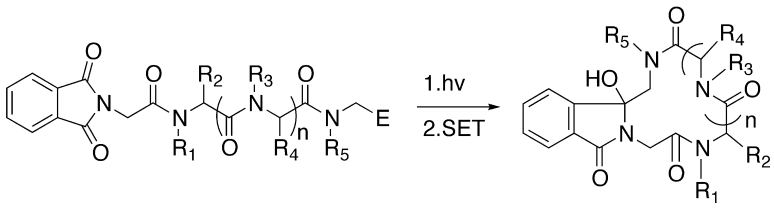
Article

A Synthetic Strategy for the Preparation of Cyclic Peptide Mimetics Based on SET-Promoted Photocyclization Processes

Ung Chan Yoon, Ying Xue Jin, Sun Wha Oh, Chan Hyo Park, Jong Hoon Park, Charles F. Campana, Xiaolu Cai, Eileen N. Duesler, and Patrick S. Mariano

J. Am. Chem. Soc., **2003**, 125 (35), 10664-10671• DOI: 10.1021/ja030297b • Publication Date (Web): 08 August 2003



More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Links to the 6 articles that cite this article, as of the time of this article download
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

J|A|C|S
ARTICLES
Published on Web 08/08/2003

A Synthetic Strategy for the Preparation of Cyclic Peptide Mimetics Based on SET-Promoted Photocyclization Processes

Ung Chan Yoon,*,† Ying Xue Jin,† Sun Wha Oh,† Chan Hyo Park,† Jong Hoon Park,† Charles F. Campana,‡ Xiaolu Cai,§ Eileen N. Duesler,§ and Patrick S. Mariano*,§

Contribution from the Department of Chemistry, College of Natural Sciences, Pusan National University, Pusan, 609-735, Korea, Bruker AXS Inc., 5465 East Cheryl Parkway, Madison, Wisconsin 53711-5373, and Department of Chemistry, University of New Mexico, Albuquerque, New Mexico 87131

Received May 16, 2003; E-mail: mariano@unm.edu; ucyoon@pusan.ac.kr

Abstract: A novel method for the synthesis of cyclic peptide analogues has been developed. The general approach relies on the use of SET-promoted photocyclization reactions of peptides that contain N-terminal phthalimides as light absorbing electron acceptor moieties and C-terminal α-amidosilane or α-amidocarboxylate centers. Prototypical substrates are prepared by coupling preformed peptides with the acid chloride of *N*-phthalimidoglycine. Irradiation of these substrates results in the generation of cyclic peptide analogues in modest to good yields. The chemical efficiencies of these processes are not significantly affected by (1) the lengths of the peptide chains separating the phthalimide and α-amidosilane or α-amidocarboxylate centers and (2) the nature of the penultimate cation radical α-heterolytic fragmentation process (i.e., desilylation vs decarboxylation). An evaluation of the effects of N-alkyl substitution on the amide residues in the peptide chain showed that N-alkyl substitution does not have a major impact on the efficiencies of the photocyclization reactions but that it profoundly increases the stability of the cyclic peptide.

Introduction

Substances that possess macrocyclic, polyheteroatom containing ring systems have played a central role in numerous investigations aimed at discovering new materials with chemically and biologically interesting properties. Crown ethers and their analogues are prime examples of members of this large family which have attracted great attention as a consequence of their selective metal and ammonium cation binding properties.[1] In addition, naturally occurring and synthetic cyclic peptides and their analogues have been the subjects of efforts aimed at exploring conformationally defined and hydrolytically more stable polypeptide mimetics.[2]

Several general methods have been developed to construct the macrocyclic ring systems present in members of the cyclic peptide and crown ether families. In some of the approaches, high dilution techniques are required to maximize cyclization reaction efficiencies. In addition, methods relying on preorganization of linear precursors by metal cation templation have found use in routes for the synthesis of crown ethers.[3] In the area of cyclic peptide synthesis,[4] the incorporation of conformationally biasing N-alkyl amino acid and proline units is known to facilitate macrocyclization processes. Also, several interesting approaches, including those that employ backbone cyclizations[5] and cyclization-ring contraction sequences,[6] have been used to efficiently generate novel cyclic peptide mimetics.

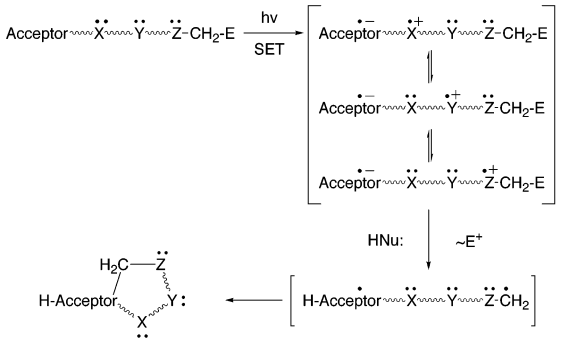
Owing to the chemical and biological significance of substances in the crown ether and cyclic peptide families, synthetic methods, which can be applied to the preparation of new targets, are still in demand. In recent reports,[7] we described a novel,

† Pusan National University.
‡ Bruker AXS Inc.
§ University of New Mexico.

(1) Gokel, G. W. *Crown Ethers and Cryptands*; Black Bear Press: Cambridge, 1991.
(2) For representative examples, see: (a) Hruby, V. J. *Life Sci.* **1982**, *31*, 189. (b) Burgess K. *Acc. Chem. Res.* **2001**, *34*, 826. (c) Wels, B.; Kruijtzer, J. A. W.; Liskamp, R. M. J. *Org. Lett.* **2002**, *4*, 2173. (d) Fairlie, D. P.; Abernante, G.; March, D. R. *Curr. Med. Chem.* **1995**, *2*, 654. (e) Brugghe, H. F.; Timmermans, H. A. M.; Van Unen, M. A.; Ten Hove, G. J.; Vande Werken, G.; Poolman, J. T.; Hoogerhut, P. *Int. J. Pept. Protein Res.* **1994**, *43*, 166. (f) Hruby, V. J. *Acc. Chem. Res.* **2001**, *34*, 389.
(3) For representative examples of templation controlled crown ether and cyclam synthesis see: (crown ethers) Greene, R. N. *Tetrahedron Lett.* **1972**, 1793. Vitali, C. A.; Masci, B. *Tetrahedron* **1989**, *45*, 2201. Bowsher, B. R.; Rest, A. J. *Inorg. Chim. Acta* **1981**, *53*, L175. (cyclams) Busch, D. H. *Acc. Chem. Res.* **1978**, *11*, 392. Beveridge, K. A.; McAuley, A.; Xu, C. *Inorg. Chem.* **1991**, *30*, 2074. Fortiewr, D. G.; McAuley, A. *J. Am. Chem. Soc.* **1990**, *112*, 2640.
(4) For a review of general approaches to cyclic peptide synthesis, see: Humphrey, J. M.; Chamberlin, A. R. *Chem. Rev.* **1997**, *97*, 2243.
(5) (a) Gilon, C.; Zeltzer, I.; Rashiti-Behar, V.; Muller, D.; Bitan, G.; Halle, D.; Bar-Akiva, G.; Seliger, Z.; Byk, G.; Yanaihara, V. J. *Peptide Chemistry*; ESCOMA: Leiden, The Netherlands, 1992; p 482. (b) Gilon, C.; Halle, D.; Choprez, M.; Seliger, Z.; Byk, G. *Biopolymers* **1991**, *31*, 745.
(6) (a) Shao, Y.; Lu, W.; Kent, B. H. *Tetrahedron Lett.* **1998**, *39*, 3911. (b) Mentermans, W. D. F.; Golding, S. W.; Bourne, G. T.; Miranda, L. P.; Dooley, M. J.; Alewood, P. F.; Smythe, M. L. *J. Am. Chem. Soc.* **1999**, *121*, 9790.
(7) Yoon, U. C.; Oh, S. W.; Lee, J. H.; Park, J. H.; Kang, K. T.; Mariano, P. S. *J. Org. Chem.* **2001**, *66*, 939. Yoon, U. C.; Oh, S. W.; Lee, C. W. *Heterocycles* **1995**, *41*, 2665. Yoon, U. C.; Kim, J. W.; Ryu, J. Y.; Cho, S. J.; Mariano, P. S. *J. Photochem. Photobiol., A* **1997**, *106*, 145.

10.1021/ja030297b CCC: $25.00

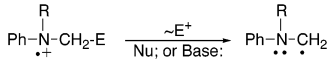
Scheme 1



general procedure for construction of cyclic polyethers, polythioethers, and polysulfonamides, in which SET-initiated photochemical reactions are used to generate the macrocyclic ring systems (Scheme 1). In the first step of this approach, a polyheteroatom containing chain is linked to an acceptor chromophore, chosen on the basis of its selective light absorbing and excited state reduction properties. Irradiation of this conjugate leads to formation of the excited acceptor moiety, which is rapidly quenched by intramolecular SET from one of the n-electron donating, heteroatom sites. By properly choosing the acceptor, one can ensure that intramolecular SET is exothermic and, as a result, that it is sufficiently rapid[8] to effectively compete with other inter- and intramolecular modes of excited-state decay. In addition, SET from heteroatom donor sites that are close to the excited acceptor will be faster than those that are more remote or that are located in other substrate molecules.[9] Consequently, the use of high dilution reaction conditions might be less important in SET-promoted photomacrocyclization processes.

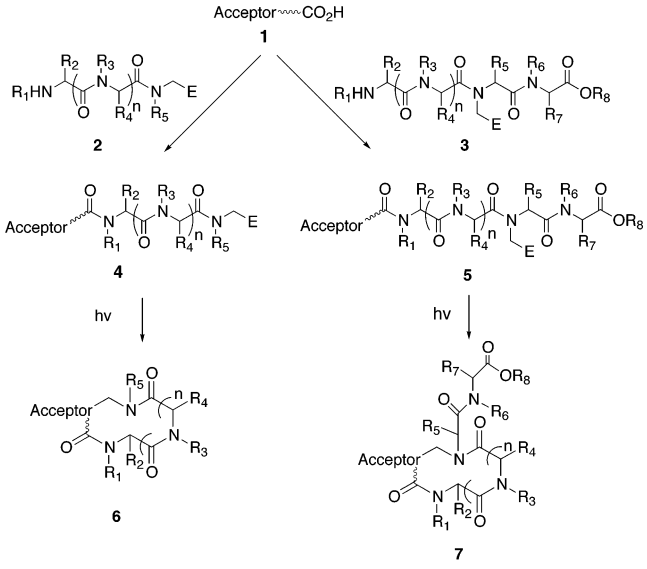
Following the initial SET event, intrachain SET should take place rapidly to produce an equilibrating mixture of zwitterionic biradicals. At equilibrium, the populations of these reactive intermediates will be governed by the stability of each cation radical group. In systems containing multiple heteroatom donors which have nearly the same oxidation potentials, a near equal population of rapidly interconverting cation radical centers will be produced. The key event controlling the selectivity of the photocyclization process is the conversion of one cation radical site to a neutral radical. Ideal processes for this purpose are α-hetrolytic fragmentation reactions which involve the transfer or loss of an electrofugal group (E^+) from a carbon center adjacent to the cation radical site.[10] The results of extensive laser flash photolysis and product distribution studies have provided important information about how the rates of α-heterolytic fragmentation reactions are governed by the nature of the cation radicals, the type of electrofugal groups, and the media.[11] Thus, based on these data, it is possible to design polyheteroatom donor substrates that contain single, highly reactive cation radical sites. In this way, the sequence initiated by excited state SET can be selectively designed to generate

Table 1. Rate Constants for α-Heterolytic Fragmentation Reactions of Anilinium Radicals[11]



E	R	Nu: or B:	*k* (25 °C, MeCN)
H	Me	AcO^-	$2.0 \times 10^5\ M^{-1}\ s^{-1}$
$SiMe_3$	Me	MeOH	$7.0 \times 10^5\ M^{-1}\ s^{-1}$
$SiMe_3$	Me	H_2O	$2.3 \times 10^6\ M^{-1}\ s^{-1}$
$SiMe_3$	COMe	MeOH	$6.0 \times 10^7\ M^{-1}\ s^{-1}$
CO_2^-	Me		$1.7 \times 10^6\ s^{-1}$
CO_2^-	COMe		$3.6 \times 10^7\ s^{-1}$

Scheme 2



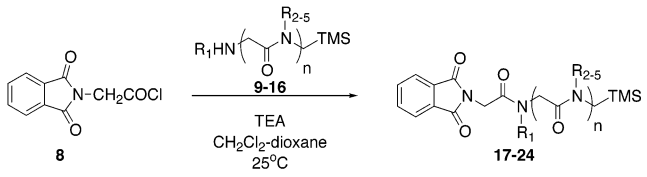
one biradical intermediate preferentially. Cyclization of the biradical then furnishes the targeted macrocyclic product.

The high degrees of regioselectivity, expected in these photocyclization processes, are a consequence of the large rate differences that exist between different cation radical, α-heterolytic fragmentation reactions. As can be seen by viewing the data gained from studies of equally substituted anilinium radicals (Table 1),[11] base (AcO^-) promoted α-deprotonation is a slow process compared to silophile (MeOH, H_2O) induced α-desilylation. In addition, unimolecular decarboxylation of α-anilinium carboxylates is the fastest process in this series. Moreover, electron withdrawing N-acyl groups enhance the rates of these fragmentation reactions.

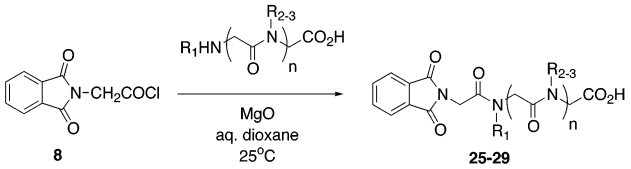
Owing to their unique features, SET-promoted photocyclization reactions are highly compatible with the requirements of strategies for efficient, regioselective construction of cyclic peptide mimetics. In one approach (Scheme 2), the substrates for the photochemical process (**4** or **5**) would be prepared by linking a carboxylic acid containing acceptor **1** to the N-terminal amino group of an intact peptide (**2** or **3**). Alternatively, the peptide chain would be sequentially added to an appropriately functionalized acceptor. The latter protocol would be ideally suited for use in the construction of cyclopeptide libraries by using combinatorial techniques. The synthetic plan used for preparation of the acceptor-linked polypeptides would be guided by the structural requirements of the target cyclic peptides. Specifically, a selectively reactive (α-carboxylate or α-trimethylsilyl) amide cation radical site would be incorporated at a

(8) Rehm, D.; Weller, A. *Isr. J. Chem.* **1970**, *8*, 259.
(9) Wasielewski, M. A. In *Photoinduced Electron Transfer*; Fox, M. A., Channon, M., Eds.; Elsevier: New York, 1988; Part A, p 161.
(10) Mariano, P. S.; Stavinoha, J. L. In *Synthetic Organic Photochemistry*; Horspool, W. M., Ed.; Plenum Press: London, 1984; Chapter 3, p 145.
(11) (a) Zhang, X. M.; Yeh, S. R.; Hong, S.; Freccero, M.; Albini, A.; Falvey, D. F.; Mariano, P. S. *J. Am. Chem. Soc.* **1994**, *116*, 4211. (b) Su, Z.; Mariano, P. S.; Falvey, D. E.; Yoon, U. C.; Oh, S. W. *J. Am. Chem. Soc.* **1998**, *120*, 10676.

Scheme 3



Scheme 4



preselected location within or at the end of the peptide chain. Irradiation of the substrate would then initiate a reaction cascade involving near neighbor SET, intrachain SET, and heterolytic fragmentation at the reactive amide cation radical position. Cyclization of the biradical, formed by this route, then produces the target cyclopeptide mimetic (**6** or **7**).

We have embarked on a broad program to investigate SET-photochemical approaches to the synthesis of cyclic polypeptide mimetics.[12] Our initial efforts in this area focused on the development of methods to prepare acceptor-linked peptides, each containing single reactive amide cation radical sites, and on the assessment of the efficiencies of photocyclization reactions of these substrates. Reported below are the results of studies with a group of substrates that contain N-terminal phthalimide groups as light absorbing acceptors and C-terminal α-amidosilane and α-amidocarboxylate moieties as reactive cation radical sites. The effects of N-alkyl substitution and cation radical desilylation versus decarboxylation on the efficiencies of the photocyclization reactions have also been evaluated in this study.

Results

Preparation of N-Terminal Phthalimidopeptides. To evaluate the SET-photochemical strategy presented above for cyclopeptide synthesis, several amides and peptides, containing an N-terminal phthalimide acceptor moiety, were prepared. Either an α-amidotrimethylsilane or α-amidocarboxylate electrofugal group is incorporated at the C-terminal position in each of these substances to direct the photocyclization process. In addition, substances having both NH and N-alkyl amide nitrogen centers were included in the series so that the effects of N-substituents on photocyclization reaction efficiencies could be determined.

The substrates were prepared by amide coupling of preformed amines and peptides to *N*-phthalimidoglycine acid chloride **8** (Schemes 3 and 4). Accordingly, condensation of the trimethylsilyl-terminated amines **9**−**10** and peptides **11**−**16** (Supporting Information) with acid chloride **8** leads to formation of the glycinamides **17**−**18** and phthalimidopeptides **19**−**24** in reasonably high yields (Scheme 3, Table 2). In a similar manner, the carboxylic-acid-terminated phthalimidoamides **25**−**27** and phthalimidopeptides **28**−**29** are efficiently generated by reaction of the corresponding amino acids and peptides with **8** (Scheme 4, Table 3). Also, the phthalimide derivative of the glycine−proline dipeptide is prepared by reaction of proline with **8** (Scheme 5). Finally, addition of potassium 3-nitrophthalimide with the silicon-substituted α-bromoacetamide **31** is used to produce the nitrophthalimidoglycinamide **32** (Scheme 6).

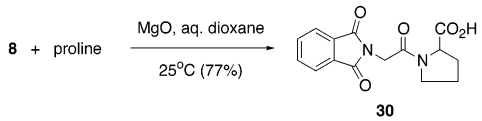
Table 2. Yields for Formation of TMS-Terminated Phthalimide-Linked Amides **17**−**18** and Peptides **19**−**24** (Scheme 3)

amine substrate	phthalimide product	*n*	R_1	R_2	R_3	R_4	R_5	% yield
9	**17**	0	H					60
10	**18**	0	Bn					91
11	**19**	1	Bn	Bn				88
12	**20**	1	Me	Bn				85
13	**21**	2	Bn	Bn	Bn			86
14	**22**	2	Me	Me	Bn			82
15	**23**	3	Bn	Bn	Bn	Bn		83
16	**24**	4	Bn	Bn	Bn	Bn	Bn	81

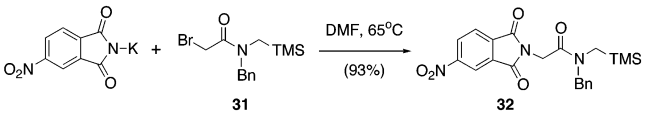
Table 3. Yields for Formation of Carboxylic-Acid-Terminated Phthalimide-Linked Amides **25**−**27** and Peptides **28**−**29** (Scheme 4)

amine substrate	phthalimide product	*n*	R_1	R_2	R_3	% yield
glycine	**25**	0	H			91
sarcosine	**26**	0	Me			95
NBn−glycine	**27**	0	Bn			95
gly−gly	**28**	1	H	H		87
gly−gly−gly	**29**	2	H	H	H	85

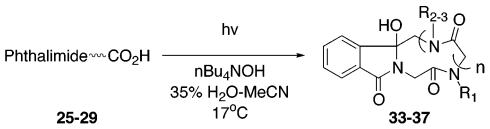
Scheme 5



Scheme 6



Scheme 7



Cyclopeptide Forming Photocyclization Reactions. Carboxylate anions, serving as the reactants in photocyclization reactions of **25**−**30**, were generated in situ by reaction of the acids **25**−**30** with ^{n}Bu$_4$NOH. Accordingly, photoreactions were conducted by irradiation of 9−13 mM solutions of **25**−**30**, containing 1 equiv of ^{n}Bu$_4$NOH, in 35% H_2O−MeCN at 17 °C by using Pyrex glass filtered light (λ > 290 nm) under an N_2 atmosphere for time periods that bring about ca. 90% conversion of the substrates. Silica gel column chromatography was used to separate the respective cyclopeptide products **33**−**38** (Schemes 7 and 8) in the yields given in Table 4.

Surprisingly, the cyclopeptide derivatives **33**, **36**, and **37**, each lacking N-alkyl amide substituents, are highly unstable materials. These substance completely decompose over a 1 day period by processes which can be monitored, but not characterized, by

(12) During the course of our investigations in this area, a similar approach to cyclopeptide analogue synthesis was reported by Griesbeck, A. G.; Heinrich, T.; Oelgemoller, M.; Lex, J.; Molis, A. *J. Am. Chem. Soc.* **2002**, *124*, 10972.

Table 4. Yields of Photocyclization Reactions of the Carboxylate-Terminated Substrates Derived from **25**−**30** (Schemes 7 and 8)

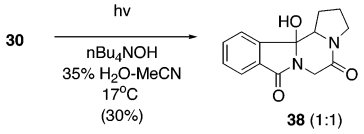
substrate	concd (mM)	irradiation time (h)	product	n	R_1	R_2	R_3	% yield
25	12.7	10	**33**	0	H			35
26	12.0	1	**34**	0	Me			63
27	9.5	1	**35**	0	Bn			65
28	10.4	10	**36**	1	H	H		20
29	8.9	10	**37**	2	H	H	H	41
30	11.0	1	**38**	0				30

Table 5. Yields of Photocyclization Reactions of the TMS-Terminated **17**−**24** (Schemes 9)

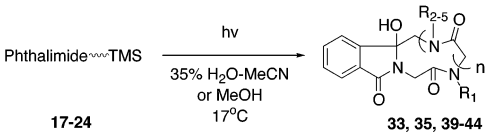
substrate	concd (mM)	solvent[a]	product[b]	n	R_1	R_2	R_3	R_4	R_5	% yield
17	11.5	A	**33**	0	H					18
18	8.8	A	**35**	0	Bn					60
19	6.3	A	**39**	1	Bn	Bn				40
20	7.4	A	**40**	1	Me	Bn				40
21	4.9	A	**41**	2	Bn	Bn	Bn			47
21	4.9	B	**41**	2	Bn	Bn	Bn			55
22	6.4	A	**42**	2	Me	Me	Bn			15
23	4.1	B	**43**	3	Bn	Bn	Bn	Bn		70
24	3.4	B	**44**	4	Bn	Bn	Bn	Bn	Bn	61

[a] Solvents: A, 35% H_2O−MeCN; B, MeOH. [b] Irradiation times: 1 h.

Scheme 8



Scheme 9

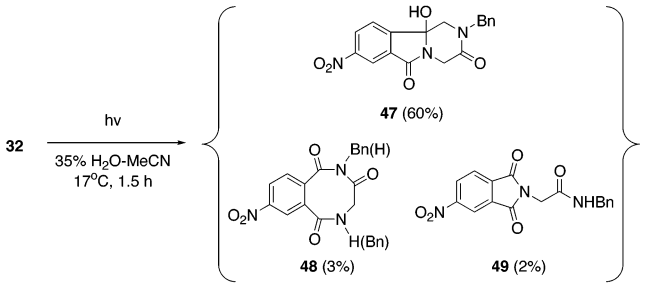


^{1}H NMR spectroscopy. In each case, the initial sharp resonances associated with the products slowly broaden and then become nondescriptive. In contrast, the corresponding N-alkyl derivatives **34**, **35**, and **38** are stable substances.

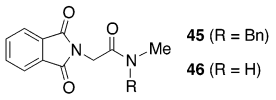
Photoreactions of the TMS-terminated phthalimidoamides and phthalimidopeptides **17**−**24** are carried out on 3−11 mM solutions in either 35% H_2O−MeCN or MeOH by using irradiation with Pyrex glass filtered light at 17 °C for 1−1.5 h time periods (ca. 90% conversion). Concentration of the crude photolysates followed by silica gel chromatography affords the cyclopeptide analogues **33**, **35**, and **39**−**44** (Scheme 9) in the yields given in Table 5.

^{1}H NMR analysis of the concentrated photolysates from the photoreactions described above in most cases does not reveal the presence of significant quantities of other identifiable photoproducts. Exceptions do exist. For example, the desilylated *N*-methylamide **45** is formed as a minor product (15%) when the *N*-benzyl-*N*-trimethylsilymethylglycinamide **18** is irradiated in 35% H_2O−MeCN. Also, the secondary amide **46** is isolated in 25% yield from the photolysate produced by irradiation of glycinamide **17** in aqueous MeCN. Finally, the nitrophthalimidoglycinamide **32** undergoes an efficient and regioselective photoreaction in aqueous MeCN to form the cyclic product **47**

Scheme 10



(Scheme 10) along with minor amounts of the diazocine-trione **48** (unknown benzyl location) and secondary amide **49**.



To obtain a qualitative evaluation of the relative efficiencies of photocyclization reactions of the TMS- and carboxylate-terminated phthalimidopeptides, time versus percent conversion profiles for photoreactions of **18** and **27** were determined. Equimolar solutions of these substrates in 35% H_2O−MeCN were irradiated while monitoring the time course for low conversion disappearance of starting materials by UV spectroscopy. The results demonstrate the photocyclization reaction of the carboxylate derivative **27** has a ca. 3-fold greater quantum efficiency than that of its TMS-substituted analogue **18**.

Stereoregular Cyclic Peptide Analogues. The TMS-terminated glycine−((*S*)-alanine)$_n$ peptides **53**−**55** were prepared in order to show that the SET-photocyclization based methodology can be used to prepare stereoregular cyclic peptide analogues. An important feature of photoreactions of these substrates resides in the fact that a new chiral center is created at the bicyclic amidol carbon in the products **57**−**59**. Earlier studies with a wide variety of related phthalimide derived photoproducts have demonstrated that configurational inversion at amidol centers of this type, via either reversible *N*-acyliminum ion or amido ketone forming pathways, is slow under neutral conditions.[13] As a consequence, stereochemical preferences in photocyclization reactions of alaninyl peptides **53**−**55** would need to be the result of kinetic factors governing the rates of cyclization of the ultimate biradical intermediates **56** (Scheme 11).

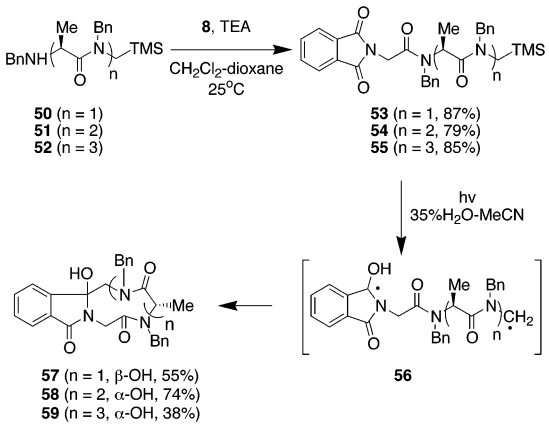
In light of these considerations, it was interesting to find that irradiation of the peptides **53**−**54** in 35% H_2O−MeCN leads to modestly efficient formation of the cyclic peptides **57**−**59**, each as a single diastereomer. X-ray crystallographic analysis was used to make structural and stereochemical assignments to these photoproducts (Table 6). As can be seen by viewing the Chem-3D plots of the atomic coordinates displayed in Figures 1−3, the macrocyclicpeptides formed by cyclization of the biradical intermediates **56** have different absolute configurations at the amidol centers (i.e., (R) for **57**, (S) for **58**, and (S) for **59**). To determine if the kinetically preferred diastereomers, produced by irradiation of the phthalimido−gly−(ala)$_n$ substrates **53**−**54**, are also the thermodynamically favored diastereomers, the cyclic peptides were subjected to reaction conditions

(13) Yoon, U. C.; Kim, D. U.; Lee, C. W.; Choi, Y. S.; Lee, Y.-J.; Ammon, H. L.; Mariano, P. S. *J. Am. Chem. Soc.* **1995**, *117*, 2698.

Table 6. X-ray Crystallographic Data for Compounds **40**, **41a**, **57**, **58**, and **59**

compd	40	41a	57	58	59
formula	$C_{21}H_{23}N_3O_5$	$C_{36}H_{34}N_4O_5 \cdot H_2O$	$C_{28}H_{27}N_3O_4$	$C_{38}H_{38}N_4O_5$	$C_{48}H_{49}N_5O_6$
fw	397.42	620.69	469.53	630.72	862.82
cryst syst	orthorombic	triclinic	orthorombic	triclinic	orthorombic
space grp	$P2_12_12_1$	$P\bar{1}$	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12_1$
Z	4	2	4	4	4
a, Å	7.469(3)	6.6763(14)	10.8635 (12)	10.2589(13)	9.8833(5)
b, Å	8.452(4)	15.329(3)	13.9599 (17)	13.3262(12)	24.7789(12)
c, Å	31.817(12)	16.572(4)	15.9849(18)	24.287(3)	37.5458(19)
α, deg	90.00	111.772(6)	90.00	90.00	90.00
β, deg	90.00	97.093(13)	90.00	90.00	90.00
γ, deg	90.00	93.043(14)	90.00	90.00	90.00
V, Å^3	2008.5(15)	1553.9(6)	2424.2(5)	3320.3(6)	9194.9(8)
temp (K)	293(2)	293(2)	294(2)	293(2)	100(2)
dat/res/par[1]	2614/0/272	4713/0/424	4254/0/317	5830/0/482	
GOF (F^2)	1.059	1.064	1.158	1.028	1.127
R_1,[a] wR_2[b]	0.1054, 0.1581	0.0576, 0.1154	0.0646, 0.1182	0.0497, 0.0877	0.0987,0.2161

Scheme 11



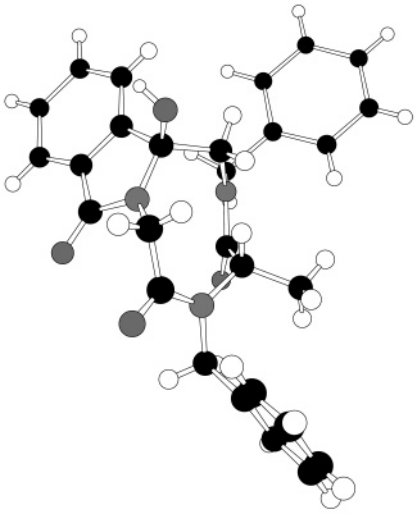


Figure 1. Chem-3D plot of the X-ray crystallographically determined atomic coordinates of macrocyclic peptide analogue **57**.

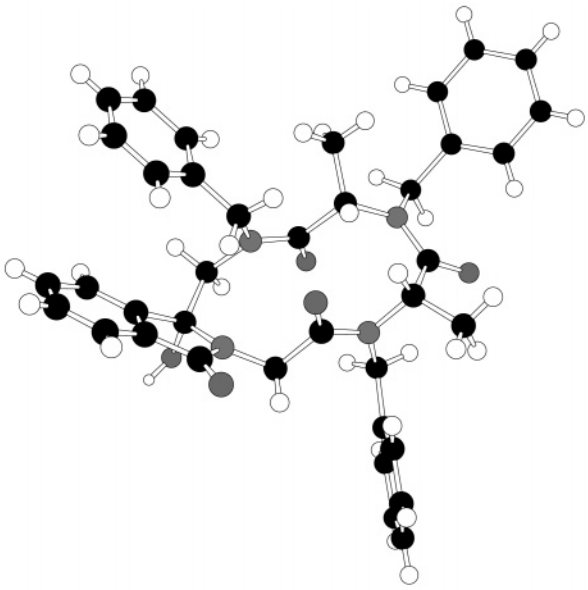


Figure 2. Chem-3D plot of the X-ray crystallographically determined atomic coordinates of macrocyclic peptide analogue **58**.

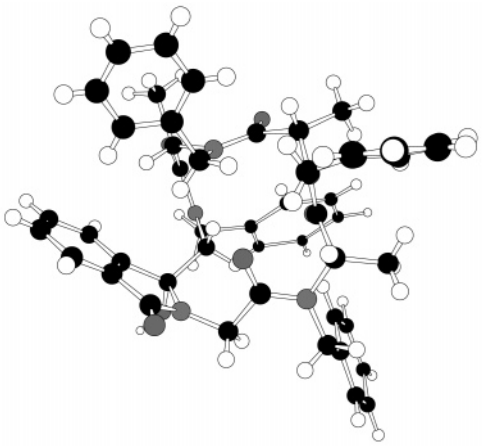


Figure 3. Chem-3D plot of the X-ray crystallographically determined atomic coordinates of macrocyclic peptide analogue **59**.

which should promote epimerization at the amidol center via a reversibly formed N-acyliminum ion. Accordingly, treatment of **58** with dilute HCl for 12 h at 25 °C results in equilibrium production of a mixture of **58** and its β-OH epimer in a ratio of 2.4:1, along with nonequilibrium formation of the dehydration product **60**. Under these conditions, **57** does not undergo epimerization. Finally, it is difficult to monitor the progress of a similar reaction of the cyclic peptide analogue **59** owing to the complexity of its ^{1}H NMR spectrum caused by the presence of slowly interconverting conformers (see below). The results suggest that **57** and **58** are the thermodynamically more stable epimers of the cyclic peptides. If this conclusion is correct, the factors governing the kinetically controlled, stereochemical course of cyclization reactions of biradicals **56** are similar to

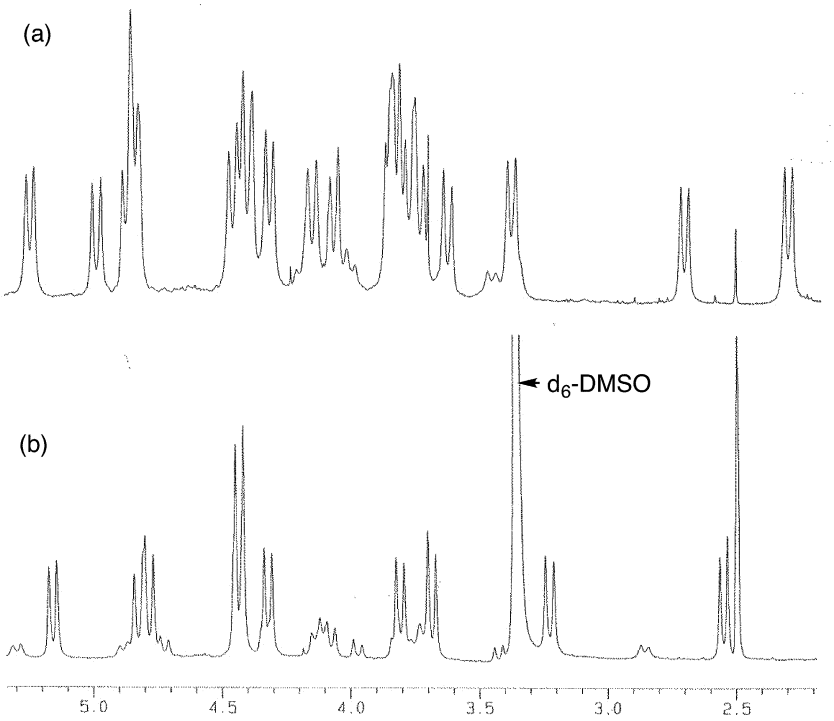
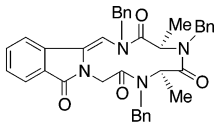


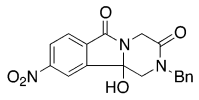
Figure 4. Regions (2.2−5.3 ppm) of ^{1}H NMR spectra of the macrocyclic peptide analogue **39** in (a) $CDCl_3$ and (b) d_6-DMSO.

those that influence the thermodynamic stability of the stereoisomeric products.



60

Assignments of Photoproduct Structures. Structure assignments to the photoproducts generated in the photoreactions described above are based on a full compliment of spectroscopic data, internal comparisons of data for related photoproducts, and, in two cases, the results of X-ray crystallographic analysis (see above). In most cases, interpretation of the data is reasonably straightforward. However, issues related to the regiochemical assignment of the nitrophthalimide derived photoproduct **47** and the structures and conformations of the macrocyclic peptides **39**−**44** do require comment. First, distinction between the regioisomeric photoproducts **47** and **47a** that could be formed by SET-induced photocyclization of nitrophthalimide **32** was made on the basis of ^{1}H NMR spectroscopic analysis. The major distinguishing feature of these substances resides in the influence of the electron withdrawing nitrocarbonyl and amide carbonyl groups on the aromatic proton resonances. In **47**, both groups have a combined influence on the ^{1}H NMR chemical shift of the easily assigned arene proton that has no vicinal arene proton neighbors. Based on data for closely related, structurally more simple analogues, this effect should cause the bis-ortho proton to resonate at ca. 8.4 ppm. In contrast, the related proton in **47a** is ortho to the NO_2 group but meta to the amide carbonyl. Consequently, it is expected to appear at ca. 7.8 ppm. Thus, the observed chemical shift of 8.45 ppm for this proton is consistent with the assignment of structure **47** to this photoproduct.



47a

The ^{1}H and ^{13}C NMR spectra of $CDCl_3$ solutions of the cyclic tripeptides **39**, **40**, and **59** demonstrate that these substances exist as two or more slowly interconverting conformers. This is reflected by the presence of two sets of approximately equal intensity resonances in the ^{1}H NMR spectrum of **39**, which indicates a ca. 1:1 mixture of conformers (Figure 4a). The situation changes when the NMR solvent is d_6-DMSO (Figure 4b). In this case, the cyclic peptide exists either as a rapidly interconverting mixture of two conformers or as one conformer nearly exclusively. In a similar manner, the ^{1}H NMR spectrum of **59** also simplifies when the solvent is changed to d_6-DMSO. Additional information about the variable conformational preferences in the macrocyclic peptides **39**−**44** arises from the observation that the cyclic tetrapeptide **41** can be isolated in two different, conformationally stable forms, **41a** (mp 155−158 °C) and **41b** (mp 163−166 °C).

Although these observations are consistent with the expected conformational properties of large ring tertiary polyamides, they cloud the unambiguous structural assignments of these photoproducts. Thus, to gain a higher level of confidence for these assignments, X-ray crystallographic analyses were performed on photoproducts **40** and **41a** (Table 6). As seen by viewing the Chem 3D plots of X-ray crystallographically derived atomic coordinates, shown in Figures 5 and 6, both substances possess the expected cyclic peptide structures. Interestingly, in contrast to the crystal structure of **40**, in which the two ring amide groups have cis stereochemistry, that of the cyclic tetrapeptide **41a** has two of its three ring amide groups with trans stereochemistry.

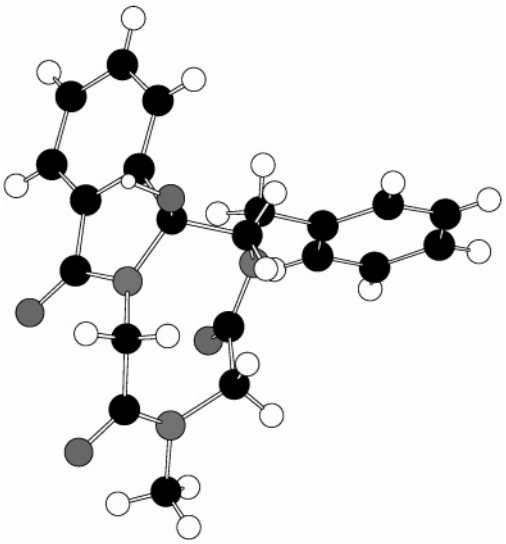


Figure 5. Chem-3D plot of the X-ray crystallographically determined atomic coordinates of macrocyclic peptide analogue **40**.

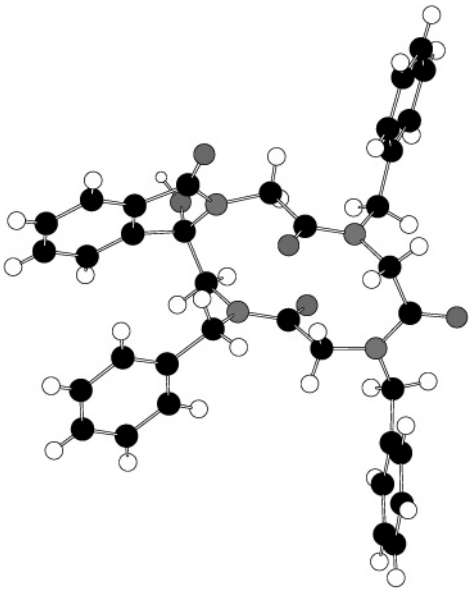


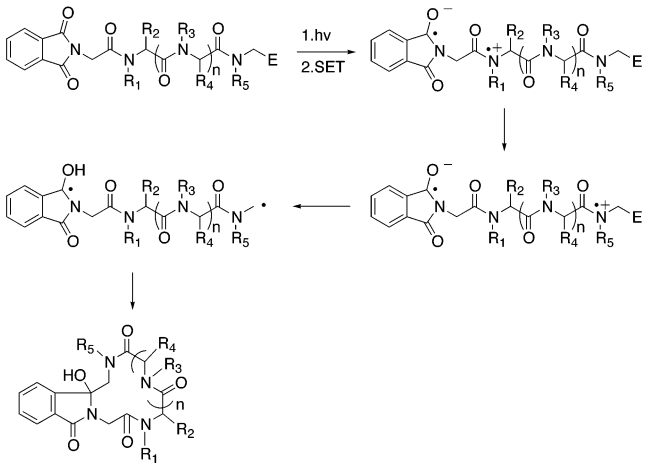
Figure 6. Chem-3D plot of the X-ray crystallographically determined atomic coordinates of macrocyclic peptide analogue **41a**.

Discussion

The results of the investigation described above demonstrate the feasibility of the photochemical based strategy for preparation of cyclic peptide analogues. The key step in routes, which follow this design, involves SET-photoinduced cyclization of N-acceptor-linked peptides that contain C-terminal α-amidotrimethylsilyl or α-amidocarboxylate groups. Photomacrocyclization reactions of the phthalimide-linked peptides take place by a sequence of events (Scheme 12) involving (1) intramolecular SET from near neighbor amide donor sites to the excited phthalimide chromophore, (2) amide cation radical migration to the α-amidosilane or α-amidocarboxylate centers, (3) desilylation or decarboxylation to form 1,*ω*-biradical intermediates, and (4) biradical cyclization.

The modestly high yields observed for photocyclization reactions of substrates, which have a phthalimide acceptor group, suggest that SET from amide donor sites in the peptide chains to the excited phthalimide chromophore occurs more rapidly

Scheme 12

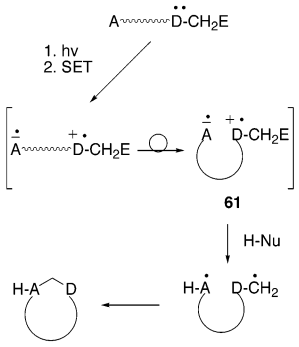


than other typical excited state reaction modes (e.g., H-atom abstraction).[14] In addition, the efficiencies of these processes are not significantly affected by the length of the ploypeptide chain separating the centers at which bonding occurs. This result indicates that, following the initial SET event, migration of the radical cation center (hole migration) to the position in the peptide chain where the reactive electrofugal group (TMS or CO_2) is located takes place at a rate which is competitive with both back electron transfer (leading to the ground-state reactant) and proton loss from benzylic sites in intervening cation radicals.[15] Furthermore, the apparent chain length independence of the efficiencies of these processes suggests that the rates of the biradical cyclization reactions that serve as ultimate mechanistic steps in the reaction sequences are not significantly influenced by entropy.[16] It is tempting to propose a universal explanation for this phenomenon, which invokes the intermediacy of conformationally preorganized biradicals as precursors of the cyclic products in intramolecular SET-promoted cyclization reactions. A unique feature of cyclization reactions of linked donor−acceptor systems, promoted in this manner, is that the final neutral biradical intermediates arise by fragmentation reactions of zwitterionic biradicals. The electronic nature of the zwitterionic biradicals could cause them to exist in folded conformations **61** that minimize the distance between the oppositely charged centers (Scheme 13). Thus, if the rates of ion radical fragmentation and biradical coupling are in the range of those for complete conformational randomization, the cyclization processes would not be as entropically disfavored as conventional non-SET promoted cyclization reactions.

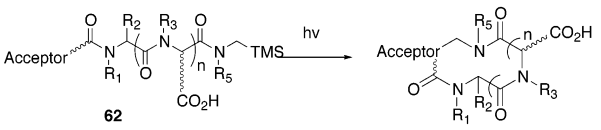
Another interesting feature of observations made in this investigation relates to the relative efficiencies of photoinduced cyclization reactions of trimethylsilyl- and carboxylate-terminated phthalimidopeptides. The finding that photocyclization of the carboxylate-terminated phthalimidoglycinamide **27** has a ca. 3-fold higher quantum efficiency than that of the similarly

(14) For a recent comprehensive review, see: Coyle, J. D. In *Synthetic Organic Photochemistry*; Horspool, W. M., Ed.; Plenum: New York, 1984; p 259.
(15) (a) For hole transfer through small peptides, see for example: Isied, S. S.; Moreira, I.; Ogawa, M. Y.; Vassilian, B. A.; Sun, J. *J. Photochem. Photobiol., A* **1994**, *82*, 203. Defelippis, M. R.; Faraggi, M.; Klapper, M. H. *J. Am. Chem. Soc.* **1990**, *112*, 5640. (b) For hole transfer through proteins, see for example: Gray, H. B.; Winkler, J. R. *Annu. Rev. Biochem.* **1996**, *65*, 537. Symons, M. C. R. *Free Radical Biol. Med.* **1997**, *22*, 1271.
(16) Kanaoka, Y. *Acc. Chem. Res*. **1978**, *11*, 407. Machida, M.; Takechi, H.; Kanaoka, Y. *Synthesis* **1982**, 1078. Coyle, J. D.; Newport, G. L. *Synthesis* **1979**, 381−382. Sato, Y.; Nakai, H.; Ogiwara, H.; Mizoguchi, T.; Migita, Y.; Kanaoka, Y. *Tetrahedron Lett*. **1973**, 4565.

Scheme 13. Schematic for Conformational Control of SET-Promoted Photocyclization Reactions of Linked Acceptor−Donor Systems



Scheme 14

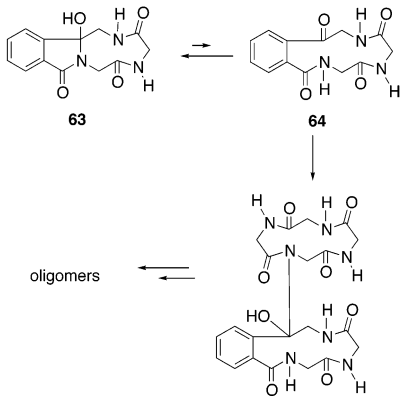


structured TMS analogue **18** is fully consistent with the relative rates of amide cation radical α-desilylation versus α-decarboxylation (Table 1).[11b] Despite this difference, the chemical yields of these processes are nearly identical (65% and 60%, respectively). Thus, the lower quantum efficiency for reaction of the TMS-substrate **18** must be a consequence of a lower ratio of the rate of zwitterionic biradical desilylation versus quenching by back electron transfer and not due to the intervention of competing, yield diminishing photochemical processes which generate side products.

This observation has a potentially important consequence on the design of photochemical based sequences for the preparation of complex cyclic peptide analogues. It is well-known that carboxylate groups, even when they are not located adjacent to amine and amide centers, participate as donors in photoinduced SET reactions with a variety of acceptors (e.g., phthalimides,[17] iminium salts[18]). As a result, photocyclization reactions of carboxylate-terminated, acceptor-linked polypeptides, which also contain other carboxylate centers (aspartate, glutamate), could be complicated by the intervention of competitive photoreactions. From this perspective, the use of TMS-terminated substrates (**62**, Scheme 14) might be more desirable in that it would avoid the need for selective carboxylate protection schemes. Thus, irradiation of substrates of this type in low pH solutions, where aspartate and glutamate side chains exist in the acid form, should bring about selective conversion to the cyclic peptide products arising by sequential SET-desilylation-biradical cyclization routes.

(17) Griesbeck, A. G.; Henz, A.; Peters, K.; Peters, E. M.; von Schering, H. G. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 474.
(18) (a) Kurauchi, Y.; Ohga, K.; Nobuhara, H.; Morita, S. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 2711. (b) Kawanisi, M.; Nozaki, H. *Tetrahedron* **1969**, *25*, 1125.
(19) Sheehan, J. C.; Frank, V. R. *J. Am. Chem. Soc.* **1950**, *72*, 1312.
(20) The preparation of this substance has been reported on several occasions: Ando, Y; Takemura, S.; Tokunaga, T.; Kurozumi, M. *Kinki Daigaku Yakugakubu Kiyo* **1963**, *4*, 45. Smirnova, N. V.; Skoldinov, A. P. *Zh. Org. Khim.* **1966**, *2*, 1269. Bartoschek, A.; Griesbeck, A. G.; Oelgemoller, M. *J. Inf. Rec.* **2000**, *25*, 119.
(21) Chrisment, J.; Delpuech, J. J.; Rajerison, W.; Selve, C. *Tetrahedron* **1986**, *42*, 4743. Scapira, C. B.; Abasolo, M. I.; Perillo, I. A. *J. Heterocycl. Chem.* **1985**, *22*, 577.

Scheme 15



One of the more unusual observations made in this study is that the cyclic peptide analogues **33**, **36**, and **37**, formed by photocyclization reactions of the secondary amide containing amide **25** and peptides **28** and **29**, are highly unstable substances. The short lifetimes of these substances appear to be associated with polymerization reactions that result in the production of insoluble oligomers. Clearly, this instability is not merely the consequence of the presence of secondary amide centers since a wide variety of stable NH-amide containing cyclic peptides have been prepared and characterized previously. A possible reason for the unique of instability of **33**, **36**, and **37** arises from a consideration of the consequences of reversible amidol forming reactions that are open to these substances. Accordingly, amidol **63** to amido ketone **64** conversion (Scheme 15) could be followed by intermolecular amidol forming reactions of **64** leading to eventual formation of oligomers.

Although the studies carried out thus far have shown that the SET-photocyclization based strategies for cyclic peptide analogue synthesis is viable, further efforts are required to probe the generality and uncover the potential limitations of this methodology. Our continuing studies in this area are designed to further explore these features. Special attention will be given to photoreactions of TMS-terminated peptides that have other photoreactive acceptor groups and those that have the capability of producing branched and diversely functionalized cyclopeptide products.

Acknowledgment. We dedicate this publication to the memory of Gary A. Epling, an outstanding teacher and sensitive person who served as the doctoral mentor of U.C.Y. and graduate student colleague of P.S.M.. U.C.Y. acknowledges the financial support provided by the Korea Science and Engineering Foundation through the program of International Cooperative Research (2002-5-123-01-2). P.S.M. acknowledges the financial support provided by the NSF (CHE-0130943 and INT-0121510).

Supporting Information Available: Contained in this information are all experimental procedures, ^{1}H and ^{13}C NMR spectra for all previously uncharacterized compounds which were prepared in this study, and X-ray crystallographic data for **40**, **41a**, **57**, **58**, and **59**. This material is available free of charge via the Internet at http://pubs.acs.org.

JA030297B