. Pure A-CH_2CO_2NSu was isolated but did not react with the amino component under the same conditions.



Scheme 1 Synthesis of donor–acceptor molecules

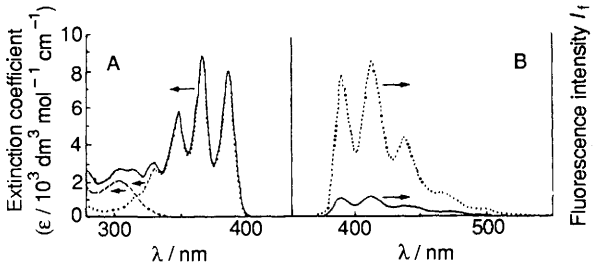


Fig. 1 (A) UV–vis. absorption spectra in acetonitrile. (——) A-CH_2CO-(Gly-Aib)$_2$-$NHCH_2$-D; (· · · ·) A-CH_2CO-(Gly-Aib)$_2$-NHBzl or A-CH_2CO-(Gly-Aib)$_2$-$NHCH_2$D + TFA (1 mm^3); (– – – –) Me-D. (B) Fluorescence emission spectra in acetonitrile (366 ± 4 nm excitation, 7 × 10^{-6} mol dm^{-3}, under argon, at 25 °C). (——) A-CH_2CO-(Gly-Aib)$_2$-$NHCH_2$-D; (· · · ·) A-CH_2CO-(Gly-Aib)$_2$-NHBzl or A-CH_2CO-(Gly-Aib)$_2$-$NHCH_2$-D + TFA (1 mm^3).

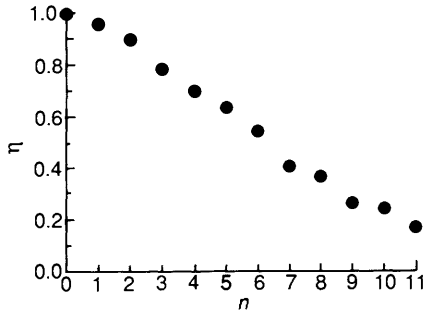


Fig. 2 Photoinduced intramolecular electron-transfer efficiency (η) in A-CH_2CO-(Gly-Aib)$_n$-$NHCH_2$-D

fluorescence emission at wavelengths above *ca.* 370 nm. All the emission spectra showed identical maxima and minima wavelengths which were the same as those of A-CH_2CO-(Gly-Aib)$_2$-NHBzl (see Fig. 1B). In solution, no exciplex emission was found at the longer wavelength region. The fluorescence increased in intensity as the size of oligomer was increased. Addition of one equivalent of Me-D to the solutions gave no change in their fluorescence spectra. However, addition of a small amount of acid, typically trifluoroacetic acid (TFA), induced recovery of the fluorescence intensities (I_f) to that of the reference anthracene having no amine in the molecule; the fluorescence spectrum of A-CH_2CO-(Gly-Aib)$_2$-$NHCH_2$-D in acetonitrile containing a small amount of TFA was almost the same as that of A-CH_2CO-(Gly-Aib)$_2$-NHBzl (see Fig. 1B).

Considering the concentration of the solutions (7 × 10^{-6} mol dm^{-3}), it is reasonable to suppose that the suppression of I_f is due to an intramolecular quenching by the amine in the molecule. Many systems reported so far[7] have shown that intramolecular quenching in acetonitrile has been induced by a photoinduced electron-transfer process. The electron-transfer efficiency η was estimated from eqn. (1) where I_f is the

$$\eta = 1 - I_f/I_f^0 \quad (1)$$

fluorescence intensity without TFA and I_f^0 is the fluorescence intensity in the presence of TFA. Fig. 2 shows that η decreases with increasing oligomerization number *n*.

Therefore, the static fluorescence quenching in the present system might be explained as follows; the average distance between 9-anthryl (A) and 4-(dimethylamino)phenyl groups (D) within the life-time of the excited singlet state of the anthracene moiety (*ca.* 6 ns) increased with elongation of the bridging oligopeptides, -(Gly-Aib)$_n$-, and an intramolecular electron-transfer process from the ground state in the amine D to the excited singlet state in the anthracene ^{1}A* gradually diminished in importance so the fluorescence intensity in the donor–acceptor molecules increased.

The rate constant k_{et} of photoinduced electron-transfer process in the donor–acceptor molecules is described[1] as in eqn. (2) where Φ_f^0 = the fluorescence quantum yield in the

$$k_{et} = (\Phi_f^0/\Phi_f - 1)/\tau_f^0 \quad (2)$$

absence of electron-transfer quencher, Φ_f = the fluorescence quantum yield in the presence of the quencher and τ_f^0 = the life-time in the absence of the quencher. On the other hand, k_{et} would be dependent on the donor–acceptor edge-to-edge distance r_{DA} as expressed in eqn. (3) where k_{et}^{max} = the

$$k_{et} = k_{et}^{max}\exp(-\beta r_{DA}) \quad (3)$$

largest rate constant and β = a coefficient.* The above two eqs. lead to eqn. (4).

$$\ln(\Phi_f^0/\Phi_f - 1) = -\beta r_{DA} + \text{constant} \quad (4)$$

In the present system, the dependence of $\ln(I_f^0/I_f - 1)(\equiv P)$ on the oligomerization number *n* is plotted in Fig. 3. For $n \geq 3$, *P* was proportional to *n* and the slope was −0.35. This showed that the donor–acceptor molecules with $n \geq 3$ took on some relatively stable and rigid conformation(s). The high solubility of the molecules in typical organic solvents supported the theory that the molecules possessed some formal secondary

* The value of β implies the barrier height of electron tunnelling in donor–acceptor systems. Usually, β varies between 1–2 Å^{-1}. In a system with a small value of β (< 1 Å^{-1}), some special mechanisms are thought to be operating; super-exchange, mediation, and so on (see ref. 1).

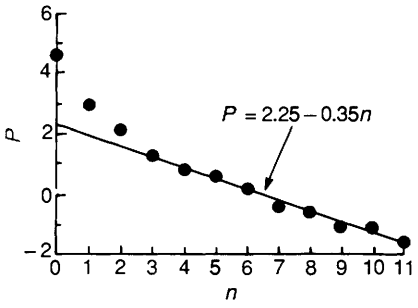


Fig. 3 The dependence of ln $(I_f^0/I_f - 1)(\equiv P)$ on the oligomerization number n in A-CH_2CO-(Gly-Aib)$_n$-$NHCH_2D$

structure such as a helix, and not a more random structure which might be less soluble. If the structure is an α-helix, the average r_{DA} must elongate with 3 Å per Gly-Aib sequence[8] and the $\beta = 0.35/3 \approx 0.1$ Å^{-1}. If the structure is an extended helix such as a π-helix,[8] elongation of more than 2 Å per Gly-Aib leads to $\beta \approx 0.2$ Å^{-1} at most. These values of β are much smaller than the usually reported values of 1–2 Å^{-1}. From the above consideration, photoinduced intramolecular electron-transfer in A-CH_2CO-(Gly-Aib)$_n$-$NHCH_2$-D should be effected by either or both of the following factors; (i) electrons move through amido and/or hydrogen bonds and β takes a small value, (ii) the donor–acceptor molecules ($n \geq 3$) have some special structure where the average edge-to-edge distance changes by 0.1–0.2 Å per residue (0.2–0.4 Å/Gly-Aib) and β takes a more usual value.

Experimental

Apparatus.—M.p.s were measured with a Yanagimoto micro melting point apparatus and are uncorrected. UV–visible spectra were measured with a Shimadzu UV-3000 spectrometer. Fluorescence spectra were measured with a Shimadzu RF-502A spectrometer. IR spectra were measured with a HORIBA FT-300 spectrometer for samples in potassium bromide disks. ^{1}H NMR spectra were recorded on a JEOL JMN-FX 400 instrument (400 MHz) for solutions in $CDCl_3$; chemical shifts (δ_H) are expressed in parts per million relative to $SiMe_4$, and *J*-values are in Hz. Mass spectra were measured with a JEOL JMS-DX-300 spectrometer; a chloroform solution of a sample was mixed with *m*-nitrobenzyl alcohol as a matrix and bombarded with a fast beam of Xe atoms. Elemental analyses were performed at the Microanalysis Center of Kyoto University.

Materials.—Dichloromethane was washed with H_2SO_4, distilled, passed through an alumina column, and used directly. Fluorescence spectrometry grade acetonitrile was purchased from Dozindo Laboratories (Luminasol®) and used without further purification. Z-Gly-ONSu,[9] H-Aib-OBzl·PTSA[10] and H-Aib-OBu^t[10] were synthesized according to the literature procedure. Other reagents and solvents were commercially available and were used as received.

(9-Anthryl)acetic Acid.—According to the procedure reported by Ciganek,[11] anthracene-9-carbaldehyde was converted into the title acid through 4 steps in an overall yield of 66%. Recrystallization from dichloromethane gave the pure title acid as yellow needles, m.p. 225–227 °C (lit.,[12] 228 °C); δ_H 4.68 (2 H, s), 7.49 (2 H, ddd, *J* 1, 6.5 and 7.5), 7.57 (2 H, ddd, *J* 1, 6.5 and 7.5), 8.15 (2 H, dd, *J* 1 and 9), 8.26 (2 H, dd, *J* 1 and 9) and 8.46 (1 H, s).

Boc-Gly-Aib-OBzl.—To a stirred dichloromethane suspension (30 cm^3) of H-Aib-OBzl·PTSA (365 mg, 1 mmol) were added triethylamine (139 mm^3, 1 mmol), Boc-Gly-OH (193 mg, 1.1 mmol) and HOBt·H_2O (184 mg, 1.2 mmol) under nitrogen, whereupon the suspension turned into a clear solution. To the ice-chilled solution were added EDC·HCl (211 mg, 1.1 mmol) and triethylamine (149 mm^3, 1.1 mmol). After being stirred overnight, the solution was condensed under reduced pressure and the residue was dissolved in ethyl acetate. The solution was washed successively with aq. 2% HCl, aq. 4% $NaHCO_3$ and brine, dried (Na_2SO_4), filtered and evaporated to give viscous oil. Storage in a refrigerator gave Boc-Gly-Aib-OBzl (343 mg, 0.98 mmol, 98%) as needles, m.p. 89.5–90.5 °C; ν_{max}/cm^{-1} 3320–3350 (NH), 1716 and 1684 (C=O); δ_H 1.45 (9 H, s), 1.58 (6 H, s), 3.74 (2 H, d, *J* 5.5), 5.06 (1 H, br t), 5.17 (2 H, s), 6.65 (1 H, br s) and 7.30–7.38 (5 H, m); *m/z* 351 (MH^+, 30%), 295 (M − Bu^t + 2 H, 65), 251 (M − Boc + 2 H, 21), 215 (M − CO_2Bzl, 5), 187 (M − Bu^t − OBzl + H, 16), 159 (M − Bu^t − CO_2Bzl + H, 17) and 91 (Bzl^+, 100).

Boc-Gly-Aib-OH.—To a methanol solution (20 cm^3) of Boc-Gly-Aib-OBzl (350 mg, 1 mmol) was added 10% palladium–charcoal (50 mg), and the mixture was stirred under hydrogen overnight, then filtered and evaporated to give a solid. The solid was triturated with hexane to afford the title acid (239 mg, 92%) as needles, m.p. 225–228 °C; ν_{max}/cm^{-1} 3415, 3290 (NH), 1701, 1684 and 1664 (C=O); δ_H 1.46 (9 H, s), 1.59 (6 H, s), 3.79 (2 H, d, *J* 6), 5.26 (1 H, br) and 6.81 (1 H, br s); *m/z* 283 (MNa^+, 9%), 261 (MH^+, 34), 205 (M − Bu^t + 2 H, 100), 187 (M − Bu^{t}O, 13), 161 (M − Boc + 2 H, 32) and 159 (M − Bu^t − CO_2H + H, 24).

Boc-(Gly-Aib)$_2$-OBzl.—A 4 mol dm^{-3} HCl–dioxane solution (10 cm^3) of Boc-Gly-Aib-OBzl (350 mg, 1 mmol) was stirred for 2 h at room temperature with exclusion of moisture and was then concentrated under reduced pressure. Diethyl ether was added to the residue and then evaporated off to give a solid, which was triturated with diethyl ether to afford H-Gly-Aib-OBzl·HCl (272 mg, 95%). The salt could be used for the following coupling without further purification.

Similarly to the synthesis of Boc-Gly-Aib-OBzl, reaction of Boc-Gly-Aib-OH and H-Gly-Aib-OBzl·HCl gave Boc-(Gly-Aib)$_2$-OBzl. Recrystallization from dichloromethane–hexane gave a pure sample in 97% yield as crystals, m.p. 187–189 °C; ν_{max}/cm^{-1} 3369, 3269 (NH), 1747, 1697, 1666 and 1643 (C=O); δ_H 1.43 (9 H, s), 1.51 (6 H, s), 1.54 (6 H, s), 3.68 (2 H, d, *J* 5.5), 3.87 (2 H, d, *J* 6), 5.15 (2 H, s), 5.37 (1 H, br), 6.66 (1 H, s), 7.25 (1 H, s) and 7.27–7.37 (5 H + 1 H, m); *m/z* 493 (MH^+, 37%), 437 (M − Bu^t + 2 H, 14), 385 (M − OBzl, 5), 329 (M − Bu^t − OBzl + H, 12), 251 (M − Boc-Gly-Aib + 2 H, 27), 244 (M − Bu^t − Aib-OBzl + H, 17), 215 (M − CO-Gly-Aib-OBzl, 6), 194 (M − Boc-Gly-Aib-Gly + 2 H, 22), 187 (M − Bu^t − Gly-Aib-OBzl + H, 22), 159 (M − Bu^t − CO-Gly-Aib-OBzl + H, 29) and 91 (Bzl^+, 100).

Boc-(Gly-Aib)$_2$-OH.—Similarly to the synthesis of Boc-Gly-Aib-OH, hydrogenation of Boc-(Gly-Aib)$_2$-OBzl gave the title acid (91%) as a powder, 193–195 °C; ν_{max}/cm^{-1} 3352, 3303 (NH), 1751, 1684, 1666 and 1633 (C=O); δ_H 1.43 (9 H, s), 1.50 (6 H, s), 1.52 (6 H, s), 3.77 (2 H, br d, *J* 4), 3.83 (2 H, d, *J* 6), 5.74 (1 H, br), 7.23 (1 H, s), 7.59 (1 H, s) and 7.80 (1 H, br); *m/z* 425 (MNa^+, 56%), 403 (MH^+, 85), 347 (M − Bu^t + 2 H, 62), 329 (M − Bu^{t}O, 21), 244 (M − Bu^t − Aib-OH + H, 49), 187 (M − Bu^t − Gly-Aib-OH + H, 59), 161 (M − Boc-Gly-Aib + 2 H, 100) and 159 (M − Bu^t − CO-Gly-Aib-OH + H, 73).

Z-Gly-Aib-OBu^t.—To a dichloromethane solution (10 cm^3) of H-Aib-OBu^t (159 mg, 1 mmol) was added Z-Gly-ONSu (306 mg, 1 mmol) under nitrogen. After the mixture had been stirred overnight, similar work-up as for Boc-Gly-Aib-OBzl gave the title amide. Recrystallization from ethyl acetate–hexane gave a

pure sample (333 mg, 95%) as needles, m.p. 96–99 °C; ν_{max}/cm^{-1} 3356, 3286 (NH), 1734, 1712 and 1668 (C=O); δ_H 1.46 (9 H, s), 1.53 (6 H, s), 3.83 (2 H, d, *J* 5.5), 5.14 (2 H, s), 5.43 (1 H, br), 6.65 (1 H, br s) and 7.30–7.36 (5 H, m); *m/z* 351 (MH^+, 22%), 295 (M − Bu^t + 2H, 65), 277 (M − OBu^t, 4), 251 (M − CO_2Bu^t + 2 H, 19), 249 (M − CO_2Bu^t, 7), 187 (M − Bzl − OBu^t, 15) and 91 (Bzl^+, 100).

A-CH_2CO-Gly-Aib-OBu^t.—Similarly to the synthesis of Boc-Gly-Aib-OH, hydrogenation of Z-Gly-Aib-OBu^t gave H-Gly-Aib-OBu^t quantitatively as a viscous oil. The oily amine was used for the following coupling without further purification; δ_H 1.47 (9 H, s), 1.56 (6 H, s), 3.29 (2 H, s) and 7.74 (1 H, br).

Similarly to the synthesis of Boc-Gly-Aib-OBzl, coupling of (9-anthryl)acetic acid with H-Gly-Aib-OBu^t in the dark gave a reaction mixture and the dichloromethane solution was washed, dried and filtered. After evaporation, column chromatography on alumina with dichloromethane as eluent and recrystallization from dichloromethane–hexane gave A-CH_2CO-Gly-Aib-OBu^t (73%) as pale yellow needles, m.p. 204–205 °C; ν_{max}/cm^{-1} 3394, 3330, 3292 (NH), 1730, 1664, 1647 and 1628 (C=O); δ_H 1.38 (6 H, s), 1.41 (9 H, s), 3.72 (2 H, d, *J* 6), 4.67 (2 H, s), 5.82 (1 H, br t, *J* 5), 6.47 (1 H, s), 7.51 (2 H, ddd, *J* 1, 6.5 and 8), 7.58 (2 H, ddd, *J* 1, 6.5 and 8), 8.06 (2 H, dd, *J* 1 and 9), 8.24 (2 H, dd, *J* 1 and 9) and 8.49 (1 H, s); *m/z* 434 (M^+, 33%), 379 (M − Bu^t + 2 H, 49), 276 (M − Aib-OBu^t, 27), 218 (A-CH=C=O$^+$, 84) and 191 (A-CH_2^+, 100).

A-CH_2CO-Gly-Aib-OH.—A TFA solution (30 cm^3) of A-CH_2CO-Gly-Aib-OBu^t (434 mg, 1 mmol) was stirred in the dark at room temperature with exclusion of moisture for 2 h. After concentration under reduced pressure to the residue was added to benzene, and evaporation gave a yellow solid, which was triturated with diethyl ether, filtered, and washed with a small amount of benzene. Recrystallization from dichloromethane gave the title acid quantitatively as a yellow powder, m.p. 222–225 °C; ν_{max}/cm^{-1} 3410, 3372, 3329 (NH), 1718, 1664 and 1626 (C=O); δ_H 1.40 (6 H, s), 3.76 (2 H, d, *J* 6), 4.68 (2 H, s), 5.98 (1 H, br t), 6.54 (1 H, br s), 7.52 (2 H, dt, *J* 1 and 8), 7.59 (2 H, dt, *J* 1 and 8), 8.07 (2 H, d, *J* 8), 8.18 (2 H, d, *J* 8) and 8.51 (1 H, s); *m/z* 401 (MNa^+, 6%), 379 (MH^+, 58), 276 (M − Aib-OH, 28), 219 (A-CH_2CO^+, 74) and 191 (A-CH_2^+, 100).

A-CH_2CONHCH$_2$-D.—Similarly to the synthesis of A-CH_2CO-Gly-Aib-OBu^t, coupling of (9-anthryl)acetic acid with 4-(dimethylamino)benzylamine dihydrochloride gave a reaction mixture, the dichloromethane solution of which was washed successively with aq. 2% $NaHCO_3$ and brine, dried over Na_2SO_4 and filtered. After evaporation, flash column chromatography on silica gel with dichloromethane and methanol (10:0 → 9:1) as eluents gave the title compound. Recrystallization from dichloromethane–hexane gave analytically pure *A-CH_2CONHCH$_2$-D* (57%) as pale yellow plates, m.p. 235–238 °C (Found: C, 81.3; H, 6.6; N, 7.6. $C_{25}H_{24}N_2O$ requires C, 81.5; H, 6.6; N, 7.6%); ν_{max}/cm^{-1} 3255 (NH), 1637 and 1614 (C=O); δ_H 2.84 (6 H, s), 4.22 (2 H, d, *J* 6), 4.64 (2 H, s), 5.39 (1 H, br), 6.48 (2 H, d, *J* 9), 6.80 (2 H, d, *J* 9), 7.50 (2 H, ddd, *J* 1, 7 and 8), 7.57 (2 H, ddd, *J* 1, 7 and 8), 8.03 (2 H, dd, *J* 1 and 9), 8.22 (2 H, dd, *J* 1 and 8) and 8.45 (1 H, s); *m/z* 368 (M^+, 100%), 219 (A-CH_2CO^+, 10) and 191 (A-CH_2^+, 47).

A-CH_2CO-Gly-Aib-NHCH$_2$D.—Similarly to the synthesis of A-CH_2CONHCH$_2$-D, coupling of A-CH_2CO-Gly-Aib-OH with 4-(dimethylamino)benzylamine dihydrochloride gave the *title amide* (53%) as pale yellow crystals (from dichloromethane–hexane), m.p. 236–238 °C (Found: C, 72.6; H, 6.7; N, 10.9. $C_{31}H_{34}N_4O_3$ requires C, 72.9; H, 6.7; N, 11.0%); ν_{max}/cm^{-1} 3344, 3246 (NH) 1653 and 1624 (C=O); δ_H 1.39 (6 H, s), 2.91 (6 H, s), 3.66 (2 H, d, *J* 6), 4.30 (2 H, d, *J* 5.5), 4.61 (2 H, s), 5.85 (1 H, t, *J* 5), 6.35 (1 H, s), 6.46 (1 H, t, *J* 5), 6.68 (2 H, d, *J* 9), 7.12 (2 H, d, *J* 9), 7.51 (2 H, ddd, *J* 1, 6.5 and 8), 7.57 (2 H, ddd, *J* 1, 6.5 and 8), 8.06 (2 H, dd, *J* 1 and 9), 8.19 (2 H, dd, *J* 1 and 9) and 8.49 (1 H, s); *m/z* 511 (MH^+).

Boc-(Gly-Aib)$_2$-NHCH$_2$-D.—Similarly to the synthesis of A-CH_2CONHCH$_2$-D, coupling of Boc-(Gly-Aib)$_2$-OH with 4-(dimethylamino)benzylamine dihydrochloride gave the title amide (91%) as a solid, m.p. 93–95 °C; ν_{max}/cm^{-1} 3317 (NH) and 1662 (C=O); δ_H 1.40 (9 H, s), 1.42 (6 H, s), 1.52 (6 H, s), 2.87 (6 H, s), 3.47 (2 H, d, *J* 5), 3.75 (2 H, d, *J* 6), 4.28 (2 H, d, *J* 5.5), 6.26 (1 H, br t), 6.63 (2 H, d, *J* 9), 7.11 (2 H, d, *J* 9), 7.34 (1 H, t, *J* 6), 7.43 (1 H, br s), 7.54 (1 H, s) and 7.85 (1 H, br t); *m/z* 535 (MH^+, 100%), 385 (M − NHCH$_2$-D, 14) and 300 (385 − Aib, 8).

A-CH_2CO-(Gly-Aib)$_2$-NHCH$_2$-D.—Similarly to the synthesis of H-Gly-Aib-OBzl·HCl, deprotection of Boc-(Gly-Aib)$_2$-NHCH$_2$-D gave H-(Gly-Aib)$_2$-NHCH$_2$-D·2HCl. Similarly to the synthesis of A-CH_2CONHCH$_2$-D, coupling of (9-anthryl)-acetic acid with H-(Gly-Aib)$_2$-NHCH$_2$-D·2HCl gave *A-CH_2CO-(Gly-Aib)$_2$-NHCH$_2$-D* (84%) (*all the compounds mentioned below were synthesized according to a similar procedure*) as yellow crystals (from dichloromethane–hexane), m.p. 135–138 °C (Found: C, 67.8; H, 6.8; N, 12.7. $C_{37}H_{44}N_6O_5$ requires C, 68.1; H, 6.8; N, 12.9%); ν_{max}/cm^{-1} 3300–3340 (NH) and 1655 (C=O); δ_H 1.23 (6 H, s), 1.54 (6 H, s), 2.84 (6 H, s), 3.51 (2 H, d, *J* 5), 3.81 (2 H, d, *J* 6), 4.31 (2 H, d, *J* 6), 4.53 (2 H, s), 5.91 (1 H, s), 6.10 (1 H, br t), 6.63 (2 H, d, *J* 9), 7.01 (3 H, m), 7.14 (2 H, d, *J* 9), 7.53 (2 H, ddd, *J* 1, 6 and 8), 7.60 (2 H, ddd, *J* 1, 7 and 8), 8.08 (2 H, dd, *J* 1 and 9), 8.15 (2 H, dd, *J* 1 and 9) and 8.51 (1 H, d, *J* 1); *m/z* 653 (MH^+, 100%), 503 (M − NHCH$_2$-D, 17), 418 (503 − Aib, 21) and 361 (418 − Gly, 17).

A-CH_2CO-(Gly-Aib)$_3$-NHCH$_2$-D.—A-CH_2CO-Gly-Aib-OH and Boc-(Gly-Aib)$_2$-NHCH$_2$-D gave the *title amide* (85%) as a pale yellow solid, m.p. 146–148 °C (Found: C, 64.7; H, 7.1; N, 13.9. $C_{43}H_{54}N_8O_7$ requires C, 65.0; H, 6.85; N, 14.1%); ν_{max}/cm^{-1} 3305 (NH) and 1655 (C=O); δ_H 1.15 (6 H, s), 1.37 (6 H, s), 1.53 (6 H, s), 2.77 (6 H, s), 3.25 (2 H, d, *J* 5), 3.48 (2 H, d, *J* 5.5), 3.59 (2 H, d, *J* 5), 4.27 (2 H, d, *J* 6), 4.60 (2 H, s), 6.54 (2 H, d, *J* 8.5), 6.95 (1 H, s), 7.05 (2 H, d, *J* 8.5), 7.16 (1 H, br t), 7.35 (1 H, s), 7.41 (1 H, s), 7.46 (2 H, dd, *J* 7 and 8), 7.47–7.54 (2 H, br), 7.52 (2 H, dd, *J* 6 and 8), 7.82 (1 H, br t), 8.00 (2 H, d, *J* 9), 8.26 (2 H, d, *J* 9) and 8.41 (1 H, s); *m/z* 795 (MH^+, 100%), 645 (M − NHCH$_2$ − D, 23), 560 (645 − Aib, 23), 503 (560 − Gly, 21), 418 (503 − Aib, 29) and 361 (418 − Gly, 11).

Boc-(Gly-Aib)$_4$-NHCH$_2$-D.—Boc-(Gly-Aib)$_2$-OH and Boc-(Gly-Aib)$_2$-NHCH$_2$-D gave the title amide (67%) as a white solid, m.p. 126–127 °C; ν_{max}/cm^{-1} 3305 (NH) and 1660 (C=O); δ_H 1.40 (6 H, s), 1.43 (9 H, s), 1.48 (6 H, s), 1.52 (6 H, s), 1.57 (6 H, s), 2.87 (6 H, s), 3.59 (2 H, br d), 3.71 (2 H, br d), 3.72 (2 H, br d), 3.82 (2 H, d, *J* 6), 4.29 (2 H, d, *J* 6), 6.48 (1 H, br), 6.63 (2 H, d, *J* 9), 7.10 (2 H, d, *J* 9), 7.61 (2 H, s), 7.66 (2 H, s), 7.71 (1 H, br t), 7.76 (1 H, br), 7.97 (1 H, br) and 8.20 (1 H, br); *m/z* 841 (MNa^+, 19%), 819 (MH^+, 100) and 669 (M − NHCH$_2$-D, 43).

A-CH_2CO-(Gly-Aib)$_4$-NHCH$_2$-D.—(9-Anthryl)acetic acid and Boc-(Gly-Aib)$_4$-NHCH$_2$-D gave the *title amide* (84%) as a pale yellow solid, m.p. 152–155 °C (Found: C, 61.7; H, 6.8; N, 14.6. $C_{49}H_{64}N_{10}O_9 \cdot H_2O$ requires C, 61.6; H, 7.0; N, 14.7%); ν_{max}/cm^{-1} 3310–3340 (NH) and 1655 (C=O); δ_H 1.24 (6 H, s), 1.25 (6 H, s), 1.47 (6 H, s), 1.55 (6 H, s), 2.74 (6 H, s), 3.19 (2 H, m), 3.31 (2 H, m), 3.63 (2 H, br d), 3.79 (2 H, br d), 4.29 (2 H, d, *J* 6), 4.60 (2 H, s), 6.53 (2 H, d, *J* 8.5), 7.05 (2 H, d, *J* 8.5), 7.08 (1 H br), 7.14 (1 H, br t), 7.31 (1 H, s), 7.41 (1 H, s), 7.47 (2 H, dd, *J* 6 and

8), 7.53 (2 H, ddd, *J* 1, 6.5 and 8), 7.64 (1 H, s), 7.64–7.70 (3 H, m), 7.98 (1 H, br t), 8.01 (2 H, d, *J* 8), 8.26 (2 H, d, *J* 9) and 8.42 (1 H, s); *m/z* 937 (MH^+, 100%), 787 (M − $NHCH_2$-D, 29), 702 (787 − Aib, 20) and 645 (702 − Gly, 17).

A-CH_2CO-(Gly-Aib)$_5$-$NHCH_2$-D.—A-CH_2CO-Gly-Aib-OH and Boc-(Gly-Aib)$_4$-$NHCH_2$-D gave the *title amide* (67%) as a pale yellow solid, m.p. 159–161 °C (Found: C, 60.3; H, 6.75; N, 15.4. $C_{55}H_{74}N_{12}O_{11}\cdot H_2O$ requires C, 60.2; H, 7.0; N, 15.3%); ν_{max}/cm^{-1} 3290–3330 (NH) and 1653 (C=O); δ_H 1.24 (6 H, s), 1.29 (6 H, s), 1.34 (6 H, s), 1.50 (6 H, s), 1.62 (6 H, s), 2.73 (6 H, s), 3.03 (2 H, m), 3.07 (2 H, m), 3.61 (2 H, m), 3.68 (2 H, m), 3.85 (2 H, m), 4.34 (2 H, d, *J* 5), 4.62 (2 H, s), 6.52 (2 H, d, *J* 9), 6.66 (1 H, br), 7.05 (2 H, d, *J* 9), 7.07 (1 H, br), 7.45 (2 H, t, *J* 8), 7.51 (1 H, br), 7.52 (2 H, t, *J* 7), 7.56 (1 H, br), 7.77 (3 H, m), 7.83 (2 H, s), 7.95 (2 H, d, *J* 8.5), 8.07 (1 H, br t), 8.30 (2 H, d, *J* 9.5), 8.35 (1 H, s) and 8.49 (1 H, br); *m/z* 1079 (MH^+, 100%), 929 (M − $NHCH_2$-D, 53), 844 (929 − Aib, 14), 787 (844 − Gly, 11), 702 (787 − Aib, 23) and 645 (702 − Gly, 26).

Boc-(Gly-Aib)$_6$-$NHCH_2$-D.—Boc-(Gly-Aib)$_2$-OH and Boc-(Gly-Aib)$_4$-$NHCH_2$-D gave the title amide (71%) as a solid, m.p. 142–144 °C; ν_{max}/cm^{-1} 3300–3340 (NH) and 1658 (C=O); δ_H 1.43 (6 H, s), 1.46 (9 H, s), 1.50 (6 H, s), 1.52 (6 H, s), 1.53 (6 H, s), 1.54 (6 H, s), 1.59 (6 H, s), 2.88 (6 H, s), 3.61 (2 H, br d, *J* 4.5), 3.72 (8 H, m), 3.82 (2 H, d, *J* 5.5), 4.31 (2 H, d, *J* 5.5), 6.22 (1 H, br), 6.64 (2 H, d, *J* 8.5), 7.11 (2 H, d, *J* 8.5), 7.42 (1 H, br t), 7.61 (1 H, s), 7.63 (1 H, s), 7.73 (3 H, m), 7.77 (1 H, s), 7.84 (1 H, br t), 7.90 (1 H, t, *J* 5), 7.95 (1 H, t, *J* 5), 8.06 (1 H, t, *J* 5) and 8.13 (1 H, br t); *m/z* 1125 (MNa^+, 16%) 1103 (MH^+, 100), 953 (M − $NHCH_2$-D, 59), 868 (953 − Aib, 23), 811 (868 − Gly, 23), 726 (811 − Aib, 21) and 669 (726 − Gly, 25).

A-CH_2CO-(Gly-Aib)$_6$-$NHCH_2$-D.—(9-Anthryl)acetic acid and Boc-(Gly-Aib)$_6$-$NHCH_2$-D gave the *title amide* (85%) as pale yellow crystals, m.p. 164–166 °C (Found: C, 59.5; H, 7.1; N, 15.6. $C_{61}H_{84}N_{14}O_{13}\cdot H_2O$ requires C, 59.1; H, 7.0; N, 15.8%); ν_{max}/cm^{-1} 3300–3320 (NH) and 1655 (C=O); δ_H 1.25 (6 H, s), 1.348 (6 H, s), 1.351 (6 H, s), 1.44 (6 H, s), 1.55 (6 H, s), 1.62 (6 H, s), 2.75 (6 H, s), 3.03 (2 H, m), 3.22 (2 H, m), 3.61 (2 H, m), 3.68 (4 H, m), 3.86 (2 H, m), 4.33 (2 H, d, *J* 5), 4.65 (2 H, s), 6.53 (2 H, d, *J* 8.5), 6.87 (1 H, br), 7.06 (2 H, d, *J* 8.5), 7.30 (2 H, br), 7.39 (1 H, br), 7.47 (2 H, t, *J* 7), 7.54 (2 H, t, *J* 7.5), 7.78 (1 H, br), 7.85 (1 H, br), 7.86 (2 H, br), 7.95 (2 H, br), 8.01 (2 H, d, *J* 8), 8.00–8.05 (2 H, br), 8.32 (2 H, d, *J* 9), 8.39 (1 H, br) and 8.42 (1 H, s); *m/z* 1243 (MNa^+, 86%), 1221 (MH^+, 100), 1071 (M − $NHCH_2$-D, 69), 986 (1071 − Aib, 43), 929 (986 − Gly, 45), 844 (929 − Aib, 30), 787 (844 − Gly, 50) and 702 (787 − Aib, 29).

A-CH_2CO-(Gly-Aib)$_7$-$NHCH_2$-D.—A-CH_2CO-Gly-Aib-OH and Boc-(Gly-Aib)$_6$-$NHCH_2$-D gave the *title amide* (60%) as pale yellow crystals, m.p. 167–169 °C (Found: C, 58.2; H, 7.0; N, 16.0. $C_{67}H_{94}N_{16}O_{15}\cdot H_2O$ requires C, 58.25; H, 7.0; N, 16.2%); ν_{max}/cm^{-1} 3305 (NH) and 1657 (C=O); δ_H 1.26 (6 H, s), 1.38 (6 H, s), 1.40 (6 H, s), 1.44 (6 H, s), 1.50 (6 H, s), 1.57 (6 H, s), 1.61 (6 H, s), 2.77 (6 H, s), 3.13 (2 H, m), 3.27 (2 H, m), 3.61 (2 H, d, *J* 5), 3.66 (2 H, d, *J* 5), 3.71 (4 H, m), 3.85 (2 H, m), 4.33 (2 H, d, *J* 5), 4.67 (2 H, s), 6.55 (2 H, d, *J* 9), 7.00 (1 H, br), 7.07 (2 H, d, *J* 9), 7.34 (1 H, br), 7.48 (2 H, t, *J* 8), 7.55 (2 H, t, *J* 8), 7.55 (1 H, s), 7.85 (1 H, s), 7.88 (1 H, br), 7.96 (5 H, m), 7.98 (1 H, br), 8.01 (1 H, s), 8.02 (2 H, d, *J* 8), 8.07 (1 H, br), 8.14 (1 H, br), 8.34 (2 H, d, *J* 9), 8.35 (1 H, br) and 8.43 (1 H, s); *m/z* 1385 (MNa^+, 68%), 1363 (MH^+, 100), 1213 (M − $NHCH_2$-D), 58), 1128 (1213 − Aib, 22), 1071 (1128 − Gly, 44), 986 (1071 − Aib, 31), 929 (986 − Gly, 48), 844 (929 − Aib, 42), 787 (844 − Gly, 40) and 702 (787 − Aib, 41).

Boc-(Gly-Aib)$_8$-$NHCH_2$-D.—Boc-(Gly-Aib)$_2$-OH and Boc-(Gly-Aib)$_6$-$NHCH_2$-D gave the title amide (72%) as a solid, m.p. 157–159 °C; ν_{max}/cm^{-1} 3307 (NH) and 1658 (C=O); δ_H 1.40 (6 H, s), 1.46 (9 H, s), 1.526 (6 H, s), 1.543 (12 H, s), 1.556 (6 H, s), 1.562 (12 H, s), 1.581 (6 H, s), 2.88 (6 H, s), 3.67 (8 H, m), 3.78 (8 H, m), 4.29 (2 H, br d), 6.56 (1 H, br), 6.63 (2 H, d, *J* 9), 7.08 (2 H, d, *J* 9), 7.74 (1 H, s), 7.89 (1 H, m), 7.91 (1 H, s), 7.94 (1 H, m), 8.08 (1 H, s), 8.12 (4 H, m), 8.21 (1 H, m), 8.30 (5 H, m) and 8.44 (1 H, m); *m/z* 1410 (MNa^+ + 1, 39%), 1387 (MH^+, 100), 1237 (M − $NHCH_2$-D, 67), 1152 (1237 − Aib, 23), 1095 (1152 − Gly, 29), 1010 (1095 − Aib, 16), 953 (1010 − Gly, 31), 868 (953 − Aib, 24), 811 (868 − Gly, 40), 726 (811 − Aib, 44) and 669 (726 − Gly, 44).

A-CH_2CO-(Gly-Aib)$_8$-$NHCH_2$-D.—(9-Anthryl)acetic acid and Boc-(Gly-Aib)$_8$-$NHCH_2$-D gave the *title amide* (84%) as a pale yellow solid, m.p. 160–162 °C (Found: C, 57.6; H, 7.0; N, 16.3. $C_{73}H_{104}N_{18}O_{17}\cdot H_2O$ requires C, 57.5; H, 7.0; N, 16.5%); ν_{max}/cm^{-1} 3305 (NH) and 1655 (C=O); δ_H 1.27 (6 H, s), 1.36 (6 H, s), 1.39 (6 H, s), 1.44 (6 H, s), 1.50 (6 H, s), 1.55 (6 H, s), 1.57 (6 H, s), 1.64 (6 H, s), 2.75 (6 H, s), 3.00 (2 H, m), 3.20 (2 H, m), 3.58 (2 H, m), 3.65 (4 H, m), 3.70 (4 H, m), 3.87 (2 H, m), 4.34 (2 H, m), 4.66 (2 H, s), 6.53 (2 H, d, *J* 8.5), 6.83 (1 H, br), 7.06 (2 H, d, *J* 8.5), 7.30 (1 H br), 7.47 (2 H, t, *J* 7), 7.54 (2 H, t, *J* 7), 7.5–7.6 (2 H, m), 7.86 (1 H, br), 7.93 (2 H, m), 7.96 (1 H, br), 8.01 (2 H, d, *J* 8), 8.02 (1 H, br), 8.10 (2 H, m), 8.12 (2 H, m), 8.18 (2 H, m), 8.25 (1 H, br), 8.34 (2 H, d, *J* 9), 8.42 (1 H, s) and 8.55 (1 H, br); *m/z* 1527 (MNa^+, 100%), 1505 (MH^+, 38), 1355 (M − $NHCH_2$-D, 30), 1270 (1355 − Aib, 10), 1213 (1270 − Gly, 12), 1128 (1213 − Aib, 9), 1071 (1128 − Gly, 13), 986 (1071 − Aib, 14), 929 (986 − Gly, 22), 844 (929 − Aib, 16) and 787 (844 − Gly, 24).

A-CH_2CO-(Gly-Aib)$_9$-$NHCH_2$-D.—A-CH_2CO-Gly-Aib-OH and Boc-(Gly-Aib)$_8$-$NHCH_2$-D gave the *title amide* (59%) as a pale yellow solid, m.p. 163–167 °C (Found: C, 57.1; H, 7.0; N, 16.5. $C_{79}H_{114}N_{20}O_{19}\cdot H_2O$ requires C, 57.0; H, 7.0; N, 16.8%); ν_{max}/cm^{-1} 3433 (NH) and 1655 (C=O); δ_H 1.26 (6 H, s), 1.36 (6 H, s), 1.40 (6 H, s), 1.42 (6 H, s), 1.44 (6 H, s), 1.51 (6 H, s), 1.55 (6 H, s), 1.56 (6 H, s), 1.58 (6 H, s), 2.76 (6 H, s), 3.01 (2 H, m), 3.20 (2 H, m), 3.58 (2 H, m), 3.64 (10 H, m), 3.87 (2 H, m), 4.34 (2 H, m), 4.66 (2 H, s), 6.54 (2 H, d, *J* 8.5), 6.85 (1 H, br), 7.06 (2 H, d, *J* 8.5), 7.31 (1 H, br), 7.47 (2 H, t, *J* 7), 7.54 (2 H, t, *J* 7), 7.55 (2 H, m), 7.87 (1 H, br), 7.97 (3 H, m), 8.01 (2 H, d, *J* 9), 8.09 (1 H, br), 8.20 (6 H, m), 8.26 (1 H, m), 8.29 (2 H, br), 8.35 (2 H, d, *J* 9), 8.42 (1 H, s) and 8.56 (1 H, br); *m/z* 1670 (MNa^+ + 1, 44%), 1647 (MH^+, 100), 1497 (M − $NHCH_2$-D, 35), 1412 (1497 − Aib, 17), 1355 (1412 − Gly, 22), 1270 (1355 − Aib, 14), 1213 (1270 − Gly, 25), 1128 (1213 − Aib, 21), 1071 (1128 − Gly, 30), 986 (1071 − Aib, 23), 929 (986 − Gly, 34) and 844 (929 − Aib, 26).

Boc-(Gly-Aib)$_{10}$-$NHCH_2$-D.—Boc-(Gly-Aib)$_2$-OH and Boc-(Gly-Aib)$_8$-$NHCH_2$-D gave the title amide (69%) as a solid, m.p. 160–163 °C; ν_{max}/cm^{-1} 3300–3330 (NH) and 1660 (C=O); δ_H 1.42 (6 H, s), 1.45 (9 H, s), 1.51 (6 H, s), 1.54 (6 H, s), 1.57 (30 H, s), 1.58 (6 H, s), 1.60 (6 H, s), 2.88 (6 H, s), 3.63 (2 H, br), 3.68 (12 H, br), 3.73 (4 H, br), 3.82 (2 H, br), 4.31 (2 H, br), 6.60 (1 H, br), 6.64 (2 H, d, *J* 9), 7.10 (2 H, d, *J* 9), 7.68 (1 H, s), 7.82 (2 H, s), 7.88 (1 H, s), 7.97 (1 H, br), 8.02 (1 H, br), 8.10 (3 H, s), 8.17 (2 H, m) and 8.24–8.32 (9 H, m); *m/z* 1693 (MNa^+, 46%), 1671 (MH^+, 100), 1521 (M − $NHCH_2$-D, 51), 1436 (1521 − Aib, 16), 1379 (1436 − Gly, 28), 1294 (1379 − Aib, 15), 1237 (1294 − Gly, 24), 1152 (1237 − Aib, 25), 1095 (1152 − Gly, 29), 1010 (1095 − Aib, 34), 953 (1010 − Gly, 36), 868 (953 − Aib, 45) and 811 (868 − Gly, 43).

A-CH_2CO-(Gly-Aib)$_{10}$-$NHCH_2$-D.—(9-Anthryl)acetic acid and Boc-(Gly-Aib)$_{10}$-$NHCH_2$-D gave the *title amide* (82%) as pale yellow plates, m.p. 183–185 °C (Found: C, 56.0; H, 6.9; N,

17.0. $C_{85}H_{124}N_{22}O_{21}\cdot 2H_2O$ requires C, 55.9; H, 7.1; N, 16.9%); ν_{max}/cm^{-1} 3305 (NH) and 1655 (C=O); δ_H 1.28 (6 H, s), 1.36 (6 H, s), 1.41 (6 H, s), 1.44 (6 H, s), 1.52 (6 H, s), 1.56 (12 H, s), 1.57 (6 H, s), 1.58 (6 H, s), 1.64 (6 H, s), 2.76 (6 H, s), 2.98 (2 H, m), 3.18 (2 H, m), 3.58 (2 H, m), 3.66 (12 H, m), 3.87 (2 H, m), 4.34 (2 H, m), 4.67 (2 H, s), 6.54 (2 H, d, *J* 8.5), 6.79 (1 H, br t), 7.06 (2 H, d, *J* 8.5), 7.48 (2 H, t, *J* 7), 7.55 (2 H, m), 7.55 (2 H, t, *J* 7), 7.86 (1 H, br), 7.94–7.96 (3 H, m), 8.02 (2 H, d, *J* 8), 8.08 (1 H, br), 8.18 (7 H, m), 8.29 (4 H, m), 8.33 (1 H, br), 8.34 (2 H, d, *J* 8), 8.43 (1 H, s) and 8.56 (1 H, br); *m/z* 1812 (MNa^+ + 1, 100%), 1789 (MH^+, 93), 1639 (M − $NHCH_2$-D, 32), 1554 (1639 − Aib, 13), 1497 (1554 − Gly, 16), 1412 (1497 − Aib, 5), 1355 (1412 − Gly, 16), 1270 (1355 − Aib, 14), 1213 (1270 − Gly, 22), 1128 (1213 − Aib, 23), 1071 (1128 − Gly, 23), 986 (1071 − Aib, 30), 929 (986 − Gly, 34) and 844 (929 − Aib, 36).

A-CH_2CO-(Gly-Aib)$_{11}$-$NHCH_2$-D.—A-CH_2CO-Gly-Aib-OH and Boc-(Gly-Aib)$_{10}$-$NHCH_2$-D gave the *title amide* (75%) as pale yellow crystals, m.p. 188–191 °C (Found: C, 55.4; H, 7.0; N, 17.2. $C_{91}H_{134}N_{24}O_{23}\cdot 2H_2O$ requires C, 55.5; H, 7.1; N, 17.1%); ν_{max}/cm^{-1} 3448 (NH) and 1653 (C=O); δ_H 1.27 (6 H, s), 1.37 (6 H, s), 1.43 (6 H, s), 1.45 (6 H, s), 1.52 (6 H, s), 1.57 (30 H, s), 1.61 (6 H, s), 2.79 (6 H, s), 3.01 (2 H, m), 3.21 (2 H, m), 3.60 (2 H, m), 3.67 (14 H, m), 3.85 (2 H, m), 4.33 (2 H, m), 4.67 (2 H, s), 6.57 (2 H, d, *J* 9), 6.62 (1 H, br), 7.08 (2 H, d, *J* 8), 7.33 (1 H, br), 7.48 (2 H, t, *J* 7), 7.55 (2 H, t, *J* 7), 7.55 (1 H, s), 7.86 (1 H, br), 7.91 (1 H, br), 7.97 (2 H, m), 8.02 (2 H, d, *J* 8), 8.06 (3 H, m), 8.14 (2 H, m), 8.18 (3 H, m), 8.28 (5 H, m), 8.34 (2 H, m), 8.34 (2 H, d, *J* 9), 8.43 (1 H, s) and 8.49 (1 H, br); *m/z* 1955 (MNa^+ + 1, 55%), 1932 (MH^+, 100), 1782 (M − $NHCH_2$-D, 13), 1697 1782 − Aib, 6), 1640 (1697 − Gly, 9), 1555 (1640 − Aib, 4), 1498 (1555 − Gly, 9), 1413 (1498 − Aib, 7), 1356 (1413 − Gly, 11), 1271 (1356 − Aib, 8), 1214 (1271 − Gly, 8), 1128 (1214 − Aib − 1, 8), 1071 (1128 − Gly, 12), 986 (1071 − Aib, 10), 929 (986 − Gly, 16), 844 (929 − Aib, 16), 787 (844 − Gly, 14), 702 (787 − Aib, 17), 645 (702 − Gly, 24), 560 (645 − Aib, 39), 503 (560 − Gly, 38), 418 (503 − Aib, 78), 361 (418 − Gly, 60), 218 (A-CH=C=O^+) and 191 (A-CH_2^+).

Boc-(Gly-Aib)$_2$-NHBzl.—Similarly to the synthesis of Boc-Gly-Aib-OBzl, coupling of Boc-(Gly-Aib)$_2$-OH and benzylamine gave the title amide (82%) as needles (from dichloromethane–hexane), m.p. 137–138 °C; ν_{max}/cm^{-1} 3305 (NH) and 1660 (C=O); δ_H 1.43 (9 H, s), 1.45 (6 H, s), 1.58 (6 H, s), 3.56 (2 H, d, *J* 5.5), 3.79 (2 H, d, *J* 6), 4.45 (2 H, d, *J* 6), 5.37 (1 H, br t), 6.53 (1 H, s), 7.18–7.22 (2 H, m), 7.27–7.31 (5 H, m) and 7.55 (1 H, br t); *m/z* 492 (MH^+, 100%), 436 (M − Bu^t + 2 H, 7), 385 (M − NHBzl, 37), 357 (M − CONHBzl, 20), 329 (M − Bu^t − NHBzl + H, 44), 300 (M − Aib-NHBzl, 16), 285 (M − Boc − NHBzl + H, 10), 244 (M − Bu^t − Aib-NHBzl + H, 34), 193 (M − Boc-Gly-Aib-Gly + 2 H, 20), 187 (M − Bu^t − Gly-Aib-NHBzl + H, 30) and 159 (M − Bu^t −CO-Gly-Aib-NHBzl + H, 31).

A-CH_2CO-(Gly-Aib)$_2$-NHBzl.—Similarly to the synthesis of A-CH_2CO-Gly-Aib-OBu^t, coupling of (9-anthryl)acetic acid and H-(Gly-Aib)$_2$-NHBzl [from deprotection of Boc-(Gly-Aib)$_2$-NHBzl and neutralization by triethylamine] gave the *title amide* (90%) as plates (from dichloromethane–hexane), m.p. 126–129 °C (Found: C, 67.9; H, 6.4; N, 11.3. $C_{35}H_{39}N_5O_5\cdot\frac{1}{2}H_2O$ requires C, 67.9; H, 6.5; N, 11.3%); ν_{max}/cm^{-1} 3296 (NH) and 1651 (C=O); δ_H 1.22 (6 H, s), 1.54 (6 H, s), 3.49 (2 H, d, *J* 5), 3.77 (2 H, d, *J* 6), 4.41 (2 H, d, *J* 6), 4.55 (2 H, s), 5.96 (1 H, s), 6.11 (1 H, t, *J* 5), 7.07 (1 H, s), 7.11 (1 H, t, *J* 6), 7.15 (1 H, t, *J* 6), 7.24 (5 H, m), 7.53 (2 H, ddd, *J* 1, 7 and 8), 7.60 (2 H, ddd, *J* 1, 6 and 8), 8.08 (2 H, d, *J* 9), 8.14 (2 H, d, *J* 9) and 8.51 (1 H, s); *m/z* 610 (MH^+, 56%), 503 (M − NHBzl, 38), 418 (503 − Aib, 36), 361 (418 − Gly, 18), 276 (361 − Aib, 11), 218 (A-CH=C=O^+, 71) and 191 (A-CH_2^+, 100).

Acknowledgements

We thank Professor Shigeru Kuwata and Dr. Takashi Yamada, Konan University, for their suggestion of this synthesis. The present work was partially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture, Japan.

References

1 S. S. Isied, *Prog. Inorg. Chem.*, 1984, **32**, 443; M. R. Wasielewski, in *Photoinduced Electron Transfer, Part A*, ed. M. A. Fox and M. Chanon, Elsevier, Amsterdam–Oxford–New York–Tokyo, 1988, p. 161.
2 C. Pac and O. Ishitani, *Photochem. Photobiol.*, 1988, **48**, 767; M. J. Therien, M. Selman, H. B. Gray, I. Chang and J. R. Winkler, *J. Am. Chem. Soc.*, 1990, **112**, 2420.
3 S. S. Isied, A. Vassilian, J. F. Wishart, C. Creutz, H. A. Schwarz and N. Sutin, *J. Am. Chem. Soc.*, 1988, **110**, 635; K. S. Schanze and K. Sauer, *J. Am. Chem. Soc.*, 1988, **110**, 1180; M. Sisido, R. Tanaka, Y. Inai and Y. Imanishi, *J. Am. Chem. Soc.*, 1989, **111**, 6790; M. R. DeFelippis, M. Faraggi and M. H. Klapper, *J. Am. Chem. Soc.*, 1990, **112**, 5640.
4 M. Narita, J.-Y. Chen, H. Sato and Y. Kim, *Bull. Chem. Soc. Jpn.*, 1985, **58**, 2494.
5 D. S. Jones, G. W. Kenner, J. Preston and R. C. Sheppard, *J. Chem. Soc.*, 1965, 6227.
6 C. H. Bamford, L. Brown, E. M. Cant, A. Elliott, W. E. Hanby and B. R. Malcolm, *Nature*, 1955, **176**, 396.
7 T. Okada, M. Migita, N. Mataga, Y. Sakata and S. Misumi, *J. Am. Chem. Soc.*, 1981, **103**, 4715; Y. Wang, M. C. Crawford and K. B. Eisenthal, *J. Am. Chem. Soc.*, 1982, **104**, 5874; H. Heitele and M. E. Michel-Beyerle, *J. Am. Chem. Soc.*, 1985, **107**, 8286; G. J. Kavarnos and N. J. Turro, *Chem. Rev.*, 1986, **86**, 401.
8 T. L. Blundell and L. N. Johnson, *Protein Crystallography*, Academic, New York–London–San Francisco, 1976, p. 31.
9 G. W. Anderson, J. E. Zimmerman and F. M. Callahan, *J. Am. Chem. Soc.*, 1964, **86**, 1839.
10 D. Leibfritz, E. Haupt, N. Dubischar, H. Lachmann, R. Oekonomopulos and G. Jung, *Tetrahedron*, 1982, **38**, 2165.
11 E. Ciganek, *J. Org. Chem.*, 1980, **45**, 1497.
12 T. Miettinen, *Acta Chem. Scand., Ser. B*, 1979, **33**, 167.

Paper 0/04087H
Received 7*th September* 1990
Accepted 15*th November* 1990