Intramolecular Photoreaction of Synthetic Oligopeptide-Linked Anthraquinone Molecules

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Photoreaction of (*N*-acetylglycyl)oligopeptide-linked anthraquinone molecules was investigated. In an acetonitrile solution, the photoexcited anthraquinone moiety abstracted intramolecularly the hydrogen atom of the methylene site of glycine residue. The biradical formed was followed by the formation of C–O bonding via radical recombination to produce ring-closure products in high yields (23–58%). A variety of oligopeptide spacers between acetylglycine and anthraquinone moieties were systematically changed, and their photoreactivities were investigated. The isolated ring-closure products showed a site-selectivity in the photoreaction; one of the carbonyl groups of anthraquinone moiety coupled with the methylene group predominantly (the selectivity was 88/12–100/0). The efficiency of the photocyclization was dependent upon the size and the sequence of the oligopeptide spacer. These results showed that the oligopeptide spacer might control the distance and the orientation among the reaction sites, glycine methylene, and anthraquinone carbonyl groups.

Introduction

Most enzyme-catalyzed reactions are stereo- and regioselective. High site-selectivity is performed in a substrate molecule with many reactive sites. Selective functionalization of a molecule is an important topic in organic chemistry as well as in biochemistry. To mimic such biological reactions molecules covalently linked with a reactant and another substrate have been examined.[1] In the molecules, the reactant tended to attack selectively one of the reactive sites of the substrate. The site-selectivity could be controlled by the structure of the spacer between the reactant and the substrate.

Intramolecular hydrogen abstraction reactions by photosensitive groups have been reported by many authors.[2] For example, Breslow, Winnik et al. investigated intramolecular photoinduced hydrogen abstraction reaction of benzophenone (BP) with steroids or alkyl chains, so-called "remote oxidation".[3] The photoreaction of BP with rigid steroids showed high site-selectivity. Moreover, the photochemistry and photophysics of BP with flexible alkyl chains gave useful information for conformational analysis of the alkyl chain in a solution. Tanimoto et al. also studied intramolecular hydrogen abstraction by anthraquinone (AQ) from alkyl chains in organic solvents and micellar solutions.[4] It was concluded that the hydrogen abstraction was followed by the formation of C–C or C–O bonding to produce many coupling products. All the above reactions of carbonyl compounds with hydrocarbons were so complex that the above authors failed to separate each coupling product. To avoid the complexity and then facilitate isolation of the products, the glycine residue was used as a hydrogen atom donor.[5] In this paper, we will report the synthesis of a series of (*N*-acetylglycyl)oligopeptide-linked anthraquinone molecules and their photoreactions and intramolecular hydrogen abstraction by anthraquinone moiety from glycine methylene site, followed by the formation of ring-closure products (Scheme I).[6] The ring-closure products were isolated and well characterized. In the present system, two carbonyl groups of the AQ moiety were distinguishable. The site-selectivity in the carbonyl groups was observed in the photoreactions. The oligopeptide spacer between acetylglycine and anthraquinone moieties was varied systematically. The efficiency of the photocyclization was dependent upon the structure of the spacer.

Results and Discussion

Synthesis of (*N*-Acetylglycyl)oligopeptide-Linked Anthraquinone Molecules. As a photosensitive group, anthraquinone-2-carboxylic acid (AQ-COOH) was used because of the high reactivity of hydrogen abstraction.[7] The AQ moiety was introduced into the side chain of the C-terminal amino acids of protected oligopeptides through ester bonding (AQ-COO–). Among three natural amino acids with a hydroxyl group (serine, threonine, and tyrosine), serine was chosen because of its high reactivity and the high stability of the ester bonding.[8] A glycine residue was located at the N-terminal of the oligopeptide. All the oligopeptides were protected by an acetyl group at the N-terminal and by a methyl ester group at the C-terminal. As a spacer between acetylglycine and serine residues, first an oligomer of α-aminoisobutyric acid (Aib) was used. Aib had no hydrogen which was bonded to secondary or tertiary carbon atoms and was resistant to hydrogen abstraction. It would be of great advantage for isolation of products that side reactions via hydrogen abstraction from the spacer could be suppressed.

Such an oligopeptide spacer was prepared by use of dicyclohexylcarbodiimide (DCC) as a coupling reagent and 1-hydroxybenzotriazole (HOBt) as a coupling promotion reagent in a CH_2Cl_2 solution. When the AA shown in Scheme II was a di- or tripeptide, the introduction of AQ moiety into the side chain of the oligopeptide (the step b in Scheme II) was carried out in low yields (at most 20%) because of steric hindrance around the hydroxyl group. When the AA was one amino acid residue, the AQ moiety

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(3) (a) Breslow, R.; Winnik, M. A. *J. Am. Chem. Soc.* **1969**, *91*, 3083. (b) Breslow, R.; Baldwin, S.; Flechtner, T.; Kalicky, P.; Lin, S.; Washburn, W. *Ibid.* **1973**, *95*, 3251. (c) Breslow, R.; Rothbard, J.; Herman, F.; Rodriguez, M. R. *Ibid.* **1978**, *100*, 1213. (d) Winnik, M. A. *Chem. Rev.* **1981**, *81*, 491.

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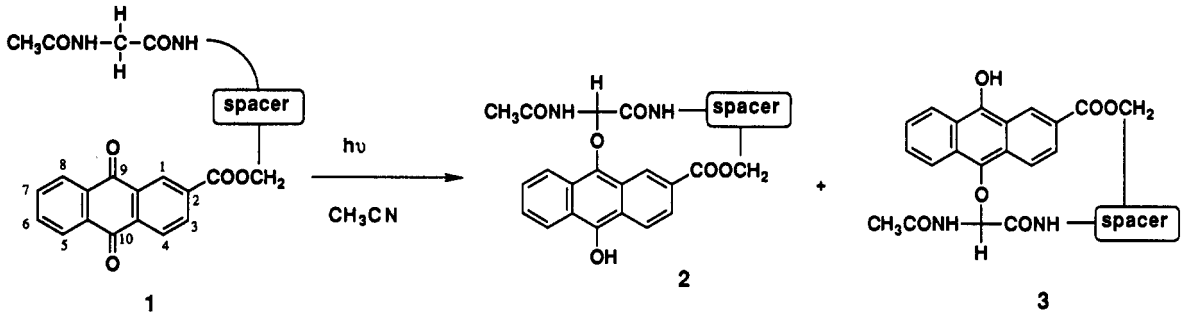
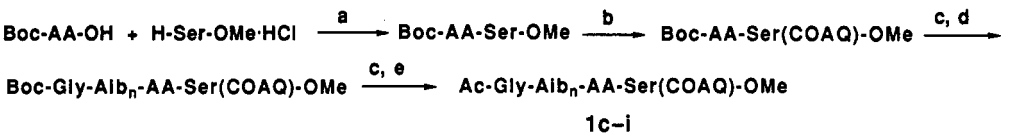
Scheme I. Photocyclization of (*N*-Acetylglycyl)oligopeptide-Linked Anthraquinones



Scheme II. Synthesis of (*N*-Acetylglycyl)oligopeptide-Linked Anthraquinones 1c–i (Serine) and Structure of 1a and b



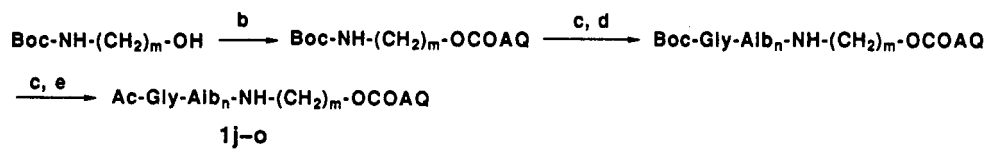
Ac-Ser(OCOAQ)-OMe 1a

Ac-Gly-Ser(OCOAQ)-OMe 1b

	n	AA
1c	0	Aib
1d	1	Aib
1e	2	Aib
1f	1	Ala
1g	1	Gly
1h	2	Ala
1i	2	Gly

a : DCC, NEt_3 / CH_2Cl_2
b : AQ-COCl, NEt_3 / CH_2Cl_2
c : 4N HCl / AcOEt
d : Boc-Gly-Alb$_n$-OH, DCC–HOBt, NEt_3 / CH_2Cl_2
e : Ac_2O, NEt_3 / CH_2Cl_2

Scheme III. Synthesis of (*N*-Acetylglycyl)oligopeptide-Linked Anthraquinones 1j–o (ω-Amino 1-Alcohol)



	n	m
1j	0	5
1k	1	5
1l	0	8
1m	2	5
1n	1	8
1o	0	11

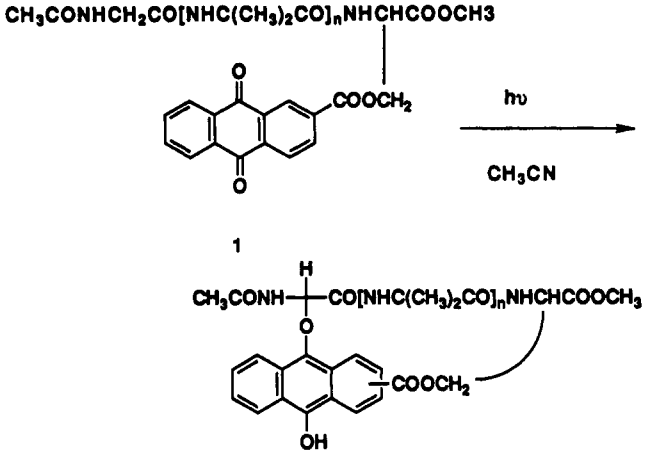
b : AQ-COCl, NEt_3 / CH_2Cl_2
c : 4N HCl / AcOEt
d : Boc-Gly-Alb$_n$-OH, DCC–HOBt, NEt_3 / CH_2Cl_2
e : Ac_2O, NEt_3 / CH_2Cl_2

was introduced efficiently (ca. 50%). Therefore, elongation of oligopeptide chains was carried out after introduction of the AQ moiety. As shown in Scheme II, the compounds **1c–1e** were synthesized in high yields (see also Experimental Section).

Similarly, **1f–1i** were prepared in which one Aib residue of **1d** and **1e** was substituted by a Gly or Ala residue. Moreover, **1j–1o** with no serine residue were synthesized as shown in Scheme III. In **1j–1o**, a part of oligopeptides of **1c–1e** was substituted by a ω-aminoalkoxy group, $-NH(CH_2)_mO-$.

Photoreaction of (*N*-Acetylglycyl)oligopeptide-Linked Anthraquinone Molecules. Irradiation (30 min) of an argon-saturated acetonitrile solution of compound **1** (1 mM) with a high-pressure mercury arc lamp through an aqueous $CuSO_4$ solution filter at room temperature gave sole or two isomeric product(s) after column chromatography over silica gel. Their ^1H NMR, IR, MS, and UV spectra showed that the product was an intramolecular ring-closure and had either a bond of the α-carbon of glycine with the carbonyl carbon of anthraquinone (C–C) or a bond of the α-carbon of Gly with the carbonyl oxygen of AQ (C–O). On the basis of their fluorescence spectra characteristic of an anthracene moiety, the structure of the product was established to be a C–O bonding ring-closure. The anthraquinone moiety of **1** had two chemically different carbonyl groups at the 9- and 10-positions. The C–O ring-closure products were classified into two types, i.e., one product (as in **2**) which was given by cyclization between the α-carbon of the glycine and the oxygen of the 9-carbonyl group in the molecule and another product (as in **3**) by cyclization between the α-carbon and the 10-carbonyl oxygen (Scheme I). The structures of two isomer **2** and **3** were determined on the basis of their NMR spectra. For example, the NOESY spectrum of **2j** showed that the α-proton of Gly was close to the proton at the C-8 position of anthraquinone moiety and the cyclization at the C-9 position was confirmed, and the strong NOE be-

Table I. Photoreaction of 1a–e (Aib-Oligomer)



	n	yield[a]/% 2	yield[a]/% 3	convn of 1/%	Φ_{313nm}[b]
1a	Ac-Ser(COAQ)-OMe			0	
1b	0	0	0	35	0.05
1c	1	27	0	64	0.22
1d	2	44	6	91	0.39
1e	3	trace	trace	30	0.08

[a] Isolated yield based on consumed 1. [b] Quantum yield of disappearance of 1, upon irradiation of 313-nm light.

tween the C_α-**H** and the C_4-**H** of **3k** showed the cyclization at the C-10 position.

The results of photoreaction of **1a–1e** were summarized in Table I. Compound **1a** (see Scheme II) having no glycine residue was so photostable that the starting **1a** was recovered quantitatively after 30 min of irradiation. The methylene and methine sites (AQ-COOCH_2C*H*–) of **1a** were resistant to inter- and intramolecular hydrogen abstraction under the above conditions. Irradiation of **1b** (see Scheme II) gave some photoproducts in a yield of 35%. Formation of such products might be ascribed to the presence of a glycine residue as a hydrogen donor. The reaction mixture was so complex that the complete structure of the products could not be determined. No ring-closure compound was detected from the ^{1}H NMR spectrum of the reaction mixture; no new doublet peak was observed in the region of 4.5–5.5 ppm due to the C_α-***H*** of glycine residue which was characteristic of the ring-closures, AcNHCH(O)CO–. This finding showed that the carbonyl group in the AQ moiety of **1b** could not come in contact with the glycine site in the molecule. The space-filling model of **1b** supported the impossibility of the intramolecular interaction. Therefore, hydrogen abstraction in **1b** might be intermolecular.[9]

However, irradiation of **1c** having one Aib residue as the spacer between acetylglycine and serine methyl ester produced a ring-closure product **2c** in a 27% isolated yield.[10] In the photoreaction of **1d** having two Aib residues as the spacer, the isolated yield of **2d** increased to 44%. In addition, isomeric ring-closure product **3d** was also given in a yield of 6%. As a result, it was suggested that the glycine site of **1c** could make a covalent bond only with one carbonyl group (9-position) of AQ moiety in the molecule, but both carbonyl groups (9- and 10-positions) in **1d** could bond to the glycyl α-carbon intramolecularly. Molecular dynamics (MD) calculations supported the above experimental results as follows. The gas-phase minimum structures of **1b–d** were obtained by MD calculation. The minimum intramolecular distance between C-9 of AQ and C-α of Gly ($d_{9\text{-}\alpha}$) was compared with that between C-10 and C-α ($d_{10\text{-}\alpha}$); $d_{9\text{-}\alpha}$ and $d_{10\text{-}\alpha}$ in **1b** were 6.9 and 6.7 Å, respectively; those in **1c** were 4.1 and 5.1 Å; those in **1d** were 4.1 and 3.5 Å. The photocoupling might be possible in $d < 5$ Å.

Irradiation of **1e** having three Aib residues afforded a trace amount of ring-closure products **2e** and **3e** (<1%). The oligopeptide spacer in **1e** was too long to undertake the desired intramolecular hydrogen abstraction, resulting in little cyclization. A low conversion (30%) of **1e** and a low quantum yield (0.08) of disappearance of **1e** supported that **1e** could hardly assume the conformation appropriate for intramolecular hydrogen abstraction. In the series, the total yield of products **2** and **3**, the conversion of **1**, and the quantum yield of disappearance of **1** changed together with the number of Aib residues in the spacer, i.e., the distance between the reaction sites, Gly methylene and AQ carbonyl groups.

In order to examine the influence of the structure of the oligopeptide spacers on the photoreaction, one Aib residue neighboring to the serine residue of **1d** and **1e** was substituted by an alanine (**1f** and **1h**) or a glycine residue (**1g** and **1i**). As shown in Table II, the substitution of a methyl group with a hydrogen atom caused a drastic change in the photoreactivity. Though compounds **1d**, **1f**, and **1g** had the same number of covalent bonds between the glycine and the anthraquinone, the yields of **2** and **3**, the conversion of **1**, and the quantum yield of disappearance of **1** were varied. Compound **1d** photoconverted to **2d** and **3d** in 44 and 6% yields, respectively. Demethylation of **1d** (Aib → Ala, **1f**) induced the predominant production of ring-closure **2f** and increased the yield of **2f** to 58%. One more demethylation of **1f** (Ala → Gly, **1g**) decreased the yield of ring-closure product **2g** to 28% and induced no formation of isomeric **3g**. In **1e**, **1h**, and **1i** with the same σ-bond framework of the spacer, the photoreactivity was also widely different each other. Compound **1e** hardly photoconverted to **2e** and **3e**. Demethylation of **1e** (Aib → Ala, **1h**) induced the formation of **3h** in a yield of 57%. Further demethylation of **1h** (Ala → Gly, **1i**) decreased the yield of ring-closure product **3i** to 23%. Irradiation of **1h** and **1i** gave a trace amount of ring-closure products **2h** and **2i**, respectively. In these cases, not only the drastic change of the yield of ring-closure products but also the high site-selectivity was realized. The insertion of only one Aib residue into **1f** and **1g** (as in **1h** and **1i**) changed the structure of the product from **2** to **3**. The great diversity would reflect the change in the conformation of molecules **1** in a solution.[11]

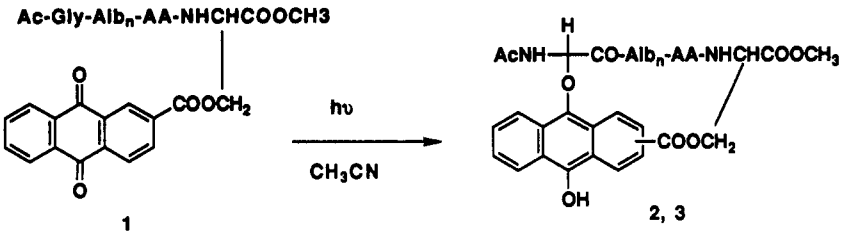
A methylene chain is more flexible than an oligopeptide linkage. It is expected that substitution of the oligopeptide link with methylene chains should change the conformation of the molecule in a solution and the photoreactivity. The photoreactions of **1j–1o** with a methylene chain –$(CH_2)_m$– were examined (see Table III). Irradiation of **1j** afforded **2j** in a yield of 41%. In spite of the same

(9) Preliminary experiments indicated quantum yield Φ of disappearance of **1b** was dependent upon the concentration; Φ of **1b** in 0.01 mM was <0.005 and 10 times smaller than that in 1 mM (0.05, see Table I).

(10) The absolute configuration around the formed asymmetric carbon AcNHC*H(O)CO– was not determined. This carbon was apart from the α-carbon of serine residue by six covalent bonds, and the biradical should combine nonstereoselectivity. Strictly speaking, **2c** might be a mixture of diastereomers. No difference between the diastereomers was observed which could not be separated in each diastereomer. The same behavior was observed for all the other ring-closure products.

(11) The MD calculations could not indicate the site selectivity.

Table II. Photoreaction of 1d–i (Substitution of Aib in 1d and 1e with Ala and Gly)

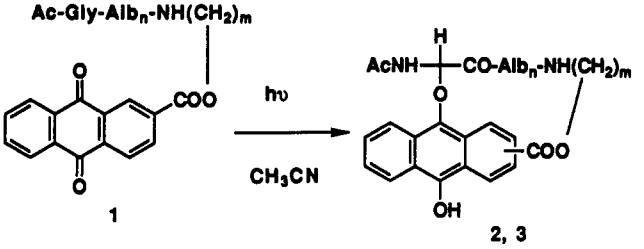


1 2, 3

	-Aib$_n$-AA-	yield[a]/% 2	3	convn of 1/%	Φ_{313nm}[b]
1d	-Aib$_2$-	44	6	91	0.39
1f	-Aib-Ala-	58	0	91	0.27
1g	-Aib-Gly-	28	0	83	0.27
1e	-Aib$_3$-	trace	trace	30	0.08
1h	-Aib$_2$-Ala-	trace	57	70	0.24
1i	-Aib$_2$-Gly-	trace	23	78	0.18

[a] Isolated yield based on consumed 1. [b] Quantum yield of disappearance of 1, upon irradiation of 313-nm light.

Table III. Photoreaction of 1c–d and 1j–o (Substitution of Oligopeptide Link in 1c–d with Methylene Chain

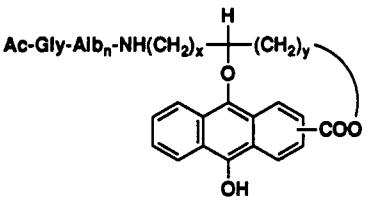


1 2, 3

	n	m	yield[a]/% 2	3	convn of 1/%	Φ_{313nm}[b]
1c			27	0	64	0.22
1j	0	5	41	0	83	0.35
1d			44	6	91	0.39
1k	1	5	18	23	70	0.32
1l	0	8	30[c]		83	0.55
1e			trace	trace	30	0.08
1m	2	5	trace	13	36	0.36
1n	1	8	40[c]		73	0.46
1o	0	11	21[c]		74	0.42

[a] Isolated yield based on consumed 1. [b] Quantum yield of disappearance of 1, upon irradiation of 313-nm light. [c] A mixture of some kinds of ring-closure products.

number of the covalent bonds between the reaction sites in **1c** and **1j**, the yield of **2j**, the conversion of **1j**, and the Φ of disappearance of **1j** were larger than that of **2c** and those of **1c**, respectively. In comparison with the yield of **2d**, the yield of **2k** decreased to 18%. On the contrary, the yield of **2k** was about four times as much as that of **3d**. The site-selectivity was changed in the photoreaction of **1d** and **1k** with the same number of the linkage covalent bond. Ring-closure products **2e** and **3e** could hardly be detected after irradiation of **1e**, but **3m** was isolated in a yield of 13% from the photoreaction mixture of **1m** in which -Aib-Ser-OMe of **1e** was substituted with a pentamethylene group. The above results might be ascribed to the variation of the conformation of molecule **1**. Irradiation of **1l** gave ring-closure products in a yield of 30%. These products were a mixture of various kinds of ring-closure products, and each product could not be isolated. In the cases of compounds **1n** and **1o**, similar ring-closure products could not be separated each other. These mixtures contained not only ring-closure products **2** and **3** but also other types of ring-closure products which were given by cyclization at the methylene group of the $-(CH_2)_m-$ spacer. When the number m in the methylene chain was



m = x + y + 1

8 or 11, the methylene chain could interact intramolecularly with the carbonyl group of AQ and undesired reactions via hydrogen abstraction from the methylene chain might occur. The presence of such reactive methylene sites besides the Gly methylene group as in **1l**, **1n**, and **1o** increased the quantum yield of disappearance of **1** and made the reaction mixture complex.

Conclusion

The synthetic (*N*-acetylglycyl)oligopeptide–anthraquinone system undertook intramolecular photocyclization and gave ring-closure products in high yields. The yield of ring-closure products was greatly dependent upon the structure of the oligopeptide link between glycine and anthraquinone moieties. As the spatial distance between the glycine and the anthraquinone carbonyl group became shorter, the yield of ring-closures increased; a short oligopeptide spacer between acetylglycine and anthraquinone groups could not give the spatial distance which was appropriate for the formation of ring-closure products, and a long oligopeptide spacer could not also give the appropriate spatial distance. Similarly, the site-selectivity in the photoreaction was explained by the spatial distance. As a result, in the biradical produced by intramolecular photoinduced hydrogen abstraction of the oligopeptide-linked anthraquinone molecule **1**, the carbon-centered radical of the glycine site tended to bind to the closer oxygen-centered radical of the anthraquinone moiety in the molecule.

The investigation of the intramolecular hydrogen abstraction gave the information on the conformation of protected oligopeptides **1** in an acetonitrile solution. Thus, this sort of investigation would give a clue to analyze the major existing conformation of peptides in solutions, which is a current and important topic in biology and pharmacology as well as chemistry.

Moreover, the photoreaction might be potentially useful for synthesis of unusual amino acids and cyclic peptides.

Experimental Section

General. UV spectra were measured in CH_3CN. IR spectra were recorded on a KBr pellet. Fluorescence spectra were recorded in a glass 2-MeTHF at 77 K by 275-nm excitation. ^1H NMR spectra were recorded in $CDCl_3$ at 400 MHz using $CHCl_3$ (7.26 ppm) as reference; exceptionally, the spectrum of **2k** was measured in CD_3OD using TMS as internal standard. MS spectra were measured in FAB mode on a *m*-nitrobenzyl alcohol matrix. Flash column chromatography was carried out using Merck silica gel (Kieselgel 60).

Materials. CH_2Cl_2 was distilled from P_2O_5 under N_2 and used. CH_3CN was distilled under N_2 and used. H-L-Ser-OMe·HCl,[12] Ac-Gly-ONSu,[13] Boc-Gly-OH,[14] Boc-Ala-OH,[14] Boc-Aib-OH,[15] and Boc-Gly-Aib-OH[16] were synthesized according to the procedure in the literature. Boc-Gly-Aib_2-OH was also synthesized according to the classical stepwise elongation method by use of Boc and benzyl groups as a protecting group and DCC–HOBt as a coupling reagent.[14] Other reagents and solvents were commercially available and used without further purification.

Synthesis of AQ-COCl. A C_6H_6 (75-mL) suspension of AQ-COOH (9.86 g, 41.7 mmol) and PCl_5 (9.6 g, 46.1 mmol) was refluxed with exclusion of moisture for 3 h. After cooling, the solvent was evaporated in vacuo and the residue was dissolved in CH_2Cl_2. Short column chromatography over silica gel (Wakogel C-200) (two times) and recrystallization from CH_2Cl_2 and hexane gave a pure title compound (9.04 g, 33.4 mmol, 80%) as yellow crystals: mp 148–151 °C (lit.[17] 147 °C). *Caution*: commercially available AQ-COCl was contaminated with AQ-COOH to a considerable extent.

Synthesis of Ac-L-Ser(COAQ)-OMe (1a). An ice-chilled CH_2Cl_2 solution (30 mL) of H-L-Ser-OMe·HCl (950 mg, 6.1 mmol), AcOH (0.36 mL, 6.3 mmol), NEt_3 (0.85 mL, 6.1 mmol), and DCC (1.3 g, 6.3 mmol) was stirred overnight with exclusion of moisture. After evaporation in vacuo, the residue was triturated with AcOEt and DCU was removed by filtration. The filtrate was condensed in vacuo, a small amount of THF was added to the residue, and NH_4Cl was removed by filtration. After evaporation in vacuo, the residue was purified by using flash column chromatography with AcOEt and MeOH as eluents to give Ac-L-Ser-OMe as a colorless oil in a yield of 93% (913 mg): ^1H NMR δ 1.87 (3 H, s), 3.58 (3 H, s), 3.72 (2 H, q, J = 4 Hz), 4.23 (1 H, br), 4.42 (1 H, q, J = 4 Hz), 7.24 (1 H, d, J = 8 Hz).

A CH_2Cl_2 solution (60 mL) of Ac-L-Ser-OMe (805 mg, 5 mmol), AQ-COCl (1.38 g, 5.1 mmol), and NEt_3 (0.71 mL, 5.1 mmol) was stirred overnight with exclusion of moisture at 0 °C. The solution was washed with aqueous 2% HCl, aqueous 4% $NaHCO_3$, and brine and dried over Na_2SO_4. After evaporation in vacuo, the residue was recrystallized from acetone and Ac-L-Ser(COAQ)-OMe (**1a**) was given in a yield of 65% (1.28 g) as pale yellow solids: mp 204–205 °C; UV λ_{max} 256, 325 nm; IR ν_{max} 3280 (NH), 1730, 1675, 1652 cm^{-1} (C=O); ^1H NMR δ 2.09 (3 H, s, CH_3CO), 3.85 (3 H, s, $COOCH_3$), 4.73 (1 H, dd, J = 4, 12 Hz, SerCH_2), 4.75 (1 H, dd, J = 4, 12 Hz, SerCH_2), 5.04 (1 H, dt, J = 8, 4 Hz, SerCH), 6.42 (1 H, d, J = 8 Hz, SerNH), 7.85 (2 H, m), 8.34 (2 H, m), 8.37 (1 H, dd, J = 1.5, 8 Hz), 8.41 (1 H, d, J = 8 Hz), 8.89 (1 H, d, J = 1 Hz); MS m/z 396 (MH^+). Anal. Calcd for $C_{21}H_{17}NO_7$: C, 63.79; H, 4.33; N, 3.54. Found: C, 63.65; H, 4.39; N, 3.54.

Synthesis of Ac-Gly-L-Ser(COAQ)-OMe (1b). A CH_2Cl_2 solution (20 mL) of H-L-Ser-OMe·HCl (2 mmol), Ac-Gly-ONSu (2 mmol), and NEt_3 (2 mmol) was stirred for 4 h with exclusion of moisture at 0 °C. After the workup similar to Ac-L-Ser-OMe (CH_2Cl_2–MeOH as eluents), recrystallization from MeOH and Et_2O gave Ac-Gly-L-Ser-OMe as white solids in a yield of 93%: mp 93–95 °C; IR ν_{max} 3200 (NH), 1740, 1700, 1640 cm^{-1} (C=O); ^1H NMR δ 2.06 (3 H, s), 3.80 (3 H, s), 3.95 (1 H, dd, J = 3, 12 Hz), 4.00 (2 H, d, J = 5 Hz), 4.01 (1 H, dd, J = 3.5, 11 Hz), 4.65 (1 H, q, J = 4 Hz), 6.29 (1 H, br), 6.97 (1 H, br).

Similar to the synthesis of **1a**, the coupling of Ac-Gly-L-Ser-OMe and AQ-COCl gave reaction mixture. After the workup similar to **1a**, flash column chromatography with CH_2Cl_2 and MeOH as eluents and recrystallization from CH_2Cl_2 and hexane gave Ac-Gly-L-Ser(COAQ)-OMe (**1b**) in a yield of 47% as pale yellow solids: mp 197–200 °C; UV λ_{max} 256, 322 nm; IR ν_{max} 3390, 3280 (NH), 1740, 1675, 1650 cm^{-1} (C=O); ^1H NMR δ 2.05 (3 H, s, CH_3CO), 3.85 (3 H, s, $COOCH_3$), 4.04 (2 H, d, J = 5.5 Hz, GlyCH_2), 4.69 (1 H, dd, J = 4, 11 Hz, SerCH_2), 4.78 (1 H, dd, J = 4, 12 Hz, SerCH_2), 5.02 (1 H, dt, J = 4, 8 Hz, SerCH), 6.43 (1 H, br, GlyNH), 7.11 (1 H, d, J = 8 Hz, SerNH), 7.85 (2 H, m), 8.33 (2 H, m), 8.38 (2 H, m), 8.85 (1 H, m); MS m/z 453 (MH^+). Anal. Calcd for $C_{23}H_{20}N_2O_8$: C, 61.06; H, 4.46; N, 6.19. Found: C, 60.84; H, 4.30; N, 6.06.

General Procedure for the Synthesis of Ac-Gly-Aib_n-AA-L-Ser-(COAQ)-OMe (1c–i). Similar to the synthesis of Ac-L-Ser-OMe, the DCC coupling of Boc-AA-OH with H-L-Ser-OMe·HCl gave Boc-AA-L-Ser-OMe.

Boc-Aib-L-Ser-OMe: 92%; white solids; mp 124–127 °C; MS m/z 305 (MH^+).

Boc-L-Ala-L-Ser-OMe: 95%; colorless oil; MS m/z 291 (MH^+).

Boc-Gly-L-Ser-OMe: 92%; colorless oil; MS m/z 277 (MH^+).

Similar to the synthesis of **1a**, the coupling of Boc-AA-L-Ser-OMe and AQ-COCl gave a reaction mixture which was washed with aqueous 10% citric acid, aqueous 4% $NaHCO_3$, and brine and dried over Na_2SO_4. Flash column chromatography (CH_2Cl_2–MeOH) and recrystallization (CH_2Cl_2–hexane) gave Boc-AA-L-Ser(COAQ)-OMe as a pale yellow solids.

Boc-Aib-L-Ser(COAQ)-OMe: 41%; mp 79–81 °C; MS m/z 539 (MH^+).

Boc-L-Ala-L-Ser(COAQ)-OMe: 48%; mp 96–98 °C; MS m/z 525 (MH^+).

Boc-Gly-L-Ser(COAQ)-OMe: 53%; mp 102–104 °C; MS m/z 511 (MH^+).

An ice-chilled 4 M HCl–AcOEt solution (40 mL) of Boc-AA-L-Ser(COAQ)-OMe (10 mmol) was stirred for 2 h with exclusion of moisture. After complete evaporation in vacuo, crude H-AA-L-Ser(COAQ)-OMe·HCl was given and used for the following step without further purification.

A CH_2Cl_2 solution (250 mL) of Boc-Gly-Aib_n-OH (n = 0–2, 40 mmol), the above H-AA-L-Ser-(COAQ)-OMe·HCl (40 mmol), NEt_3 (40 mmol), DCC (44 mmol), and HOBt·H_2O (40 mmol) was stirred for 15 h under N_2 at 0 °C. After evaporation in vacuo, the residue was triturated with AcOEt and DCU was removed by filtration. The workup similar to Boc-AA-L-Ser(COAQ)-OMe gave Boc-Gly-Aib_n-AA-L-Ser(COAQ)-OMe as pale yellow solids.

Boc-Gly-Aib-L-Ser(COAQ)-OMe: 60%; mp 191–193 °C; MS m/z 596 (MH^+).

Boc-Gly-Aib_2-L-Ser(COAQ)-OMe: 45%; mp 138–140 °C; MS m/z 681 (MH^+).

Boc-Gly-Aib_3-L-Ser(COAQ)-OMe: 29%; mp 126–127 °C; MS m/z 766 (MH^+).

Boc-Gly-Aib-L-Ala-L-Ser(COAQ)-OMe: 65%; mp 123–125 °C; MS m/z 667 (MH^+).

Boc-Gly-Aib-Gly-L-Ser(COAQ)-OMe: 47%; mp 103–106 °C; MS m/z 653 (MH^+).

Boc-Gly-Aib_2-L-Ala-L-Ser(COAQ)-OMe: 65%; mp 89–92 °C; MS m/z 752 (MH^+).

Boc-Gly-Aib_2-Gly-L-Ser(COAQ)-OMe: 27%; mp 121–123 °C; MS m/z 739 (MH^+).

A 4 M HCl–AcOEt (10 mL) of Boc-Gly-Aib_n-AA-L-Ser-(COAQ)-OMe (1 mmol) was stirred for 2 h with exclusion of moisture at 0 °C. After complete evaporation in vacuo, CH_2Cl_2 (30 mL), Ac_2O (1 mmol), and NEt_3 (2 mmol) were added and stirred overnight. After the workup similar to **1b**, recrystallization (AcOEt–Et_2O–hexane) gave an analytically pure sample of Ac-Gly-Aib_n-AA-L-Ser-(COAQ)-OMe (**1c–i**) as pale yellow solids.

Ac-Gly-Aib-L-Ser(COAQ)-OMe (1c): 77%; mp 211–214 °C; UV λ_{max} 256, 324 nm; IR ν_{max} 3267 (NH), 1745, 1734, 1680, 1655 cm^{-1} (C=O); ^1H NMR δ 1.57 (3 H, s, AibCH_3), 1.58 (3 H, s, AibCH_3), 2.05 (3 H, s, CH_3CO), 3.81 (1 H, dd, J = 5.5, 16 Hz,

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GlyCH_2), 3.82 (3 H, s, COOCH_3), 3.92 (1 H, dd, J = 5, 16 Hz, GlyCH_2), 4.75 (1 H, d, J = 4.5 Hz, SerCH_2), 4.76 (1 H, d, J = 4 Hz, SerCH_2), 4.98 (1 H, dt, J = 8, 4 Hz, SerCH), 6.71 (1 H, br, GlyNH), 6.77 (1 H, s, AibNH), 7.51 (1 H, d, J = 7 Hz, SerNH), 7.85 (2 H, m), 8.34 (2 H, m), 8.40 (1 H, d, J = 8 Hz), 8.44 (1 H, dd, J = 2, 8 Hz), 8.87 (1 H, d, J = 1.5 Hz); MS m/z 538 (MH^+). Anal. Calcd for $C_{27}H_{27}N_3O_9$: C, 60.33; H, 5.06; N, 7.82. Found: C, 60.12; H, 5.07; N, 7.84.

Ac-Gly-Aib$_2$-L-Ser(COAQ)-OMe (1d): 65%; mp 97–99 °C; UV λ_{max} 253, 326 nm; IR ν_{max} 3303 (NH), 1734, 1676, 1662 cm^{-1} (C=O); ^1H NMR δ 1.36 (3 H, s, AibCH_3), 1.44 (3 H, s, AibCH_3), 1.51 (3 H, s, AibCH_3), 1.54 (3 H, s, AibCH_3), 2.10 (3 H, s, CH_3CO), 3.67 (1 H, dd, J = 5, 16 Hz, GlyCH_2), 3.78 (3 H, s, COOCH_3), 3.80 (1 H, dd, J = 5, 15 Hz, GlyCH_2), 4.69 (1 H, dd, J = 4, 11 Hz, SerCH_2), 4.77 (1 H, dd, J = 5, 11 Hz, SerCH_2), 5.08 (1 H, dt, J = 8, 4 Hz, SerCH), 6.55 (1 H, s, AibNH), 6.67 (1 H, s, AibNH), 6.84 (1 H, br, GlyNH), 7.76 (1 H, d, J = 8.5 Hz, SerNH), 7.85 (2 H, m), 8.33 (2 H, m), 8.38 (1 H, d, J = 8 Hz), 8.49 (1 H, dd, J = 8.5 Hz), 8.93 (1 H, d, J = 1.5 Hz); MS m/z 623 (MH^+). Anal. Calcd for $C_{31}H_{34}N_4O_{10}$: C, 59.80; H, 5.50; N, 9.00. Found: C, 59.56; H, 5.78; N, 8.75.

Ac-Gly-Aib$_3$-L-Ser(COAQ)-OMe (1e): 67%; mp 123–125 °C; UV λ_{max} 255, 324 nm; IR ν_{max} 3303 (NH), 1734, 1680, 1660 cm^{-1} (C=O); ^1H NMR δ 1.32 (6 H, s, AibCH_3), 1.39 (3 H, s, AibCH_3), 1.41 (3 H, s, AibCH_3), 1.54 (3 H, s, AibCH_3), 1.55 (3 H, s, AibCH_3), 2.06 (3 H, s, CH_3CO), 3.77 (3 H, s, COOCH_3), 3.81 (1 H, dd, J = 6, 16 Hz, GlyCH_2), 3.88 (1 H, dd, J = 6, 16 Hz, GlyCH_2), 4.74 (2 H, d, J = 6 Hz, SerCH_2), 5.07 (1 H, dt, J = 8, 4 Hz, SerCH), 6.56 (2 H, s, AibNH), 6.68 (1 H, m, GlyNH), 7.15 (1 H, s, AibNH), 7.84 (2 H, m), 7.87 (1 H, d, J = 8 Hz, SerNH), 8.36 (3 H, m), 8.52 (1 H, dd, J = 1.5, 8 Hz), 8.92 (1 H, d, J = 1.5 Hz); MS m/z 709 (MH^+ + 1). Anal. Calcd for $C_{35}H_{41}N_5O_{11}$: C, 59.39; H, 5.84; N, 9.90. Found: C, 59.57; H, 5.97; N, 9.63.

Ac-Gly-Aib-L-Ala-L-Ser(COAQ)-OMe (1f): 82%; mp 79–82 °C; UV λ_{max} 255, 326 nm; IR ν_{max} 3303 (NH), 1736, 1662, 1649 cm^{-1} (C=O); ^1H NMR δ 1.41 (3 H, d, J = 7 Hz, AlaCH_3), 1.46 (6 H, s, AibCH_3), 2.01 (3 H, s, CH_3CO), 3.74 (2 H, br, GlyCH_2), 3.81 (3 H, s, COOCH_3), 4.52 (1 H, quintet, J = 7 Hz, AlaCH), 4.70 (1 H, dd, J = 5.5, 11 Hz, SerCH_2), 4.75 (1 H, dd, J = 4, 11 Hz, SerCH_2), 5.01 (1 H, dt, J = 8, 4 Hz, SerCH), 6.76 (1 H, br, GlyNH), 6.93 (1 H, s, AibNH), 7.00 (1 H, d, J = 8 Hz, AlaNH), 7.75 (1 H, d, J = 8 Hz, SerNH), 7.82 (2 H, m), 8.30 (2 H, m), 8.35 (1 H, d, J = 8 Hz), 8.40 (1 H, dd, J = 2, 8 Hz), 8.85 (1 H, d, J = 1.5 Hz); MS m/z 609 (MH^+). Anal. Calcd for $C_{30}H_{32}N_4O_{10}$: C, 59.20; H, 5.30; N, 9.21. Found: C, 58.92; H, 5.23; N, 9.12.

Ac-Gly-Aib-Gly-L-Ser(COAQ)-OMe (1g): 51%; mp 102–105 °C; UV λ_{max} 255, 326 nm; IR ν_{max} 3303 (NH), 1734, 1660, 1655 cm^{-1} (C=O); ^1H NMR δ 1.42 (3 H, s, AibCH_3), 1.45 (3 H, s, AibCH_3), 2.07 (3 H, s, CH_3CO), 3.77 (1 H, dd, J = 5, 17 Hz, GlyCH_2), 3.79 (3 H, s, COOCH_3), 3.83 (1 H, dd, J = 5, 12 Hz, GlyCH_2), 3.88 (1 H, dd, J = 4, 12 Hz, GlyCH_2), 4.17 (1 H, dd, J = 7, 17 Hz, GlyCH_2), 4.76 (1 H, dd, J = 4, 11 Hz, SerCH_2), 4.78 (1 H, dd, J = 5, 11 Hz, SerCH_2), 5.10 (1 H, dt, J = 8, 5 Hz, SerCH), 6.96 (1 H, s, AibNH + 1 H, br, GlyNH), 7.30 (1 H, t, J = 6 Hz, GlyNH), 7.84 (2 H, m), 7.93 (1 H, d, J = 8 Hz, SerNH), 8.32 (2 H, m), 8.37 (1 H, d, J = 8 Hz), 8.46 (1 H, dd, J = 2, 8 Hz), 8.91 (1 H, d, J = 1.5 Hz); MS m/z 595 (MH^+). Anal. Calcd for $C_{29}H_{30}N_4O_{10}\cdot 1/2H_2O$: C, 57.71; H, 5.06; N, 9.28. Found: C, 57.84; H, 5.12; N, 9.19.

Ac-Gly-Aib$_2$-L-Ala-L-Ser(COAQ)-OMe (1h): 73%; mp 136–139 °C; UV λ_{max} 255, 326 nm; IR ν_{max} 3297 (NH), 1736, 1676, 1662, 1655 cm^{-1} (C=O); ^1H NMR δ 1.39 (3 H, s, AibCH_3), 1.41 (3 H, s, AibCH_3), 1.42 (3 H, d, J = 7 Hz, AlaCH_3), 1.42 (6 H, s, AibCH_3), 2.06 (3 H, s, CH_3CO), 3.74 (1 H, dd, J = 5.5, 16 Hz, GlyCH_2), 3.81 (1 H, dd, J = 6, 16 Hz, GlyCH_2), 3.82 (3 H, s, COOCH_3), 4.49 (1 H, quintet, J = 7.5 Hz, AlaCH), 4.65 (1 H, dd, J = 6, 11 Hz, SerCH_2), 4.81 (1 H, dd, J = 4, 11 Hz, SerCH_2), 4.98 (1 H, ddd, J = 4, 6, 8 Hz, SerCH), 6.51 (1 H, s, AibNH), 6.55 (1 H, s, AibNH), 6.84 (1 H, br, GlyNH), 7.43 (1 H, d, J = 8 Hz, AlaNH), 7.83 (1 H, d, J = 8 Hz, SerNH), 7.84 (2 H, m), 8.33 (2 H, m), 8.37 (1 H, d, J = 8 Hz), 8.45 (1 H, dd, J = 2, 8 Hz), 8.90 (1 H, d, J = 1.5 Hz); MS m/z 694 (MH^+). Anal. Calcd for $C_{34}H_{39}N_5O_{11}\cdot 1/2H_2O$: C, 58.11; H, 5.59; N, 9.97. Found: C, 58.31; H, 5.66; N, 9.99.

Ac-Gly-Aib$_2$-Gly-L-Ser(COAQ)-OMe (1i): 67%; mp 100–102 °C; UV λ_{max} 255, 325 nm; IR ν_{max} 3302 (NH), 1734, 1676, 1660, 1655 cm^{-1} (C=O); ^1H NMR δ 1.34 (3 H, s, AibCH_3), 1.39 (3 H, s, AibCH_3), 1.41 (3 H, s, AibCH_3), 1.43 (3 H, s, AibCH_3), 2.04 (3 H, s, CH_3CO), 3.77 (3 H, s, COOCH_3), 3.83 (2 H, d, J = 5 Hz, GlyCH_2), 3.85 (1 H, dd, J = 5, 17 Hz, GlyCH_2), 4.02 (1 H, dd, J = 7, 17 Hz, GlyCH_2), 4.72 (1 H, dd, J = 5, 11 Hz, SerCH_2), 4.77 (1 H, dt, J = 5, 11 Hz, SerCH_2), 4.97 (1 H, dt, J = 5, 7 Hz, SerCH), 6.90 (1 H, s, AibNH), 7.12 (1 H, s, AibNH), 7.18 (1 H, br, GlyNH), 7.82 (2 H, m), 7.88 (1 H, t, J = 6 Hz, GlyNH), 8.00 (1 H, d, J = 7 Hz, SerNH), 8.31 (2 H, m), 8.35 (1 H, d, J = 8 Hz), 8.47 (1 H, dd, J = 1.5, 8 Hz), 8.87 (1 H, d, J = 1.5 Hz); MS m/z 681 (MH^+ + 1). Anal. Calcd for $C_{33}H_{37}N_5O_{11}\cdot 1/2H_2O$: C, 57.55; H, 5.56; N, 10.17. Found: C, 57.58; H, 5.54; N, 9.88.

General Procedure for the Synthesis of Ac-Gly-Aib$_n$-NH-(CH$_2$)$_m$-OCOAQ (1j–o). The reaction of 5-amino-1-pentanol with Boc_2O[14] produced Boc-NH-(CH$_2$)$_5$-OH. Commercially available 8-aminocaprylic acid (H_2N-(CH$_2$)$_7$-COOH) and 11-aminoundecanoic acid (H_2N-(CH$_2$)$_{10}$-COOH) were protected with the Boc group,[14] and both acids were esterified with MeOH by use of DCC and DMAP[18] to give Boc NH-(CH$_2$)$_{m-1}$-COOCH$_3$ (m = 8, 11). According to the procedure by Soai et al.,[19] the reduction of the esters with $NaBH_4$ gave Boc-NH-(CH$_2$)$_m$-OH (m = 8, 11).

Similar to the synthesis of Boc-AA-L-Ser(COAQ)-OMe, the reaction of Boc-NH-(CH$_2$)$_m$-OH (m = 5, 8, 11) with AQ-COCl afforded Boc-NH-(CH$_2$)$_m$-OCOAQ as pale yellow solids.

Boc-NH-(CH$_2$)$_5$-OCOAQ: 62%; mp 134–135 °C; MS m/z 438 (MH^+).

Boc-NH-(CH$_2$)$_8$-OCOAQ: 41%; mp 117–119 °C; MS m/z 480 (MH^+).

Boc-NH-(CH$_2$)$_{11}$-OCOAQ: 31%; mp 98–100 °C; MS m/z 522 (MH^+).

Similar to the synthesis of Boc-Gly-Aib$_n$-AA-L-Ser(COAQ)-OMe, the DCC-HOBt coupling of Boc-Gly-Aib$_n$-OH with HCl·H_2N-(CH$_2$)$_m$-OCOAQ (deprotection of Boc-NH-(CH$_2$)$_m$-OCOAQ) afforded Boc-Gly-Aib$_n$-NH-(CH$_2$)$_m$-OCOAQ as pale yellow solids.

Boc-Gly-NH-(CH$_2$)$_5$-OCOAQ: 86%; mp 190–192 °C; MS m/z 495 (MH^+).

Boc-Gly-Aib-NH-(CH$_2$)$_5$-OCOAQ: 83%; mp 175–176 °C; MS m/z 580 (MH^+).

Boc-Gly-NH-(CH$_2$)$_8$-OCOAQ: 67%; mp 117–119 °C; MS m/z 537 (MH^+).

Boc-Gly-Aib$_2$-NH-(CH$_2$)$_5$-OCOAQ: 83%; mp 176–178 °C; MS m/z 665 (MH^+).

Boc-Gly-Aib-NH-(CH$_2$)$_8$-OCOAQ: 73%; mp 168–171 °C; MS m/z 622 (MH^+).

Boc-Gly-NH-(CH$_2$)$_{11}$-OCOAQ: 51%; mp 73–75 °C; MS m/z 580 (MH^+ + 1).

Similar to the synthesis of Ac-Gly-Aib$_n$-Ser(COAQ)-OMe, deprotection of Boc-Gly-Aib$_n$-NH-(CH$_2$)$_m$-OCOAQ and acetylation gave Ac-Gly-Aib$_n$-NH-(CH$_2$)$_m$-OCOAQ (1j–o) as pale yellow solids.

Ac-Gly-NH-(CH$_2$)$_5$-OCOAQ (1j): 78%; mp 195–196 °C; UV λ_{max} 254, 326 nm; IR ν_{max} 3290 (NH), 1727, 1672, 1653 cm^{-1} (C=O); ^1H NMR δ 1.53 (2 H, quintet, J = 7 Hz, NHCH$_2$CH$_2$CH$_2$), 1.66 (2 H, quintet, J = 7 Hz, NHCH$_2$CH$_2$), 1.86 (2 H, quintet, J = 7 Hz, COOCH$_2$CH$_2$), 2.04 (3 H, s, CH_3CO), 3.34 (2 H, q, J = 7 Hz, NHCH$_2$), 3.93 (2 H, d, J = 5 Hz, GlyCH_2), 4.42 (2 H, t, J = 6 Hz, COOCH$_2$), 6.16 (1 H, br), 6.38 (1 H, br), 7.85 (2 H, m), 8.35 (2 H, m), 8.40 (1 H, d, J = 8 Hz), 8.44 (1 H, dd, J = 2, 8 Hz), 8.91 (1 H, d, J = 1 Hz); MS m/z 437 (MH^+). Anal. Calcd for $C_{24}H_{24}N_2O_6$: C, 66.04; H, 5.54; N, 6.42. Found: C, 65.92; H, 5.47; N, 6.43.

Ac-Gly-Aib-NH-(CH$_2$)$_5$-OCOAQ (1k): 91%; mp 142–145 °C; UV λ_{max} 254, 325 nm; IR ν_{max} 3351, 3267 (NH), 1726, 1682, 1668 cm^{-1} (C=O); ^1H NMR δ 1.56 (6 H, s, AibCH_3), 1.62–1.67 (4 H, m, NHCH$_2$CH$_2$CH$_2$), 1.85 (2 H, quintet, J = 7 Hz, COOCH$_2$CH$_2$), 2.05 (3 H, s, CH_3CO), 3.31 (2 H, q, J = 6.5 Hz, NHCH_2), 3.85 (2 H, d, J = 5 Hz, GlyCH_2), 4.41 (2 H, t, J = 6 Hz, COOCH_2), 6.35 (1 H, br, NH), 6.54 (1 H, br, NH), 6.70 (1 H, s, AibNH), 7.85 (2 H, m), 8.34 (2 H, m), 8.40 (1 H, d, J = 8 Hz), 8.44 (1 H, dd, J = 2, 8 Hz), 8.91 (1 H, d, J = 1.5 Hz); MS m/z 522 (MH^+). Anal. Calcd for $C_{28}H_{31}N_3O_7$: C, 64.48; H, 5.99; N, 8.06. Found: C, 64.45; H, 6.02; N, 7.94.

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Ac-Gly-NH-$(CH_2)_8$-OCOAQ (1l): 63%; mp 179–180 °C; UV λ_{max} 254, 326 nm; IR ν_{max} 3290 (NH), 1716, 1674, 1645 cm^{-1} (C=O); ^1H NMR δ 1.36 (4 H, br), 1.42–1.56 (6 H, m), 1.82 (2 H, m), 2.04 (3 H, s, CH_3CO), 3.27 (2 H, q, J = 7 Hz, $NHCH_2$), 3.89 (2 H, d, J = 5 Hz, $GlyCH_2$), 4.40 (2 H, t, J = 7 Hz, $COOCH_2$), 6.02 (1 H, br, NH), 6.29 (1 H, br, NH), 7.84 (2 H, m), 8.35 (2 H, m), 8.40 (1 H, d, J = 8 Hz), 8.44 (1 H, dd, J = 2, 8 Hz), 8.93 (1 H, d, J = 2 Hz); MS m/z 479 (MH^+). Anal. Calcd for $C_{27}H_{30}N_2O_6$: C, 67.76; H, 6.32; N, 5.86. Found: C, 67.59; H, 6.30; N, 5.74.

Ac-Gly-Aib_2-NH-$(CH_2)_5$-OCOAQ (1m): 85%; mp 172–174 °C; UV λ_{max} 254, 325 nm; IR ν_{max} 3332, 3288 (NH), 1724, 1676, 1655 cm^{-1} (C=O); ^1H NMR δ 1.49 (6 H, s, $AibCH_3$), 1.51 (6 H, s, $AibCH_3$), 1.55–1.66 (4 H, m, $NHCH_2CH_2CH_2$), 1.86 (2 H, quintet, J = 7 Hz, $COOCH_2CH_2$), 2.07 (3 H, s, CH_3CO), 3.28 (2 H, q, J = 5.5 Hz, $NHCH_2$), 3.78 (2 H, d, J = 5.5 Hz, $GlyCH_2$), 4.43 (2 H, t, J = 7 Hz, $COOCH_2$), 6.49 (1 H, s, AibNH), 6.62 (1 H, br, NH), 6.65 (1 H, s, AibNH), 7.01 (1 H, br, NH), 7.85 (2 H, m), 8.34 (2 H, m), 8.40 (1 H, d, J = 8 Hz), 8.44 (1 H, dd, J = 2, 8 Hz), 8.92 (1 H, d, J = 1.5 Hz); MS m/z 607 (MH^+). Anal. Calcd for $C_{32}H_{38}N_4O_8$: C, 63.35; H, 6.31; N, 9.24. Found: C, 63.25; H, 6.30; N, 9.21.

Ac-Gly-Aib-NH-$(CH_2)_8$-OCOAQ (1n): 64%; mp 149–152 °C; UV λ_{max} 256, 324 nm; IR ν_{max} 3398 (NH), 1724, 1676, 1653 cm^{-1} (C=O); ^1H NMR δ 1.36 (6 H, br), 1.45–1.52 (4 H, m), 1.56 (6 H, s, $AibCH_3$), 1.82 (2 H, quintet, J = 7 Hz, $COOCH_2CH_2$), 2.05 (3 H, s, CH_3CO), 3.25 (2 H, q, J = 7 Hz, $NHCH_2$), 3.85 (2 H, d, J = 5.5 Hz, $GlyCH_2$), 4.40 (2 H, t, J = 7 Hz, $COOCH_2$), 6.26 (1 H, br, NH), 6.33 (1 H, br, NH), 6.63 (1 H, s, AibNH), 7.85 (2 H, m), 8.35 (2 H, m), 8.41 (1 H, d, J = 8 Hz), 8.44 (1 H, dd, J = 2, 8 Hz), 8.94 (1 H, d, J = 1.5 Hz); MS m/z 564 (M^+). Anal. Calcd for $C_{31}H_{38}N_3O_7$: C, 65.94; H, 6.78; N, 7.44. Found: C, 65.76; H, 6.49; N, 7.16.

Ac-Gly-NH-$(CH_2)_{11}$-OCOAQ (1o): 65%; mp 149–151 °C; UV λ_{max} 255, 325 nm; IR ν_{max} 3294 (NH), 1718, 1674, 1647 cm^{-1} (C=O); ^1H NMR δ 1.29 (12 H, m), 1.48 (4 H, m), 1.82 (2 H, quintet, J = 7 Hz, $COOCH_2CH_2$), 2.04 (3 H, s, CH_3CO), 3.26 (2 H, q, J = 7 Hz, $NHCH_2$), 3.88 (2 H, d, J = 5 Hz, $GlyCH_2$), 4.40 (2 H, t, J = 7 Hz, $COOCH_2$), 5.89 (1 H, br, NH), 6.23 (1 H, br, NH), 7.84 (2 H, m), 8.34 (2 H, m), 8.40 (1 H, d, J = 8 Hz), 8.44 (1 H, dd, J = 2, 8 Hz), 8.94 (1 H, d, J = 1.5 Hz); MS m/z 521 (MH^+). Anal. Calcd for $C_{30}H_{36}N_2O_6$: C, 69.21; H, 6.97; N, 5.38. Found: C, 69.19; H, 6.98; N, 5.39.

Photoreaction of (*N*-Acetylglycyl)oligopeptide-Linked Anthraquinone Molecules 1. The title molecule 1 (1 mmol) was dissolved in CH_3CN (100 mL) in a Pyrex tube and saturated with Ar. The solution was irradiated with a 300-W high-pressure mercury arc lamp through an aqueous $CuSO_4$ solution filter at room temperature. After 30 min irradiation, the reaction mixture was concentrated in vacuo and the starting molecule 1 and the ring-closure products 2 and 3 were isolated by flash column chromatography (CH_2Cl_2–MeOH).

Physical Properties of the Ring-Closure Products 2 and 3. 2c: pale yellow solids; mp 135–140 °C; UV λ_{max} 259 nm; fluorescence λ_{max} 420, 452, 490, 534 nm; IR ν_{max} 3350 (OH, NH), 1735, 1660 cm^{-1} (C=O); ^1H NMR δ 1.28 (3 H, s), 1.54 (3 H, s), 1.87 (3 H, s), 3.87 (3 H, s), 3.90 (2 H, br), 5.03 (1 H, d, J = 10 Hz, $GlyC_\alpha H$), 5.29 (1 H, m), 6.30 (1 H, br), 6.45 (1 H, m), 7.05 (1 H, br), 7.50 (1 H, dt, J = 1, 7.5 Hz, C_7H), 7.72 (1 H, dt, J = 1, 7.5 Hz, C_6H), 8.15 (1 H, dd, J = 1, 8 Hz, C_8H), 8.17 (1 H, d, J = 8 Hz, C_5H), 8.19 (1 H, dd, J = 1.5, 8 Hz, C_3H), 8.30 (1 H, d, J = 8 Hz, C_4H), 8.55 (1 H, d, J = 1.5 Hz, C_1H); MS m/z 538 (MH^+); HRMS found 538.1792, calcd for $C_{27}H_{27}N_3O_9 \cdot H^+$ 538.1826.

2d: pale yellow solids; mp 206–208 °C; UV λ_{max} 261 nm; fluorescence λ_{max} 417, 447, 481, 521 nm; IR ν_{max} 3382 (OH, NH), 1727, 1645 cm^{-1} (C=O); ^1H NMR δ 1.38 (3 H, s), 1.44 (3 H, s), 1.51 (3 H, s), 1.55 (3 H, s), 1.62 (3 H, s), 3.84 (3 H, s), 4.46 (1 H, m), 4.64 (1 H, m), 4.79 (1 H, d, J = 7 Hz, $GlyC_\alpha H$), 4.85 (1 H, m), 5.13 (1 H, s), 6.71 (1 H, d, J = 7 Hz), 7.20 (1 H, s), 7.55 (2 H, m, C_7H), 7.73 (1 H, t, J = 7 Hz, C_6H), 8.18 (3 H, m, $C_{3,5,8}H$), 8.27 (1 H, d, J = 8 Hz, C_4H), 8.56 (1 H, d, J = 1 Hz, C_1H); MS m/z 623 (MH^+); HRMS found 623.2305, calcd for $C_{31}H_{34}N_4O_{10} \cdot H^+$ 623.2353.

3d: pale yellow solids; mp 181–183 °C; UV λ_{max} 239, 280 (sh) nm; fluorescence λ_{max} 410, 440, 474 nm; IR ν_{max} 3348 (OH, NH), 1734, 1662 cm^{-1} (C=O); ^1H NMR δ 1.21 (3 H, s), 1.30 (3 H, s), 1.36 (3 H, s), 1.47 (3 H, s), 2.16 (3 H, s), 3.97 (3 H, s), 4.49 (1 H, dd, J = 3, 11 Hz), 4.72 (1 H, d, J = 7 Hz, $GlyC_\alpha H$), 4.74 (1 H, m), 5.07 (1 H, m), 5.25 (1 H, dd, J = 4, 11 Hz), 5.68 (1 H, s), 5.92 (1 H, s), 6.49 (1 H, d, J = 7 Hz), 6.87 (1 H, s), 7.54 (1 H, m), 7.56 (1 H, t, J = 7 Hz, C_7H), 7.71 (1 H, t, J = 7 Hz, C_6H), 7.79 (1 H, d, J = 7 Hz, C_5H), 8.23 (1 H, d, J = 8 Hz, C_8H), 8.35 (1 H, d, J = 8 Hz, C_4H), 8.52 (1 H, dd, J = 2, 8 Hz, C_3H), 8.67 (1 H, d, J = 2 Hz, C_1H); MS m/z 623 (MH^+); HRMS found 623.2363, calcd for $C_{31}H_{34}N_4O_{10} \cdot H^+$ 623.2353.

2f: pale yellow solids; mp 213–216 °C; UV λ_{max} 276 nm; fluorescence λ_{max} 419, 449, 483, 523 nm; IR ν_{max} 3430 (OH), 3303 (NH), 1736, 1662 cm^{-1} (C=O); ^1H NMR δ 1.40 (3 H, d, J = 7 Hz), 1.49 (3 H, s), 1.54 (3 H, s), 1.69 (3 H, s), 3.79 (3 H, s), 4.53 (1 H, dd, J = 3, 11.5 Hz), 4.57 (1 H, dd, J = 7, 12 Hz), 4.75 (1 H, d, J = 8 Hz, $GlyC_\alpha H$), 4.89 (1 H, dd, J = 4, 11 Hz), 5.02 (1 H, m), 5.67 (1 H, d, J = 8.5 Hz), 5.81 (1 H, s), 6.21 (1 H, d, J = 7 Hz), 7.51 (1 H, d, J = 7 Hz), 7.52 (1 H, t, J = 7 Hz, C_7H), 7.61 (1 H, s), 7.70 (1 H, dt, J = 1, 7 Hz, C_6H), 8.12 (2 H, m, $C_{5,8}H$), 8.15 (1 H, dd, J = 1.5, 8 Hz, C_3H), 8.25 (1 H, d, J = 8 Hz, C_4H), 8.52 (1 H, d, J = 1.5 Hz, C_1H); MS m/z 609 (MH^+); HRMS found 609.2315, calcd for $C_{30}H_{32}N_4O_{10} \cdot H^+$ 609.2197.

2g: pale yellow solids; mp 195–197 °C; UV λ_{max} 275 nm; fluorescence λ_{max} 435, 456, 489, 530 nm; IR ν_{max} 3349 (OH, NH), 1734, 1670 cm^{-1} (C=O); ^1H NMR δ 1.39 (3 H, s), 1.67 (3 H, s), 1.68 (3 H, s), 3.88 (3 H, s), 3.93 (1 H, dd, J = 7, 16 Hz), 3.99 (1 H, dd, J = 7, 16 Hz), 4.60 (1 H, dd, J = 3, 11 Hz), 4.83 (1 H, dd, J = 3, 11 Hz), 4.88 (1 H, d, J = 10 Hz, $GlyC_\alpha H$), 4.95 (1 H, m), 6.27 (1 H, d, J = 10 Hz), 6.72 (1 H, br), 6.85 (1 H, t, J = 5 Hz), 7.15 (1 H, s), 7.37 (1 H, d, J = 7 Hz), 7.52 (1 H, dt, J = 1, 7 Hz, C_7H), 7.72 (1 H, dt, J = 1, 7 Hz, C_6H), 8.12 (2 H, dt, J = 1, 8 Hz, $C_{3,5}H$), 8.16 (1 H, d, J = 8 Hz, C_8H), 8.25 (1 H, d, J = 8 Hz, C_4H), 8.53 (1 H, d, J = 1 Hz, C_1H); MS m/z 595 (MH^+); HRMS found 595.2118, calcd for $C_{29}H_{30}N_4O_{10} \cdot H^+$ 595.2040.

3h: pale yellow solids; mp 197–199 °C; UV λ_{max} 276 nm; fluorescence λ_{max} 419, 449, 484, 523 nm; IR ν_{max} 3408 (OH), 3303 (NH), 1734, 1660 cm^{-1} (C=O); ^1H NMR δ 1.23 (3 H, d, J = 7 Hz), 1.31 (3 H, s), 1.46 (3 H, s), 1.51 (3 H, s), 1.52 (3 H, s), 1.85 (3 H, s), 3.91 (3 H, s), 4.41 (1 H, dd, J = 7, 11 Hz), 4.59 (1 H, m), 4.83 (1 H, d, J = 8 Hz, $GlyC_\alpha H$), 5.15 (1 H, dd, J = 3, 11 Hz), 5.30 (1 H, m), 5.71 (1 H, d, J = 8 Hz), 6.03 (1 H, s), 6.66 (1 H, s), 6.82 (1 H, br), 7.50 (1 H, d, J = 8.5 Hz), 7.55 (1 H, dt, J = 1, 8 Hz, C_7H), 7.72 (1 H, dt, J = 1, 8 Hz, C_6H), 7.86 (1 H, d, J = 7 Hz, C_5H), 8.10 (1 H, dd, J = 1.5, 8 Hz, C_3H), 8.19 (1 H, d, J = 8 Hz, C_8H), 8.24 (1 H, d, J = 8 Hz, C_4H), 8.50 (1 H, d, J = 1 Hz, C_1H); MS m/z 694 (MH^+); HRMS found 694.2775, calcd for $C_{34}H_{39}N_5O_{11} \cdot H^+$ 694.2724.

3i: pale yellow solids; mp 199–200 °C; UV λ_{max} 276 nm; fluorescence λ_{max} 419, 450, 485, 526 nm; IR ν_{max} 3303 (OH, NH), 1732, 1664 cm^{-1} (C=O); ^1H NMR δ 1.26 (3 H, s), 1.42 (3 H, s), 1.46 (3 H, s), 1.51 (3 H, s), 1.89 (3 H, s), 3.86 (1 H, m), 3.94 (3 H, s), 4.17 (1 H, dd, J = 8, 17 Hz), 4.46 (1 H, dd, J = 5, 11.5 Hz), 4.88 (1 H, d, J = 8 Hz, $GlyC_\alpha H$), 5.17 (1 H, dd, J = 2, 11 Hz), 5.30 (1 H, m), 5.8 (1 H, br), 5.89 (1 H, s), 5.99 (1 H, d, J = 7 Hz), 6.71 (1 H, br), 6.78 (1 H, s), 7.29 (1 H, s), 7.54 (1 H, dt, J = 1, 7 Hz, C_7H), 7.70 (1 H, dt, J = 1, 7 Hz, C_6H), 7.72 (1 H, d, J = 7 Hz), 7.82 (1 H, d, J = 8 Hz, C_5H), 8.09 (1 H, dd, J = 1.5, 8 Hz, C_3H), 8.17 (1 H, dd, J = 1, 7 Hz, C_8H), 8.23 (1 H, d, J = 8 Hz, C_4H), 8.57 (1 H, d, J = 1.5 Hz, C_1H); MS m/z 680 (MH^+); HRMS found 680.2707, calcd for $C_{33}H_{37}N_5O_{11} \cdot H^+$ 680.2568.

2j: pale yellow solids; mp 188–190 °C; UV λ_{max} 278 nm; fluorescence λ_{max} 418, 449, 483, 525 nm; IR ν_{max} 3356 (OH, NH), 1722, 1660 cm^{-1} (C=O); ^1H NMR δ 0.88 (2 H, m), 1.55 (3 H, s), 1.85 (4 H, m), 3.16 (1 H, m), 3.55 (1 H, m), 4.19 (1 H, m), 4.71 (1 H, m), 4.93 (1 H, d, J = 9 Hz, $GlyC_\alpha H$), 5.47 (1 H, d, J = 9 Hz), 6.76 (1 H, br), 7.52 (1 H, dt, J = 1, 7.5 Hz, C_7H), 7.70 (1 H, dt, J = 1, 7.5 Hz, C_6H), 8.08 (1 H, d, J = 7 Hz, C_5H), 8.14 (1 H, dd, J = 1.5, 8 Hz, C_3H), 8.15 (1 H, dd, J = 1.5, 8 Hz, C_8H), 8.28 (1 H, d, J = 8 Hz, C_4H), 8.57 (1 H, d, J = 1.5 Hz, C_1H); MS m/z 437 (MH^+). Anal. Calcd for $C_{24}H_{24}N_2O_6 \cdot {}^1/_2H_2O$: C, 64.71; H, 5.66; N, 6.29. Found: C, 64.69; H, 5.50; N, 6.30.

2k: pale yellow solids; mp 217–219 °C; UV λ_{max} 277 nm; fluorescence λ_{max} 415, 446, 481 nm; IR ν_{max} 3332 (OH, NH), 1709, 1660 cm^{-1} (C=O); ^1H NMR δ 1.42 (3 H, s), 1.50 (3 H, s), 1.59 (3 H, s), 1.62 (2 H, m), 1.83 (2 H, m), 1.97 (2 H, m), 3.28 (1 H, m), 3.47 (1 H, m), 4.33 (1 H, m), 4.43 (1 H, m), 4.89 (1 H, br, $GlyC_\alpha H$), 7.48 (1 H, dt, J = 1, 7 Hz, C_7H), 7.72 (1 H, dt, J = 1, 7 Hz, C_6H), 7.90 (1 H, m), 8.01 (1 H, dd, J = 2, 7 Hz, C_5H), 8.13 (1 H, dd, J

= 1, 8 Hz, C_4H), 8.19 (1 H, d, J = 8 Hz, C_3H), 8.22 (1 H, d, J = 8 Hz, C_8H), 8.56 (1 H, d, J = 1 Hz, C_1H); MS m/z 522 (MH^+); HRMS found 522.2220, calcd for $C_{28}H_{31}N_3O_7 \cdot H^+$ 522.2240.

3k: pale yellow solids; mp 184–186 °C; UV λ_{max} 238, 280 (sh) nm; fluorescence λ_{max} 408, 438, 473, 513 nm; IR ν_{max} 3498 (OH), 3318 (NH), 1726, 1674, 1651 cm^{-1} (C=O); ^1H NMR δ 1.23 (3 H, s), 1.25 (3 H, s), 1.30–1.50 (4 H, m), 1.75 (2 H, m), 2.16 (3 H, s), 2.77 (1 H, m), 3.60 (1 H, m), 4.18 (1 H, m), 4.77 (1 H, d, J = 7 Hz, $GlyC_\alpha H$), 4.88 (1 H, m), 5.19 (1 H, m), 6.05 (1 H, s), 6.46 (1 H, d, J = 7 Hz), 6.91 (1 H, s), 7.55 (1 H, dt, J = 4, 9 Hz, C_7H), 7.69 (1 H, dt, J = 1, 7 Hz, C_6H), 7.78 (1 H, d, J = 7 Hz, C_5H), 8.23 (1 H, d, J = 7 Hz, C_9H), 8.33 (1 H, d, J = 8 Hz, C_4H), 8.55 (1 H, d, J = 2, 8 Hz, C_3H), 8.80 (1 H, d, J = 1.5 Hz, C_1H); MS m/z 522 (MH^+). Anal. Calcd for $C_{28}H_{31}N_3O_7 \cdot {}^1/_2H_2O$: C, 63.39; H, 6.08; N, 7.92. Found: C, 63.22; H, 5.81; N, 7.74.

3m: pale yellow solids; mp 149–151 °C; UV λ_{max} 229, 275 (sh) nm; fluorescence λ_{max} 404, 443, 446, 504 and 419, 452, 488, 530 nm; IR ν_{max} 3388 (OH, NH), 1724, 1662 cm^{-1} (C=O); ^1H NMR δ 1.47 (6 H, s), 1.56 (4 H, m), 1.58 (6 H, s), 1.85 (2 H, m), 1.90 (3 H, s), 3.23 (2 H, m), 4.38 (1 H, m), 4.58 (1 H, m), 4.89 (1 H, d, J = 8.5 Hz, $GlyC_\alpha H$), 6.01 (1 H, s), 6.16 (1 H, d, J = 8.5 Hz), 6.34 (1 H, s), 6.38 (1 H, t, J = 5.5 Hz), 6.73 (1 H, s), 7.53 (1 H, dt, J = 1, 7.5 Hz, C_7H), 7.70 (1 H, dt, J = 1, 8 Hz, C_6H), 7.99 (1 H, d, J = 8 Hz, C_5H), 8.10 (1 H, d, J = 8 Hz, C_4H), 8.18 (1 H, dd, J = 1, 8 Hz, C_9H), 8.32 (1 H, dd, J = 2, 8 Hz, C_3H), 8.88 (1 H, d, J = 2 Hz, C_1H); MS m/z 607 (MH^+); HRMS found 607.2788, calcd for $C_{32}H_{38}N_4O_8 \cdot H^+$ 607.2768.

Measurement of Quantum Yield of Disappearance of Starting Anthraquinones 1. A 300-W high-pressure mercury projector lamp was used as a light source. A combination of Corning 7-54 glass filter and an aqueous K_2CrO_4 solution filter was used for isolation of 313-nm light.[20] Light intensity was determined by potassium ferrioxalate actiometry. An CH_3CN solution (1 mM) of starting anthraquinones 1 in a quartz cell under Ar was irradiated for 40 s; the conversion of 1 was less than 10%. The amount of 1 that disappeared was determined by measuring the amount of 1 before and after irradiation by HPLC (Cosmosil $5C_{18}$ column) with 40% H_2O and 60% MeOH as eluents. Methyl benzoate was used for a standard. Each quantum yield was an average value of more than two experiments.

Molecular Dynamics (MD) Calculations. All model building and calculations were performed on either a Silicon Graphics 4D/35 or a Cray YMP2E, using the program Discover (CVFF was employed as molecular mechanics force field and the dielectric constant = 1). Molecular structures of 1 were constructed by use of Builder module of Insight II, energy minimized and used as an initial structure for MD calculations. At 1000 K, MD were performed for 100 ps (1 fs/step). Conformational sampling was done every 1000 steps (1 ps), and the structure was energy minimized. On the 100 conformers, the distances C_9–C_α and C_{10}–C_α were estimated.

Abbreviations

Gly = glycine, Ala = alanine, Ser = serine, Aib = α-aminoisobutyric acid, DCU = dicyclohexylurea, HONSu = *N*-hydroxysuccinimide, HOBt = 1-hydroxybenzotriazole, AQ– = 2-anthraquinonyl.

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Supplementary Material Available: IR and ^1H NMR spectral data of Boc-protected compounds, ^1H NMR spectra for photoproducts 2 and 3, NOESY spectra of **2j** and **2k**, and the fluorescence spectrum of **3k** (18 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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Prediction of Ring Conformations of Indolactams. Crystal and Solution Structures

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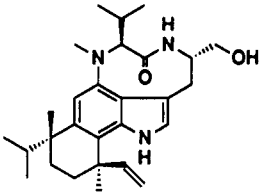
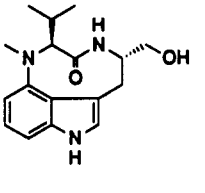
The preferred ring conformations of the nine-membered lactam rings of indolactams, which are extremely sensitive to substituent groups on the ring, were predicted by a high-temperature molecular dynamics calculation method. Two new ring conformations were predicted as preferred ones in two congeners, indolactam G and epiindolactam V. The predicted structures were validated by analyses of the crystal and solution structures by X-ray crystallography and NMR spectroscopy.

Introduction

Indolactam-V,[1-3] which has a partial structure of a potent tumor promoter teleocidin,[4] is known to be the minimum-sized tumor promoter. Both teleocidin (1) and indolactam-V (2) exist in an equilibrium of two conformational states of the nine-membered lactam ring, the twist and sofa forms, as shown in Figure 1, with a ratio of about 2:1 in methanol solution.[5] On the other hand, in the crystalline state, either of the conformations was alternatively found in several telecidin congeners,[6-8] although indolactam-V itself did not afford crystals suitable for crystal analysis.



teleocidin B-4 (1)



indolactam-V (2)

The twist form has a cis amide bond, whereas the sofa form has a trans amide. Since these two conformations

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