Application of Remote Photocyclization with a Pair System of Phthalimide and Methylthio Groups. A Photochemical Synthesis of Cyclic Peptide Models[1)]

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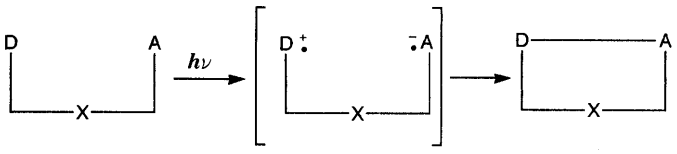
Application of regioselective remote photocyclization of a pair system consisting of a phthalimide group and a methylthio group to a homologous series of *N*-substituted phthalimides (4 and 5) possessing a terminal sulfide function in the amide side chain was investigated. On irradiation, medium to large membered cyclic peptide-like compunds (6, 7 and 9), up to a thirty-eight membered ring product (6f), were synthesized in moderate yields.

Keywords photochemistry; regioselective remote photocyclization; sulfide-containing phthalmide; donor–acceptor pair system; macrocyclic synthesis; cyclic peptide model

Syntheses of macrocycles have recently attracted much attention in view of the chemical and biological importance of naturally occurring and synthetic macrocycles.[2,3)] Synthesis of cyclic peptides has received much attention because a number of biologically active natural products including antibiotics and peptide hormones have been found.[4)] For synthesizing cyclic peptides it is generally essential to effect cyclization of linear peptide substrates with a selected activating group such as azide at high dilutions. Although many ground-state reactions for the construction of macrocycles are known, much less information is available on photochemical macrocyclic syntheses.[5)]

During the course of our systematic studies on imide photochemistry,[6)] we have found that certain phthalimides [1*H*-isoindole-1,3(2*H*)-diones] possessing a terminal sulfide function in their *N*-side chain undergo unusually facile photocyclization to give azathiacyclols.[7,8)] We have now extended this type of reaction to general synthesis of macrocycles on the basis of regioselective remote photocyclization of a pair system which consists of, in this case, a phthalimide group and a methylthio group. With this particular pair, macrocycles,[9)] crown ether analogs,[10)] and macrolide models[11)] have been synthesized. While the phthalimide ring is a good electron acceptor (A), the sulfide is a donor (D). Therefore, it is assumed that complex formation in the excited states may facilitate the reaction, suggesting the general working hypothesis that compounds possessing certain appropriate D–A pair groups, even separated by a long chain, are capable of forming a new carbon–carbon bond on irradiation (Chart 1). To establish the scope and limitations of this synthetic method, examination of compounds with systematic structural variations in the connecting portion (X), which links the donor and the acceptor pair, is needed. We have already investigated the photocyclization of phthalimides containing ether and ester bonds in their long side chain (**1a—b**).[10,11)] In addition, we have previously communicated the results of the photocyclization of such a pair system with amide bonds in the connecting part (**1c**).[8,11)] Here, we present a full account of this photochemical synthesis of cyclic peptide models.



1 X = a: [-O-], b: [-CO_2-], c: [-CONH-]

Chart 1

A series of *N*-substituted phthalimides (**4** and **5**) possessing a terminal sulfide function and amide bonds in their long side chain were prepared by the following procedures. Condensation of *N*-ethoxy-carbonyl phthalimide and ω-aminoalkanoic acids gave the carboxylic acid derivatives (**2**) in moderate yields.[12)] Coupling of the compounds (**2**) with ω-aminoalkanoates (methiamines) also took place smoothly, giving **3** (**4**), which were further coupled with the corresponding methiamine to afford the *N*-substituted phthalimides (**4**) in fairly good yields. On the other hand, compound (**5**) was obtained through the following successive reaction steps. Condensation of phthalic anhydride and 1,12-diaminododecane gave ω-aminoalkyl phthalimide (**2d**), which was coupled with the ω-(methylthio)undecanoic acid chloride, affording the compound (**5**) in a moderate yield (Chart 2, Tables I and II). The assignment of these structures was made on the basis of elemental analyses and spectral properties. The substrates thus obtained have peptide-like side chains with a terminal sulfide group which is located at a remote position from the imide carbonyl.

Irradiation of **4a** with a 400 W high-pressure mercury lamp in acetone solution at room temperature for 30 min afforded a cyclic peptide-like compound (**6a**) in a moderate yield (Chart 3 and Table III). The ^{1}H-nuclear magnetic resonance (^{1}H-NMR) spectrum of **6a** showed a new peak of a methylene moiety at δ 2.40—4.70 in place of the original sulfide methyl group signal in **4a**, and a singlet peak due to a hydroxyl group appeared at δ 6.67, indicating that the cyclization had occurred at the terminal sulfide methyl group. The infrared (IR) spectrum of **6a** showed absorptions at ν 3370, 3060, 1740, 1695 and 1665 cm^{-1} due to hydroxyl, amide (NH) and carbonyl(s) groups. All other spectral and analytical data supported the structure (**6a**).[6-11,13)] In agreement with the assigned structure, the cyclic peptide analog (**6a**) was readily con-

Dedicated to the memory of Emeritus Prof. Shigehiko Sugasawa (University of Tokyo).

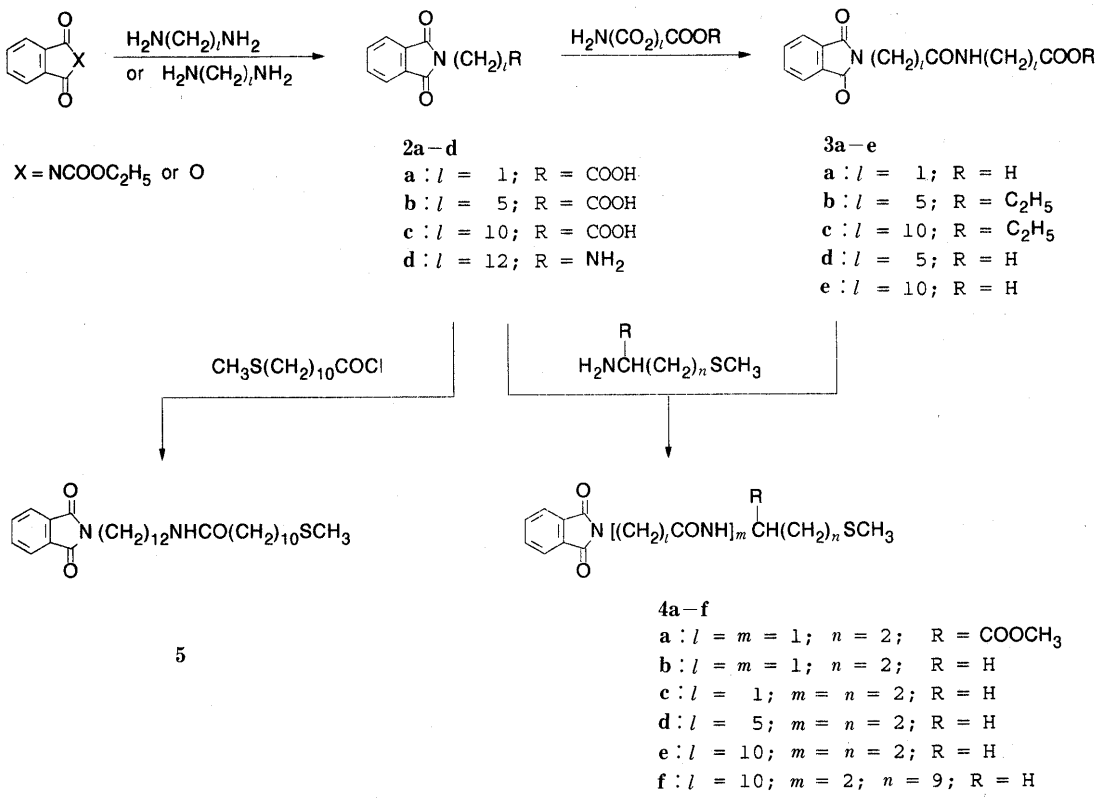


Chart 2

TABLE I. Physico-Chemical Data for the Substrates **4** and **5**

Substrate 4 or 5	Method	Yield (%)	mp (°C) (Recryst. from)[a]	Formula (M.W.)	Elemental analysis (%) Calcd (Found)			
					C	H	N	S
4a	I	72	170—171 (A)	$C_{16}H_{18}N_2O_5S$ (350.32)	54.85 (54.88	5.18 5.18	8.00 7.89	9.13 9.14)
4b	III	97	166—167 (A)	$C_{14}H_{16}N_2O_3S$ (292.28)	57.53 (57.73	5.52 5.61	9.95 9.31	10.95 10.86)
4c	II	93	171—172 (A)	$C_{16}H_{19}N_3O_4S$ (349.34)	55.01 (55.10	5.48 5.54	12.03 11.79	9.16 9.07)
4d	II	35	133—134 (B)	$C_{24}H_{35}N_3O_4S$ (461.54)	62.45 (62.43	7.64 7.63	9.11 9.22	6.93 6.95)
4e	II	72	130—132 (C)	$C_{34}H_{55}N_3O_4S$ (601.80)	67.85 (67.67	9.21 9.15	6.98 6.97	5.31 5.45)
4f	I	79	132—134 (D)	$C_{41}H_{69}N_3O_4S$ (699.99)	70.35 (70.29	9.94 9.79	5.95 6.00	4.57 4.57)
5	III	75	132—133 (D)	$C_{32}H_{52}N_2O_3S$ (544.84)	70.54 (70.46	9.62 9.79	5.14 5.04	5.88 5.63)

a) Recrystallization solvent: A = ethyl acetate, B = methanol–ether, C = chloroform–ethyl acetate–ether, D = chloroform–methanol.

verted into the dehydrated product (**8a**) through treatment with *p*-toluenesulfonic acid in an excellent yield. In the ^{1}H-NMR spectrum of **8a**, a singlet peak due to an olefinic proton appeared at δ 6.35 (Tables IV—VIII).

Irradiation of homologous *N*-substituted phthalimides (**4b—f** and **5**) was performed in a similar manner (Table III). From **4b**, a mixture of the expected cyclols was obtained, and was separated by silica gel column chromatography into **6b** and **7b**. The ^{1}H-NMR spectrum of **6b** had a similar pattern to that described above, while that of the minor product (**7b**), in which the sulfide methylene group is involved in the cyclization, showed the peaks of a sulfide methyl group at δ 2.35 and hydroxyl group at δ 6.32, each as singlet. The IR spectrum showed a hydroxyl group absorption at ν 3290 cm^{-1}. The stereochemistry of the minor product (**7b**) is undertermined. In support of the cyclol moiety, **6b** similarly afforded the dehydrated compound (**8b**) upon acid treatment. From **4c** and **4d**, the thirteen-membered cyclol (**6c**) and twenty-one membered one (**6d**) were obtained as a result of carbon–carbon bond formation between the imide carbonyl group and the terminal sulfide methyl group, respectively. In the ^{1}H-NMR spectra of **6c** and **6d**, peaks due to the sulfide methylenes appeared at δ 2.30—3.80 and 2.80—3.70 instread of the sulfide methyl signals of the substrates (**4c** and **4d**). Compounds **6c** and **6d** showed ν 3260 and

TABLE II. Spectral Data for the Substrates **4** and **5**

Substrate **4** or **5**	IR ν_{max}^{Nujol} cm^{-1}	UV $\lambda_{max}^{CHCl_3}$nm (ε)	MS m/z (M^+)	^{1}H-NMR ($CDCl_3$) δ
4a	1550, 1660, 1730, 1770, 3070, 3290	296 (2250)	350	1.82—2.35 (2H, m), 2.05 (3H, s), 2.52 (2H, m), 3.73 (3H, s), 4.40 (2H, s), 4.70 (1H, m), 6.75 (1H, d, J=7.2 Hz), 7.50—8.05 (4H, m)
4b	1560, 1660, 1730	295 (2140)	292	1.50—2.10 (2H, m), 2.03 (3H, s), 2.51 (2H, t, J=6.9 Hz), 3.36 (2H, m), 4.30 (2H, s), 6.36 (1H, m), 7.55—8.05 (4H, m)
4c	1560, 1640, 1665, 1725, 1765, 3090, 3290	296 (2220)	349	($CDCl_3$–DMSO-d_6): 1.50—2.00 (2H, m), 2.06 (3H, s), 2.50 (2H, t, J=7.0 Hz), 3.31 (2H, m), 3.85 (2H, d, J=5.4 Hz), 4.36 (2H, s), 7.10—8.10 (2H, each m), 7.60—8.00 (4H, m)
4d	1540, 1630, 1660, 1695, 1765, 3070, 3300	295 (2050)	461	1.00—1.95 (14H, m), 1.95—2.35 (4H, m), 2.09 (3H, s), 2.53 (2H, t, J=6.9 Hz), 3.28 (4H, m), 3.67 (2H, t, J=6.6 Hz), 5.60—6.30 (2H, m), 7.60—7.90 (4H, m)
4e	1535, 1630, 1710, 1720, 1765, 3300	294 (2530)	601	1.00—2.00 (34H, m), 2.10 (3H, s), 2.18 (4H, m), 2.57 (2H, t, J=7.0 Hz), 3.20 (2H, t, J=7.0 Hz), 3.40 (2H, t, J=7.0 Hz), 3.67 (2H, t, J=7.0 Hz), 6.03, 6.07 (2H, each br s), 7.50—8.00 (4H, m)
4f	1535, 1635, 1715, 1770, 3060, 3300	294 (1970)	699	0.66—2.06 (48H, m), 2.10 (3H, s), 2.17 (4H, m), 2.50 (2H, t, J=7.0 Hz), 3.50—3.94 (4H, m), 3.69 (2H, t, J=7.0 Hz), 5.53 (2H, m), 7.77 (4H, m)
5	1640, 1700, 1770, 3300		544	1.10—1.80 (36H, m), 2.09—2.20 (2H, m), 2.06 (3H, s), 2.48 (2H, t, J=7.0 Hz), 3.22 (2H, q), 3.67 (2H, t, J=7.5 Hz), 5.46 (1H, br s), 7.28—7.89 (4H, m)

TABLE III. A Photochemical Synthesis of Cyclic Peptide Models

Substrate					Weight	Conc./mM	Time	Yield (%)	Ring	mp (dec.) (°C)	Yield (%)	Ring	mp (dec.) (°C)
4 (**5**)	l	m	n	R	g (mmol)	(Light source (W))	(min)	**6** (**9**)	size	(Recryst. from)[c]	**6** (**9**)	size	(Recryst. from)[c]
4a	1	1	2	$COOCH_3$	1.23 (3.5)	11.8 (400)	30	46	10	198—200 (A)	15	8	
4b	1	1	2	H	1.23 (4.2)	14.0 (400)	40	48	10	(219—222) (B)	15	9	(193—194) (B)
4c	1	2	2	H	1.29 (3.7)	12.4 (400)	210	16	13	>270 (C)			
4d	5	2	2	H	0.50 (1.1)	4.3 (400)	15	64	21	115—117 (D)			
					0.44 (0.8)	2.0 (500)	5	(69)	28	(160—163) (E)			
Substrates (**5**)					0.55 (1.0)	2.0[a] (500)	30	(57)					
					0.22 (0.4)	2.0 (sun-light)	360	(69)					
4e	10	2	2	H	0.70 (1.2)	0.9[b] (200)	60	35	31	223—225 (B)			
4f	10	2	9	H	0.60 (0.9)	0.7[b] (200)	70	36	38	142—143 (F)			

a) Irradiation was carried out through a Pyrex filter in acetonitrile solution. *b*) A mixture solvent of *tert*-butanol : acetonitrile : acetone = 1 : 1 : 6.3 was used for the irradiation. *c*) A = ethyl acetate, after preparative TLC (developed three times with benzene : ethyl acetate = 1 : 1), B = methanol, after preparative TLC (developed five times with chloroform : ethyl acetate = 1 : 1 or chloroform : ethyl acetate : methanol = 10 : 5 : 1), C = methanol–chloroform–ether, after preparative TLC (chloroform : methanol = 9 : 1), D = ether, after preparative TLC (chloroform : methanol = 10 : 1), E = acetonitrile, after preparative TLC (chloroform : methanol = 20 : 1), F = ethanol–ether, after preparative TLC (chloroform : ethyl acetate : methanol = 6 : 3.5 : 0.5).

TABLE IV. A Photochemical Synthesis of Cyclic Peptide Models

Substrate					Condition		Time	Compound **8**	
6	l	m	n	R	Weight mg (mmol)	Solvent	(min)	Yield (%)	mp (°C) (Recryst. from)[a]
6a	1	1	2	$COOCH_3$	150 (0.43)	$CHCl_3$	60	81	255—256 (A)
6b	1	1	2	H	100 (0.34)	C_6H_6	120	96	236—238 (B)
6d	5	2	2	H	300 (0.68)	CH_3OH	60	90	199—201 (C)
6e	10	2	2	H	170 (0.28)	CH_3OH	60	73	208—213 (D)
6f	10	2	9	H	150 (0.22)	CH_2Cl_2	45	38	137—142[b]

a) A = ethyl acetate, B = methanol, C = methanol–acetonitrile, D = ethanol–acetonitrile. *b*) Compound **8f** was purified by silica gel preparative TLC with chloroform : ethyl acetate = 1 : 1 or chloroform : methanol = 1 : 1.

3280 cm^{-1} absorptions due to the hydroxyl groups in the IR spectra, and ultraviolet (UV) maxima at λ 242 (ε=4500) and 247 nm (ε=4730 in methanol, respectively, supporting the presence of the tertiary cyclol moiety. The crystalline product (**6d**) was similarly converted to the dehydrated product (**8d**) as a sole product [^{1}H-NMR δ: 6.03 (1H, s, olefinic proton)]. These twenty-one membered ring compounds (**6d** and **8d**) are nearly equivalent to a cyclic hexapeptide (Chart 3). Moreover, the substrate (**5**) was readily cyclized to give the twenty-eight membered compound (**9**) in a similar manner. Irradiation with sunlight was also effective, affording **9** in a good yield. The ^{1}H-NMR and IR spectra of **9** showed similar patterns to those of the cyclized products described above. From the substrate **4e**, the azathiacyclol (**6e**) with a thirty-one membered ring was obtained. The ^{1}H-NMR spectrum of **6e** showed the signal of a sulfide methylene moiety at δ 2.70—3.60 together with other methylene proton signals. All other spectral and analytical data were consistent with the structure **6e**. On acid treatment with *p*-toluenesulfonic acid, **6e** afforded the dehydrated compound (**8e**) [^{1}H-

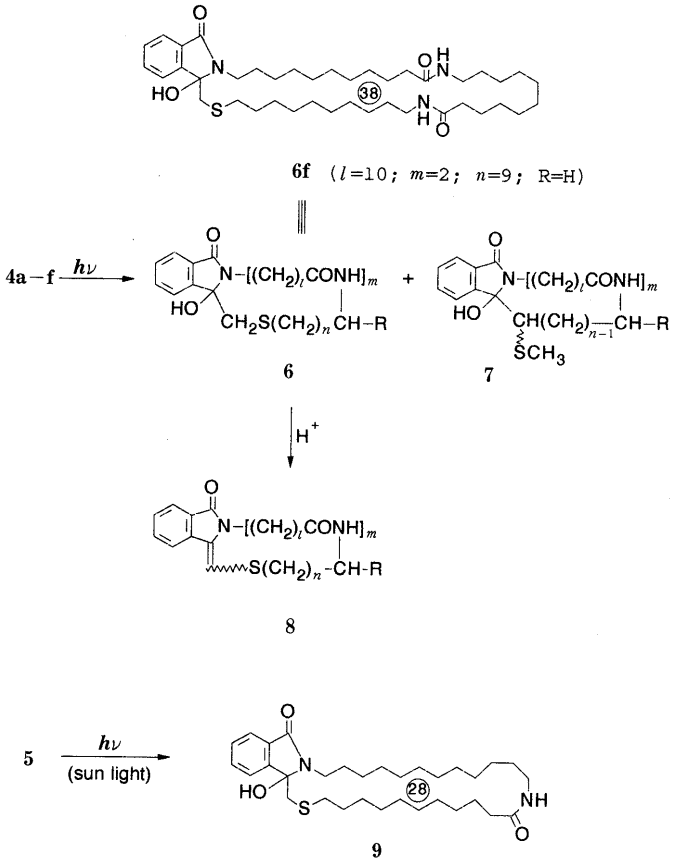


Chart 3

TABLE V. Analytical Data for the Photoproducts **6**, **7** and **9**

Compd. No.	Formula (M.W.)	M.W./ Found[a] (solvent)	Elemental analysis (%) Calcd (Found) C	H	N	S
6a	$C_{16}H_{18}N_2O_5S$ (350.32)		54.85 (54.65)	5.18 5.36	8.00 7.95	9.13 9.18)
6b	$C_{14}H_{16}N_2O_3S\cdot 1/4CH_3OH$ (300.29)		56.98 (57.47)	5.70 5.50	9.33 9.53	10.67 10.79)
7b	$C_{14}H_{16}N_2O_3S$ (292.28)		57.53 (57.47)	5.52 5.63	9.59 9.48	10.95 10.91)
6c	$C_{16}H_{19}N_3O_4S$ (349.34)		55.01 (55.07)	5.48 5.85	12.03 11.98	9.16 9.15)
6d	$C_{24}H_{35}N_3O_4S$ (461.54)	478 (CH_3OH)	62.45 (62.60)	7.64 7.69	9.11 9.31	6.93 7.08)
6e	$C_{34}H_{55}N_3O_4S$ (601.80)	608 (CH_3OH)	67.85 (67.79)	9.21 9.14	6.98 6.95	5.31 5.43)
6f	$C_{41}H_{69}N_3O_4S$ (699.99)	707 ($CHCl_3$)	70.35 (70.33)	9.94 9.81	6.00 5.77	4.57 4.43)
9	$C_{32}H_{52}N_2O_3S$ (544.84)		70.54 (70.54)	9.62 9.67	5.14 5.03	5.88 5.70)

a) Vapor-pressure method.

TABLE VI. Spectral Data for the Photoproducts **6**, **7** and **9**

Compound No.	IR ν_{max}^{Nujol} cm^{-1}	UV $\lambda_{max}^{CH_3OH}$ nm (ε)	MS *m/z* M^+ (M^+-18)	^{1}H-NMR (solvent) δ
6a	1530, 1610, 1665, 1695, 1740, 3060, 3370	246 (5370)	350 (332)	($CDCl_3$–DMSO-d_6): 1.90—2.30 (2H, s), 2.40—4.70 (9H, m), 3.68 (2H, s), 6.67 (1H, s), 7.30—7.90 (4H, m), 8.05 (1H, d, J=4.9 Hz)
6b	1535, 1660, 1645, 1680, 3050, 3260		292 (274)	($CDCl_3$–DMSO-d_6): 1.45—2.20 (2H, m), 2.58 (2H, t, J=6.0 Hz), 2.98 (2H, m), 2.79, 3.57 (2H, each d, J=13.0 Hz), 3.79, 4.57 (2H, each d, J=17.0 Hz), 6.64 (1H, s), 7.00—7.90 (5H, m)
7b	1610, 1655, 3060, 3180, 3290		292 (277)	($CDCl_3$–DMSO-d_6): 0.70—1.50, 1.70—2.40 (2H, each m), 2.35 (3H, s), 2.70—3.25 (2H, m), 3.41 (ABX q, J=12.0, 3.0 Hz), 3.95, 4.78 (2H, each d, J=18.0 Hz), 6.32 (1H, s), 7.05 (1H, br m), 7.30—8.30 (4H, m)
6c	1540, 1560, 1610, 1650, 1680, 3070, 3260	242 (4500)	349 (311)	(measured in DMSO-d_6 after deuterium exchange): 1.44—1.80 (2H, m), 2.30—3.80 (8H, m), 3.90, 4.17 (2H, each d, J=16.6 Hz), 7.40—7.80 (4H, m)
6d	1550, 1640, 1680, 3090, 3280	247 (4730)	461 (443)	($CDCl_3$–DMSO-d_6): 1.00—2.00 (14H, m), 2.00—2.30 (4H, m), 2.37 (2H, m), 2.80—3.70 (8H, m), 6.45 (1H, s), 7.12 (2H, m), 7.30—7.80 (4H, m)
6e	1555, 1640, 1665, 1680, 3100, 3270	252 (5310)	601 (583)	(measured in DMSO-d_6 after deuterium exhange): 1.00—1.70 (34H, m), 2.01 (4H, m), 2.70—3.60 (10H, m), 7.30—7.70 (4H, m)
6f	1550, 1640, 1675, 3100, 3280	250 (4580)	699 (681)	($CDCl_3$): 1.00—2.00 (43H, m), 2.00—2.50 (6H, m), 3.00—3.70 (8H, m), 5.42 (1H, s), 6.05 (2H, m), 7.30—7.70 (4H, m)
9	1580, 1630, 1680, 3100, 3260		544 (526)	(DMSO-d_6): 1.00—1.70 (36H, m), 2.17 (2H, t, J=6.0 Hz), 2.36 (2H, br s), 2.80—3.31 (6H, m), 6.46 (1H, s), 7.30—7.70 (5H, m)

a) *m/z* 277 is M^+-15.

NMR δ: 6.37 and 6.57 (1H, each s, *syn* and *anti* olefinic protons)]. In the case of **4f**, the thirty-eight membered azathiacyclol (**6f**) was obtained in 36% yield. In the ^{1}H-NMR spectrum, a signal at δ 3.00—3.70 was assigned as a new methylene moiety in place of the original sulfide methyl group in **4f**. The UV absorption showed a maximum at λ 250 nm (ε=4850) in methanol, and the IR spectrum showed absorptions at ν 3280, 3100, 1675 and 1640 cm^{-1} due to hydroxyl, amide(s) (NH) and carbonyl(s) groups, as expected for the cyclol moiety. The molecular weight values determined by the vapor-pressure method[14] and by mass spectrometry were 707 and 699, respectively, in agreement with a monomeric structure (699), thus excluding the alternative possibility of an intermolecular coupling reaction. On treatment with *p*-toluenesulfonic acid, the compound (**6f**) again afforded the dehydrated compound (**8f**). In the ^{1}H-NMR spectrum of **8f**, two singlet peaks due to a mixture of two stereoisomers (*syn* and *anti*) were observed at δ 5.99 and 6.11, as also described for **8e** (Tables III—VIII).

TABLE VII. Analytical Data for the Dehydrated Compounds **8a—b** and **8d—f**

Compd. 8	Formula (M.W.)	M.W./ Found[a] (solvent)	Elemental analysis (%) Calcd (Found) C	H	N	S
8a	$C_{16}H_{16}N_2O_4S$ (332.30)		57.83 (57.79	4.85 4.97	8.43 8.44	9.63 9.61)
8b	$C_{14}H_{14}N_2O_2S$ (274.27)		61.31 (61.02	5.15 5.13	10.21 10.11	11.67 11.78)
8d	$C_{24}H_{33}N_3O_3S$ (443.53)	452 (CH_3OH)	64.99 (57.47	7.50 5.63	9.47 9.48	7.21 10.91)
8e	$C_{34}H_{53}N_3O_3S$ (583.79)		69.95 (70.08	9.15 9.12	7.20 6.95	5.48 5.33)
8f	$C_{41}H_{67}N_3O_3S$ (681.97)		72.20 (71.76	9.90 9.75	6.16 5.94	4.69 4.71)

a) Vapor-pressure method.

The expected cyclic peptide analogs were obtained as a result of regioselective carbon–carbon bond formation between the imide carbonyl group and the sulfide methyl group (Chart 3 and Table III). In some cases, cyclized products in which the sulfide methylene group is involved were isolated, mostly in less than 15% yield. Although the mechanism of this remote photocyclization is unknown, quantitative and mechanistic studies are under way. Tentatively, this cyclization may be rationalized in terms of electron transfer followed by rapid proton transfer from the radical-cation sulfide methyl group with favorable entropy factors by virtue of charge-transfer complex formation in the excited state (Chart 4[6,9]). To estimate the efficiency of this remote reaction, the quantum yields were measured at 313 nm. The quantum yields for the cyclization of **4d** and **5** (in acetonitrile, 10 mM) were ϕ 0.01 and 0.03, respectively.

From the viewpoint of photochemical macrocyclic synthesis, it is important that substrates (**4** and **5**) having an amide functional group smoothly undergo selective remote photocyclization at the sulfide methyl group without cyclization into the chain interior. Usually in the Norrish type II photocyclization of flexible long-chain substrates, mixtures of various products are obtained with a statistical distribution along the chain methylenes.[5] The number of amino acid residues in linear peptide substrates is important in determining the efficiency to give cyclic peptides.[4a] Phthalimides with long side chains containing

TABLE VIII. Spectral Data for the Dehydrated Compounds **8a**, **b** and **8d—f**

Compound 8	IR ν_{max}^{Nujol} cm^{-1}	UV $\lambda_{max}^{CH_3OH}$ nm (ε)	MS *m/z* M$^+$	^{1}H-NMR ($CDCl_3$) δ
8a	1545, 1610, 1650, 1700, 1720, 3080, 3290	223 (23900) 261 (14600) 334 (12000)	332	1.82, 2.56 (2H, m), 2.90 (2H, m), 3.70 (3H, s), 4.80 (1H, m), 4.22, 5.34 (2H, each d, J=18.0 Hz), 6.05 (1H, d), 6.35 (1H, s), 7.40—7.96 (4H, m)
8b	1545, 1610, 1650, 1700, 3060, 3260	223 (21600) 262 (10870) 336 (8860)	274	1.36—2.28 (2H, m), 2.93 (2H, t, J=5.0 Hz), 3.10, 4.96 (2H, each m), 4.16, 5.30 (2H, each d, J=18.0 Hz), 5.52 (1H, m), 6.34 (1H, s), 7.40—8.00 (4H, m)
8d	1550, 1610, 1640, 1685, 3080, 3310	271 (5320) 353 (16900)	443	*a*) 1.10—2.50 (18H, m), 2.92 (2H, t, J=7.2 Hz), 3.15—3.60 (4H, m), 3.78 (2H, m), 5.90—6.50 (2H, m), 6.03 (1H, s), 7.35—8.95 (3H, m), 8.12 (1H, m)
8e	1550, 1610, 1635, 1685, 3080, 3290	270 (4260) 350 (15100)	583	1.00—2.20 (38H, m), 2.80—3.35 (6H, m), 3.77 (2H, t, J=7.0 Hz), 6.37, 6.57 (1H, each s, *syn* and *anti* olefinic protons), 7.34—8.20 (4H, m)
8f	1550, 1640, 1680, 3080, 3290	270 (5450) 352 (15500)	681	1.00—2.00 (48H, m), 2.20—2.50 (4H, m), 2.87 (2H, t, J=6.1 Hz), 2.90—3.40 (4H, m, 3.78 (2H, t, J=6.9 Hz), 5.99, 6.11 (1H, each s, *syn* and *anti* olefinic protons), 5.70—6.20 (2H, m), 7.35—7.95 (3H, m), 8.10—8.25 (1H, m)

a) Compound **8d** was measured in $CDCl_3$–DMSO-d_6 at 50°C after deuterium exchange.

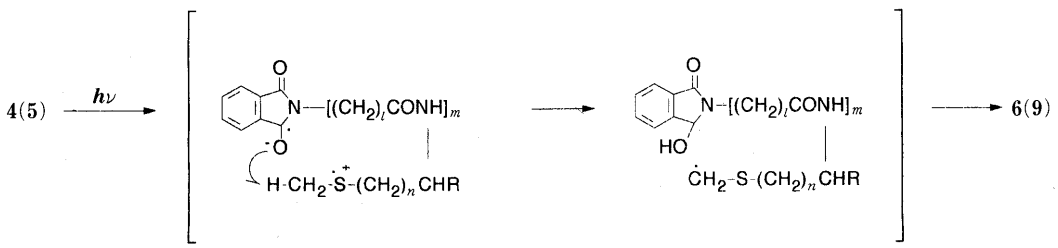


Chart 4

at least two amide bonds (**4** and **5**) were cyclized in moderate yields, demonstrating the ability of this synthetic photoreaction to afford macrocycles with up to a thirty-eight membered ring (**6f**), which is nearly equivalent in size to a cyclic tridecapeptide. The ligand capacity of cyclic peptides is highly dependent on the nature and arrangement of the component amino acids,[3,4] so "heteromeric" cyclic peptides like compounds **6**—**9** are of considerable interest in cyclic and cylindrical peptides chemistry.[15]

Experimental

All melting points were determined with a Yanagimoto capillary melting point apparatus (Model MP-1) and are uncorrected. Infrared (IR) spectra were recorded on a Hitachi IR-215 spectrophotometer. ^{1}H-Nuclear magnetic resonance (^{1}H-NMR) spectra were determined on a JEOL JNM MH 60 instrument in $CDCl_3$ (containing tetramethylsilane as an internal standard), unless otherwise specified. The chemical shifts are expressed in δ (ppm) values, coupling constants (J) are given in Hz and the following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Mass spectra (MS) were measured on a Hitachi RMS-4 mass spectrometer. Ultraviolet (UV) spectra were recorded on a Hitachi 323 recording spectrophotometer. Molecular weight were measured on a Hitachi–Perkin–Elmer molecular weight measuring apparatus, model 115 (vaporpressure method).

11-(2,3-Dihydro-1,3-dioxo-1*H*-isoindol-2-yl)undecanoic Acid (2c) *N*-Ethoxycarbonyl phthalimide[12] (21.9 g, 0.1 mol) was added to a stirred solution of 11-aminoundecanoic acid (20.1 g, 0.1 mol) and Na_2CO_3 (10.6 g, 0.1 mol) in H_2O (150 ml) at 25 °C for 1 h. Insoluble material was filtered off, then the filtrate was acidified with 10% HCl and the precipitate was collected by suction, washed with cold water, and dried *in vacuo* to give 20.8 g (63.0%) of **2c** as colorless needles from ether, mp 90—91 °C. IR (Nujol): 1610, 1715, 1765, 2200—2750 cm^{-1}. UV $\lambda_{max}^{chloroform}$ nm (ε): 296 (1840). MS m/z: 331 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 1.10—2.00 (16H, m), 2.34 (2H, m), 3.66 (2H, t, J = 7.0 Hz), 7.55—7.95 (4H, m), 9.00—10.50 (1H, br). *Anal.* Calcd for $C_{19}H_{25}NO_4$: C, 68.86; H, 7.60; N, 4.23. Found: C, 68.66; H, 7.54; N, 4.32.

2-(12-Aminododecyl)-1*H*-isoindole-1,3(2*H*)-dione Hydrochloride (2e) Phthalic anhydride (14.8 g, 0.1 mol) in CH_2Cl_2 (400 ml) was added to a solution of 1,12-diaminododecane (20.0 g, 0.1 mol) in CH_2Cl_2 (100 ml) at 25 °C and the mixture was stirred for 5 h. The precipitates were collected by suction and dried *in vacuo* to give a powder. Dry HCl gas was bubbled into a solution of the above powder in EtOH (500 ml) for 1 h, then the whole was evaporated to give a pale yellow residue, which was recrystallized from EtOH to give 23.5 g (64.0%) of **2e** as colorless needles, mp 141—142 °C. IR (Nujol): 1710, 1770 cm^{-1}. MS m/z: 330 (M^+ − HCl). ^{1}H-NMR ($CDCl_3$) δ: 1.00—2.00 (20H, m), 2.98 (2H, br s), 3.60 (2H, t, J = 7.0 Hz), 7.65—7.89 (4H, m), 8.33 (br s). *Anal.* Calcd for $C_{20}H_{31}ClN_2O_3$: C, 65.47; H, 8.52; Cl, 9.66; N, 7.63. Found: C, 65.42; H, 8.61; Cl, 9.64; N, 7.48.

Ethyl 6-[6-(2,3-Dihydro-1,3-dioxo-1*H*-isoindol-2-yl)hexanamido]hexanoate (3b) A solution of isobutyl chloroformate (6.28 g, 46 mmol) in tetrahydrofuran (THF, 40 ml) was added to a solution of **2b**[16a,b] (10.4 g, 40 mmol) and Et_3N (4.65 g, 46 mmol) in THF (60 ml) and *N*,*N*-dimethylformamide (DMF, 30 ml) at −35 °C. The mixture was stirred for 1 h, then a solution of ethyl 6-aminohexanoate hydrochloride[16c] (9.0 g, 46 mmol) and Et_3N (4.65 g, 46 mmol) in CH_2Cl_2 (100 ml) was added to the reaction mixture over a period of 1 h. The mixture was stirred for 2 h at the same temperature and further stirred for 1 h at 25 °C. After removal of the solvent, the residue was poured into water, and extracted with $CHCl_3$. The extracts were successively washed with 5% $NaHCO_3$, brine, dilute HCl, and brine, dried over Na_2SO_4 and concentrated *in vacuo* to give 14.2 g (88%) of **3b** as colorless needles from ether–hexane, mp 85—86 °C. IR (Nujol): 1545, 1610, 1640, 1720, 1780, 3060, 3310 cm^{-1}. MS m/z: 402 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 1.00—2.00 (12H, m), 1.24 (3H, t), 2.00—2.50 (4H, m), 3.23 (2H, m), 3.78 (2H, t, J = 6.2 Hz), 5.62 (1H, m), 6.11 (2H, q, J = 7.1 Hz), 7.50—8.00 (4H, m). *Anal.* Calcd for $C_{22}H_{30}N_2O_5$: C, 65.65; H, 7.51; N, 6.96. Found: C, 65.80; H, 7.39; N, 7.09.

Ethyl 11-[11-(2,3-Dihydro-1,3-dioxo-1*H*-isoindol-2-yl)undecanamido]-undecanoate (3c) Condensation of **2c** (20.5 g, 62 mmol) and ethyl 11-aminoundecanoate hydrochloride[16d] (18.9 g, 71.3 mmol) was performed in a manner similar to that described for the preparation of **3b** to give 28.5 g (84.8%) of **3c** as colorless crystals from AcOEt–hexane, mp 97—98 °C. IR (Nujol): 1540, 1610, 1640, 1700, 1730, 1765, 3320 cm^{-1}. MS m/z: 542 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 1.12—2.00 (35H, m), 2.06—2.40 (4H, m), 3.25 (2H, m), 3.65 (2H, t, J = 6.0 Hz), 4.10 (2H, q, J = 7.0 Hz), 5.50 (1H, m), 7.52—7.96 (4H, m). *Anal.* Calcd for $C_{32}H_{50}N_2O_5$: C, 70.81; H, 9.29; N, 5.16. Found: C, 70.56; H, 9.10; N, 5.28.

6-[6-(2,3-Dihydro-1,3-dioxo-1*H*-isoindol-2-yl)hexanamido]hexanoic Acid (3d) A mixture of **3b** (14.0 g, 34.8 mmol), concentrated HCl (20 ml), and AcOH (100 ml) was refluxed for 1 h. After removal of the solvent, the residue was poured into cold water. The precipitate was collected by suction filtration, washed with cold water, and dried *in vacuo* to give 11.4 g (87.6%) of **3d** as colorless crystals from CH_2Cl_2–ether, mp 106—108 °C. IR (Nujol): 1535, 1635, 1700—1730, 1780, 2000—2750, 3300 cm^{-1}. MS m/z: 374 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 1.00—2.00 (12H, m), 2.00—2.50 (4H, m), 3.21 (2H, m), 3.66 (2H, t, J = 6.7 Hz), 6.06 (2H, m), 7.55—7.95 (4H, m), 9.01 (1H, s). *Anal.* Calcd for $C_{20}H_{26}N_2O_5$: C, 64.15; H, 7.00; N, 7.48. Found: C, 64.23; H, 6.88; N, 7.61.

11-[11-(2,3-Dihydro-1,3-dioxo-1*H*-isoindol-2-yl)undecanamido]undecanoic Acid (3e) Hydrolysis of **3c** (28.0 g, 51.8 mmol) was performed in a manner similar to that described for the preparation of **3d** to give 25.6 g, (96.3%) of **3e** as colorless crystals from CH_2Cl_2–ether, mp 116—118 °C. IR (Nujol): 1535, 1635, 1705, 1720, 1765, 2250—2800, 3290 cm^{-1}. MS m/z: 514 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 1.00—2.00 (32H, m), 2.00—2.50 (4H, m), 3.20 (2H, m), 3.66 (2H, t), 5.69 (1H, s). 7.55—7.90 (4H, m), 9.89 (1H, s). *Anal.* Calcd for $C_{30}H_{46}N_2O_5$: C, 70.00; H, 9.01; N, 5.44. Found: C, 69.85; H, 8.89; N, 5.38.

General Procedure for the Preparation of Substrates (4 and 5; See Tables I and II) Method I (for **4a** and **4f**): A solution of isobutyl chloroformate (40 mmol) was added to a stirred solution of **2** or **3** (R = H) (40 mmol) and Et_3N (40 mmol) in THF (30 ml) at −25 °C. After stirring for 15—40 min, a solution of methyl methionate hydrochloride[16e] or 10-(methylthio)decylamine hydrochloride[16i] (40 mmol) in $CHCl_3$ (50 ml) was added dropwise to the reaction mixture, and the whole was further stirred for 90 min. The mixture was washed with 5% $NaHCO_3$, 10% HCl and brine, and the solvent was removed *in vacuo* to give the desired compound(s), followed by recrystallization.

Method II (for **4c**, **4d** and **4e**): A solution of isobutyl chloroformate (11.5 mmol) in anhydrous DMF (10 ml) was added to a solution of **3**[16g-h] (R = H, 10 mmol) and Et_3N (11.5 mmol) in anhydrous DMF (50 ml) at −25 °C. After 40 min, a solution of 3-(methylthio)propylamine (11.5 mmol) in $CHCl_3$ (10 ml) was added, and the reaction mixture was stirred for 2.5 h at −25 °C and for 2.5 h at 25 °C. The solvent was removed *in vacuo* and the residue was poured into water. The precipitate was collected by suction filtration and purified by recrystallization to give the desired compound(s).

Method III (for **4b** and **5**): Oxalyl chloride (40 mmol) was added dropwise to a stirred solution of *N*-phthaloylglycine or 11-(methylthio)-undecanoic acid (20 mmol) in ether (20 ml) at 0 °C. The mixture was stirred at 25 °C for 1.5 h, then added dropwise to a stirred solution of 3-(methylthio)propylamine or *N*-phthaloyldodecylamine (20 mmol) and Et_3N (44 mmol) in CH_2Cl_2 (400 ml) at 0 °C for 1.5 h. The whole was washed with brine, and the solvent was removed *in vacuo* to give the desired compound(s), followed by recrystallization.

General Procedure for the Irradiation A solution of a substrate **4** or **5** (0.2—1.3 g, 0.4—4.2 mmol) in acetone (0.2—14.0 mM) was irradiated with a 400 W high pressure mercury lamp at room temperature for 15—210 min in an atmosphere of argon, unless otherwise specified. After removal of the solvent *in vacuo*, the residue was purified by silica gel preparative thin-layer chromatography (TLC), followed by recrystallization of each fraction (see Tables III, V, and VI).

General Procedure for the Preparation of the Dehydrated Compound (8) A solution of **6** (0.1—0.3 g, 0.2—0.7 mmol) and *p*-toluenesulfonic acid trihydrate (15 mg) in the appropriate solvent (30 ml) was refluxed for 45—120 min, then the reaction mixture was washed with 5% $NaHCO_3$ solution and brine. The solvent was evaporated *in vacuo* to give the desired compound, which was purified by recrystallization or by silica gel preparative TLC with $CHCl_3$: AcOEt = 1 : 1 or $CHCl_3$: MeOH = 20 : 1 (see Tables IV, VII, and VIII).

Quantum Yields An acetonitrile solution of **4d** or **5** (10 mM) in Pyrex tubes was degassed by five freeze-pump-thaw cycles and sealed *in vacuo* at $\leqq 10^{-3}$ Torr. Quantum yields were measured relative to a 0.012 M potassium ferrioxalate actinometer[17] on parallel irradiation of samples of identical volumes (5 ml). Irradiations were performed on a merry-go-round apparatus with a Eikosha 500 W high-pressure mercury lamp

contained in a water-cooled, quartz immersion well. A chemical filter of 1.4 mM potassium chromate in 0.1% aqueous sodium carbonate[18] was used to isolate the 313 nm line. After the irradiation, the products were isolated by silica gel preparative TLC (Merck pre-coated PLC 60F-254; $CHCl_3$: MeOH = 20 : 1) and the product yields were determined by measurement of optical densities in ethanol at 250 nm. The values obtained as above were $\phi = 0.01$ and 0.03 for the formation of **6d** and **9**, respectively.

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References and Notes

1) *a*) Photochemistry of the Phthalimide System, 43. Part 42, H. Takechi, M. Machida, and Y. Kanaoka, *Chem. Pharm. Bull.*, **36**, 3770 (1988); *b*) Photo-induced Reactions. 121. Part 120, K. Ohkura, K. Seki, M. Terashima, and Y. Kanaoka, *Chem. Pharm. Bull.*, **39**, 3168 (1991); *c*) Present address: *Toyama Women's College, Gankaiji, Toyama 930, Japan.*
2) *a*) P. Läuger, *Science*, **178**, 24 (1972); *b*) B. C. Pressman, *Annu. Rev. Biochem.*, **45**, 501 (1976); *c*) Y. A. Ovchinnikov, "Membrane-Active Complexenones," Elsevier Scientific Publishing Co., Amsterdam, 1974, p. 1.
3) *a*) D. J. Cram and J. M. Cram, *Science*, **183**, 803 (1974); *b*) *Idem, Acc. Chem. Res.*, **11**, 8 (1978); *c*) J.-M. Lehn, *ibid.*, **11**, 49 (1978); *d*) H. Dugas and C. Penny, "Bioorganic Chemistry," ed. by R. Frost, Springer Verlag, New York, 1981, p. 255.
4) *a*) E. Shröder and K. Lübke, "The Peptides," Vol. 1 (translated by E. Gross), Academic Press, New York, 1965, p. 277; *b*) M. Bodanszky and D. Perlman, *Science*, **163**, 352 (1969); *c*) C. M. Deber, V. Madison, and E. R. Blout, *Acc. Chem. Res.*, **9**, 106 (1976); *d*) B. Witkop, *Angew. Chem., Int. Ed. Engl.*, **16**, 559 (1977); *e*) J. S. Bradshow and P. E. Stott, *Tetrahedron*, **36**, 461 (1980); *f*) G. Illuminati and L. Mandolini, *Acc. Chem. Res.*, **14**, 95 (1981); *g*) K. Tanizawa, K. Okumura, Y. Hatanaka, and Y. Kanaoka, *Heterocycles*, **24**, 1849 (1986).
5) *a*) R. Breslow, *Chem. Soc. Rev.*, **1**, 553 (1972); *b*) M. A. Winnik, *Chem. Rev.*, **81**, 491 (1981).
6) *a*) Y. Kanaoka, *Acc. Chem. Res.*, **11**, 407 (1978); *b*) P. H. Mazzocchi, "Organic Photochemistry," Vol. 5, ed. by A. Padwa; Marcel Dekker Inc., New York, 1981, p. 421.
7) *a*) Y. Sato, H. Nakai, H. Ogiwara, T. Mizoguchi, Y. Migita, and Y. Kanaoka, *Tetrahedron Lett.*, **1973**, 4565; *b*). Y. Sato, H. Nakai, M. Wada, T. Mizoguchi, Y. Hatanaka, Y. Migita, and Y. Kanaoka, *Justus Liebigs Ann. Chem.*, **1985**, 1099.
8) *a*) Y. Sato, H. Nakai, T. Mizoguchi, M. Kawanishi, and Y. Kanaoka, *Chem. Pharm. Bull.*, **21**, 1164 (1973); *b*) Y. Sato, H. Nakai, T. Mizoguchi, M. Kawanishi, Y. Hatanaka, and Y. Kanaoka, *Chem. Pharm. Bull.*, **30**, 1263 (1982).
9) Y. Sato, H. Nakai, T. Mizoguchi, Y. Hatanaka, and Y. Kanaoka, *J. Am. Chem. Soc.*, **98**, 2349 (1976).
10) *a*) M. Wada, H. Nakai, Y. Sato, and Y. Kanaoka, *Tetrahedron Lett.*, **23**, 3077 (1982); *b*) M. Wada, H. Nakai, Y. Sato, Y. Hatanaka, and Y. Kanaoka, *Chem. Pharm. Bull.*, **31**, 429 (1983).
11) *a*) M. Wada, H. Nakai, K. Aoe, K. Kotera, Y. Sato, and Y. Kanaoka, *Chem. Pharm. Bull.*, **30**, 2275 (1982); *b*) M. Wada, H. Nakai, Y. Sato, and Y. Kanaoka, *ibid.*, **30**, 3414 (1982); *c*) M. Wada, H. Nakai, K. Aoe, K. Kotera, Y. Sato, Y. Hatanaka, and Y. Kanaoka, *Tetrahedron*, **39**, 1273 (1983); *d*) M. Wada, H. Nakai, Y. Sato, Y. Hatanaka, and Y. Kanaoka, *ibid.*, **39**, 2691 (1983).
12) *a*) G. H. L. Nefkens, G. I. Tesser, and J. F. Nivard, *Rev. Trav. Chem.*, **79**, 688 (1960); *b*) G. H. L. Nefkens, *Nature* (London), **185**, 309 (1960).
13) Y. Sato, H. Nakai, T. Mizoguchi, and Y. Kanaoka, *Tetrahedron Lett.*, **1976**, 1889.
14) Hitachi–Perkin molecular weight measuring apparatus Model 115; in methanol.
15) Recent studies of the conformation of cyclic and "cylindrical" peptides have been particularly useful in developing our understanding of the general physicochemical behavior of polypeptides and proteins; C. H. Hassall and W. S. Thomas, *Chem. Br.*, **7**, 145 (1971).
16) *a*) S. Gabriel, *Chem. Ber.*, **40**, 2647 (1907); *b*) S. Gabriel and J. Colman, *ibid.*, **41**, 2014 (1908); *c*) K. A. Böttcher, *ibid.*, **46**, 3158 (1913); *d*) C. S. Marvel, J. R. Elliott, F. E. Boettner, and H. Yuska, *J. Am. Chem. Soc.*, **68**, 1681 (1946); *e*) N. N. Rydon and J. J. Savrda, *J. Chem. Soc.*, **1965**, 4246; *f*) J. H. Billman and W. F. Harting, *J. Am. Chem. Soc.*, **70**, 1473 (1948); *g*) J. C. Scheehan and V. S. Frank, *ibid.*, **71**, 1856 (1949); *h*) K. Yamashita and M. Yashiro, *Nippon Nogeikagaku Kaishi*, **28**, 674 (1954); *i*) J. Walker, *J. Chem. Soc.*, **1950**, 193.
17) C. G. Hatchard and C. A. Parker, *Proc. R. Soc. London*, **A 235**, 518 (1956).
18) S. L. Murov, "Handbook of Photochemistry," Marcel Dekker Inc., New York, 1973, p. 99.