Five- and Six-Membered Ring Opening of Pyroglutamic Diketopiperazine

Dennis A. Parrish and Lon J. Mathias*

School of Polymers and High Performance Materials, The University of Southern Mississippi, Hattiesburg, Mississippi 39406-0076

lon.mathias@usm.edu

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A variety of ring-opening reactions of pyroglutamic diketopiperazine at both the five-membered and six-membered rings is described. Mild, basic conditions facilitate nucleophilic attack by amines at the diketopiperazine carbonyls giving pyroglutamides in excellent yield. Reaction with nucleophiles under acidic conditions give bis-glutamate derivatives of 2,5-diketopiperazine (DKP). These reactions provide simple, two-step sequences to pyroglutamides and symmetrical diketopiperazines from commercial pyroglutamic acid with control of product dictated by reaction conditions, catalyst, and nucleophile.

Introduction

Recent reports describing research in the area of 2,5-diketopiperazines (DKP) show that this class of compounds is useful in medicinal chemistry, self-assembly, and targeted organic synthesis. A variety of DKPs have been found to possess biological activity, and studies of their synthesis and modes of action have been reported.[1−9] For example, proline-based DKPs demethoxyfumitremorgin C, tryprostatin B, and several synthetic analogues have been found to inhibit cell cycle progression at the G_2/M checkpoint, the stage at which cells enter mitosis.[1−3] The DKP cyclo(His-Pro) is endogenous in humans and is prevalent throughout the central nervous system. It is believed that cyclo(His-Pro) is synthesized from thyroid-releasing hormone (TRH) and is involved in appetite suppression, alcohol intake, and pancreatic hormone release.[4] In addition to the naturally occurring compounds, a number of DKPs have been prepared as peptidomimetics analogous in structure to non-DKP peptides.[5−7]

The combined hydrogen-bond acceptor and donor sites of DKP *cis*-amides have been used to form various supramolecular structures. For example, it has been shown that symmetrical DKPs form molecular tapes, or one-dimensional aggregates, and that aspartic DKP ((2*S*,5*S*)-3,6-dioxo-2,5-piperazinediacetic acid) is useful as a scaffold for the construction of three-dimensional structures.[10−12] DKP-based tetrapeptides form microcapsules in water when solutions at pH 7.7 were lowered to pH 2.4.[13] The effect of stereochemistry on supramolecular architecture may be seen in work involving a racemic mixture of a bridged DKP that forms an extended chain while the (*R*,*R*)-enantiomer forms cyclic tetramers.[14] The intermolecular hydrogen bonding between DKP *cis*-amides may also be used to reversibly gel organic solvents, a potentially useful application for oil containment and disposal, drug delivery, and encapsulation of food additives.[15−17]

Synthetically, DKPs have been used for a number of applications. Cyclo(His-Phe) has been shown to catalyze the addition of HCN to aldehydes.[18−20] DKP catalyzed addition of HCN to imines followed by hydrolysis has been used to synthesize optically pure amino acids in high yield.[21] DKPs have also been used as templates for amino acid synthesis,[22,23] combinatorial chemistry,[24−27] and as chiral auxiliaries for Diels−Alder reactions.[28]

The DKP of pyroglutamic acid (PyDKP, **3**) has been studied for over 50 years. It is prepared from glutamic acid (Figure 1), although there was some dispute between

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(19) Kim, H. J.; Jackson, W. R. *Tetrahedron*: *Asymmetry* **1992**, *3*, 1421−1430.
(20) Iyer, M. S.; Gigstad, K. M.; Namdev, N. D.; Lipton, M. A. *J. Am. Chem. Soc*. **1996**, *118*, 4910−4911.
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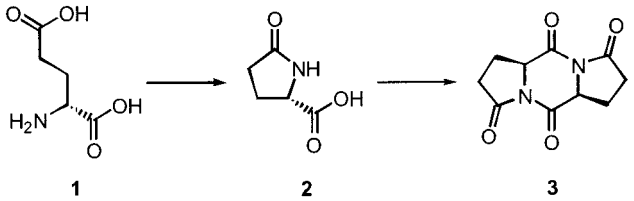


Figure 1. Conversion of glutamic acid to pyroglutamic diketopiperazine.

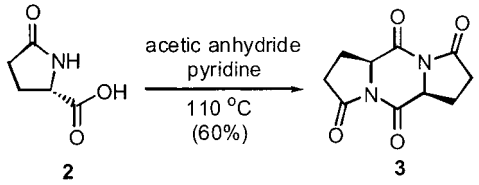
research groups until the structure was finally established.[29−33] Surprisingly, despite these and other reports related to its structure and synthesis, pyroglutamic diketopiperazine has found little use as a synthetic precursor for DKPs or other heterocyclic compounds. We have studied **3** as a source of symmetrical DKPs but were surprised to learn that nucleophiles, under basic conditions, open the DKP ring to give pyroglutamates. This is unexpected considering the perceived stability of the central six-membered ring over the less hindered and presumably more strained five-membered segments. One apparently erroneous patent report in the literature describes the reaction of **3** with diamines to give DKP-containing polyamides.[34,35] We have been unable to reproduce those results under the reported conditions. Based on results described here, the product in that report must have been a bis-pyroglutamate species. In addition, several additional patents[36,37] reported the use of sulfuric acid to catalyze the opening of the five-membered rings with water and alcohols to give symmetrical DKPs, a process that we have reevaluated and extended.

This paper will detail our findings on control of these competitive ring-opening reactions. This work has immediate impact on the synthesis of peptides containing terminal pyroglutamic acid units that are chiral or racemic. It also leads to new families of organogelators,[38] multifunctional bis-pyroglutamides,[39] and even new methacrylate derivatives containing pendent pyroglutamides.[40]

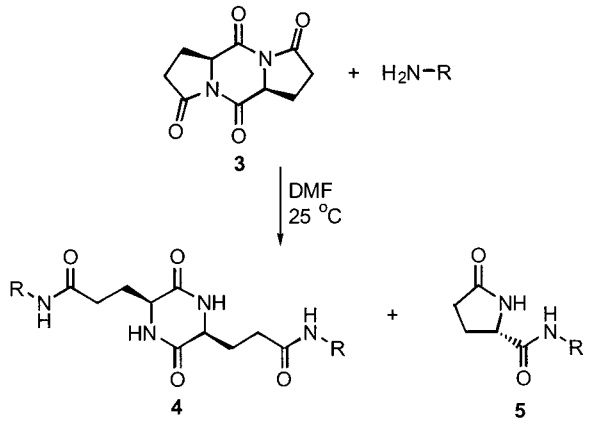
Results and Discussion

Synthesis of 3. King and McMillan reported yields of 60% for their preparation of **3**.[29] Modification of their procedure by changing the ratio of acetic anhydride to pyridine to 5:1 and maintaining a temperature of exactly 110 °C instead of reflux gave similar yields (Scheme 1). They reported reaction in the absence of pyridine, but at 110 °C without pyridine, our yields dropped significantly. Yields of **3** also diminished significantly at temperatures below 110 °C even with pyridine catalysis, while at temperatures higher than 110 °C, the product displayed a yellow-orange discoloration, necessitating an extra purification step, but without the benefit of increased yield. X-ray crystallographic analysis of **3** showed the retention of the two (*S*) stereocenters (Supporting Information).

Scheme 1



Scheme 2



Minor Product

4a: R = Pr
4b: R = Bn
4c: R = -CH_2CH_2OH
4d: R = -CH_2CO_2H
4e: R = -$CH(CH_3)_2$
4h: R = -$(CH_2)_3NHCH_3$

Major Product

5a: R = Pr
5b: R = Bn
5c: R = -CH_2CH_2OH
5d: R = -CH_2CO_2H
5e: R = -$CH(CH_3)_2$
5f: R = (S)-$CH(CH_3)Ph$
5g: R = (R)-$CH(CH_3)Ph$
5h: R = -$(CH_2)_3NHCH_3$

Six-Membered Ring Opening. We anticipated that reaction of **3** with amines would give derivatives of DKP **4**, but surprisingly found pyroglutamides **5** were formed as the major product (Scheme 2). Reaction with propylamine gave **5a**, the structure of which was confirmed by direct preparation from pyroglutamic acid and propylamine using *N*,*N*′-dicyclohexylcarbodiimide (DCC) and 1-hydroxybenztriazole. Compound **5a** was also prepared by transamidation of ethyl pyroglutamate with propylamine. ^{13}C and ^{1}H NMR analyses of **5a** prepared by different routes gave identical results in all cases. Car-

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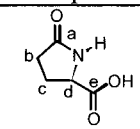
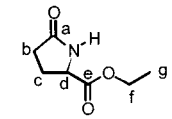
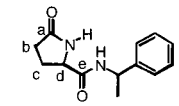
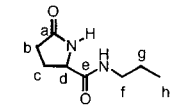
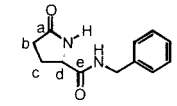
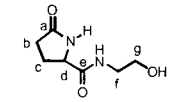
Table 1. ^{13}C NMR Chemical Shifts for Selected Carbons for Derivatives of 2

		Chemical Shift (DMSO-d_6)			
		Carbonyls		-CH_x-	
Entry	Compound	a	e	b	c
1[a]		177.1	174.5	29.1	24.7
2[a]		177.0	172.9	28.9	24.5
3[a]		177.4	171.5	29.3	25.2
4		177.4	172.2	29.3	25.4
5		177.6	172.6	29.4	25.5
6		177.1	172.4	29.4	25.4

[a] Purchased or prepared by another method.

bonyls at 177 and 172 ppm in the ^{13}C NMR spectrum are consistent with esters and amides of pyroglutamic acid (Table 1). Additionally, carbonyl peaks at 171 and 167 ppm in the ^{13}C NMR spectrum of **4a** are consistent with the structure of similar DKPs reported in the literature[41−43] and synthesized in our laboratory (Table 2).

Reaction of **3** with primary amines (Table 3) proceeded smoothly despite its insolubility in most solvents. In DMF, for example, **3** was only partially soluble but gradually reacted with propylamine to give a clear, homogeneous solution followed by rapid precipitation of **4a**. Isolation of products was carried out by gravity or vacuum filtration. Elevated and depressed reaction temperatures gave lower and higher yields of pyroglutamide **5a**, respectively. Reaction in chloroform proceeded in a similar manner except that the reaction mixture remained heterogeneous throughout. This reaction was followed by NMR and was found to be complete in about 2 h at room temperature. Filtration was used to separate and purify amides **4a** and **5a**. Reaction of **3** with ethanolamine gave amides **4c** and **5c** exclusively in 4% and 94% yields, respectively, with no ester byproduct (Table 3, Entry 7).

In early experiments, 2,2,2-trifluoroethanol (TFE) was used as the reaction solvent since it readily dissolves **3**. However, in the presence of amines, TFE reacted with **3** to form trifluoroethyl ester **6**, which then underwent transamidation (Scheme 3). Evidence for this was obtained from NMR analysis in which the trifluoroethyl ester was observed as an unreacted byproduct. When triethylamine was used as catalyst with no additional amine, the ester was isolated as the major product. However, TFE would not react with **3** when amine catalyst was absent.

TFE was found to be the best solvent for the reaction of **3** with glycine. While the solubility of glycine was limited in TFE, neutralization of the acid with triethylamine facilitated dissolution. Glycine reacted to give pyroglutamyl glycine dipeptide **5d** in 81% yield. The dipeptide was formed in one step, and no DKP byproduct was observed in this reaction (Scheme 2, Table 3, entry 9).

Also included in Table 3 are reactions of **3** with α-substituted primary amines. We found that these reactions frequently gave mixtures of products and unreacted **3**. However, when **3** was reacted with excess (5.0 equiv) isopropylamine, DKP **4e** and pyroglutamide **5e** were obtained in 2.2% and 97% yields, respectively.

An important question about the ring-opening reaction of **3** is whether the product retained the stereochemistry of the starting material. To study this, **3** was reacted with (*S*)-(−)-1-phenylethylamine and (*R*)-(+)-1-phenylethylamine using the conditions described above. It was expected that if racemization occurred during reaction, two pairs of diastereomers would be obtained. The ^{13}C NMR spectrum of **5f** and **5g** gave only one set of peaks, indicating that each product is a single enantiomer. Analysis of a physical mixture of **5f** and **5g** showed two sets of peaks, indicating a diastereomeric mixture. Comparison of **5f** and **5g** to pure samples prepared from (*S*)-pyroglutamic acid and the appropriate enantiomer of 1-phenylethylamine confirmed retention of chirality during the ring-opening reaction.

The ring-opening reaction of **3** with secondary amines was also studied. Unfortunately, reaction with a variety of secondary amines in DMF, $CHCl_3$, and TFE failed to give product regardless of temperature or excess amounts of amine. When TFE was used as solvent, a complex mixture of products was obtained. The major products were trifluoroethyl ester **6**, which apparently failed to react with diisoproylamine, and pyroglutamic acid, the hydrolysis product of **6**. By taking advantage of this limitation under these conditions, it was possible to synthesize a 2° amine terminated pyroglutamide in one step from **3** reacted with 1-methyl-1,3-propanediamine. (Table 3, entry 16).

Alcohols (other than TFE) failed to react with **3** despite the presence of tertiary amine. It has been reported, however, that KCN is an effective catalyst in solution and solid-phase ring-opening alcoholysis of *N*-*t*-Boc-pyroglutamates.[44−46] The structural similarity of *N*-*t*-Boc protected pyroglutamates to **3** prompted investigation into the application of KCN as a catalyst for the ring-opening reaction of **3**. It was found that KCN facilitated the reaction of ethanol with **3** but only under alcoholysis

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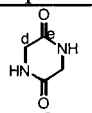
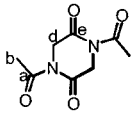
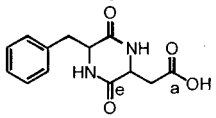
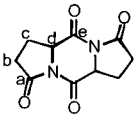
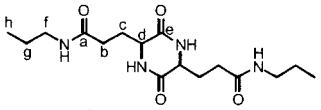
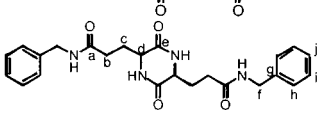
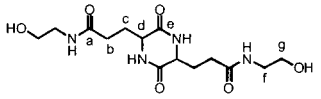
(46) de Blas J.; Dominguez, E.; Ezquerra, J. *Tetrahedron Lett.* **2000**, *41*, 4567−4571.

Table 2. ^{13}C NMR Chemical Shifts for Selected Carbons of DKP Derivatives

		Chemical Shift (DMSO-d_6)			
		Carbonyls		-CH_x-	
Entry	Compound	a	e	b	c
1[a]		--	166.1	--	--
2[a]		170.5	166.9	26.3	--
3[a]		171.5	166.7	--	--
4		172.7	165.7	31.2	18.9
5		171.1	167.5	30.9	30.5
6		171.5	167.7	30.8	29.1
7		171.6	167.7	30.9	29.3

[a] Purchased or prepared by another method.

Table 3. Reaction of 3 with Amines

				yield (%)	
entry	amine	solvent	T (°C)	**4**	**5**
1	propylamine	DMF	25	5	89
2	propylamine	DMF	100	14	85
3	propylamine	DMF	−15	1	98
4	propylamine	$CHCl_3$	25	5	93
5	benzylamine	DMF	25	2	93
6	benzylamine	$CHCl_3$	25	7	86
7	ethanolamine	$CHCl_3$	25	4	94
8	ethanolamine	MeOH	0	<1	99
9	glycine	TFE[a]	0	0	81
10	isopropylamine	$CHCl_3$	25	2	97
11	1-phenylethylamine	$CHCl_3$	0		84
12	dipropylamine	DMF	25	0	0
13	dipropylamine	$CHCl_3$	25	0	0
14	dipropylamine	MeOH	25	0	0
15	dipropylamine	TFE[a]	0	0	0
16	1-methyl-1,3-propanediamine	MeOH	0	0	93

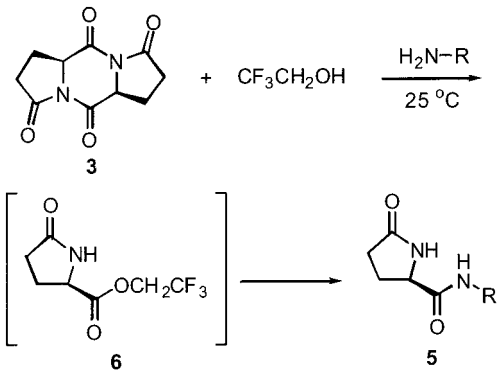
[a] TFE = 2,2,2-trifluoroethanol.

conditions. Reaction of **3** with ethanol required an excess of the alcohol but gave quantitative yield of the product (Scheme 4). Reaction of **3** with a stoichiometric amount of ethanol in $CHCl_3$ failed to give product.

Other DKPs with analogous structure were reacted with amines to determine if the ring-opening reaction would occur or if it was unique to the imide functionality of **3**. *N*,*N*′-Diacetyl-2,5,-diketopiperazine (**8**)[47,48] and cyclo(prolylproline) (**11**)[33] contain imide groups and a tricyclic ring system, respectively. Reaction of propylamine with **8** (Scheme 5) gave DKP **9** and amide **10** with no indication of DKP ring opening. Attempted reaction with **11** gave only starting material and no product (Scheme 6). Formation of **10** involved amine attack *only* at the carbonyl that in **3** would lead to DKP bisglutamates. Clearly, the structure of **3** controls amine reaction through a combination of steric and electronic effects that are not obvious.

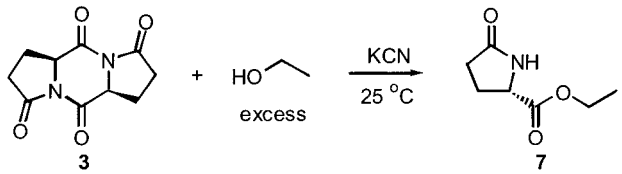
To further explore the possibility of ring-opening reactions in analogous DKP imides, bicyclic DKP **12**

Scheme 3



3 6 5

Scheme 4

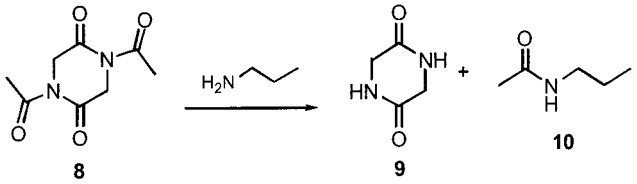


3 7

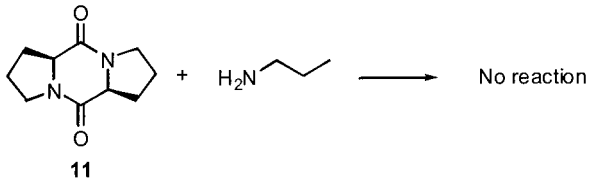
(47) Kanmera, T.; Lee, S.; Aoyagi, H.; Izumiya, N. *Tetrahedron Lett.* **1979**, 4483−4486.

(48) Sera, A.; Okada, M.; Ohhata, A.; Yamada, H.; Itoh, K.; Kubo, Y. *Heterocycles* **1993**, *5*, 1039−1046.

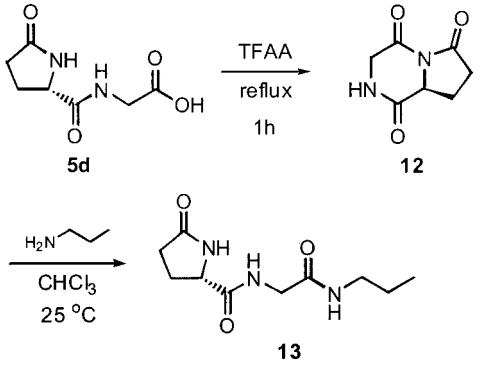
Scheme 5



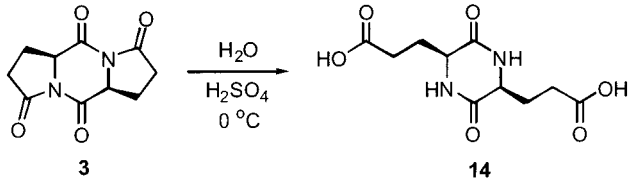
Scheme 6



Scheme 7



Scheme 8



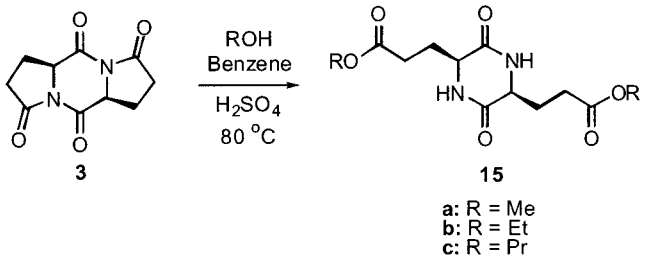
(Scheme 7) was prepared from dipeptide **5d** using a modified literature procedure.[49] Addition of propylamine to DKP **12** in chloroform gave pyroglutamide **13** with no indication of product resulting from five-membered ring-opening.

Five-Membered Ring Opening. Despite the intriguing results of base-catalyzed reactions of **3**, a convenient route to symmetrical disubstituted DKPs was needed. Several techniques are described in the literature. The Fisher procedure uses amino acid esters to form the DKP in one step, but yields are low and reaction times are long.[24,50] Alternatively, dipeptides may be synthesized and then cyclized, but this approach requires several protection and deprotection steps. Two patent procedures show that DKPs may also be synthesized by the acid-catalyzed reaction of **3** with water to give diacid or with alcohols to give DKP diesters.[36,37]

Using this procedure, dissolution of **3** in cold sulfuric acid followed by the addition of water gives glutamic DKP **14** in 76% yield (Scheme 8). It was also reported that addition of alcohols followed by precipitation with water gives esters of glutamic DKP, but we have found this approach to be unreliable, as it often gives the diacid

(49) Harden, M. R. *J. Chem. Soc. C* **1967**, 2341−2351.
(50) Fisher, E.; Koenigs, E. *Chem. Ber.* **1907**, *40*, 2048−2061.

Scheme 9



instead. Alternatively, we synthesized esters **15a**−**c** by refluxing **3** with the appropriate nucleophile in benzene, but low yields were obatined (below 35%) (Scheme 9). ^{13}C NMR analyses of the diesters showed carbonyls at 173 or 172 and 167, characteristic of DKPs.

The use of Lewis acid catalysis for the reaction of **3** with amines has been briefly examined to extend this approach. The ring-opening aminolysis of *N*-acyllactams with $AlCl_3$ has been reported to occur in high yields.[51] Reaction of **3** with propylamine in the presence of $AlCl_3$, however, gave unreacted **3** and propylamine hydrochloride. Similarly, reaction of **3** with boron trifluoride−ethylamine complex gave unreacted **3**. Reaction of **3** with ethanol in the presence of boron trifluoride diethyl etherate gave **15b** but in only 7% yield. The use of other Lewis acid catalysts for the reaction of **3** with alcohols and amines is currently being examined. Other nonacidic catalytic systems that promote the six-membered ring-opening reaction of **3** with secondary amines, alcohols, and thiols are also being explored.

Conclusions

Nucleophiles react with pyroglutamic diketopiperazine to open either the five- or six-membered rings depending upon the reaction conditions. Reaction with amines under basic conditions generally gives greater than 90% yield of the corresponding pyroglutamide, which results from regioselective reaction at the DKP ring. The chirality of the pyroglutamate moiety and the amine nucleophile are retained during the ring-opening process. Reactions with α-amino acids and esters leads to a general synthesis of pyroglutamic acid dipeptides and may allow incorporation of pyroglutamyl terminal groups in longer peptides without the need for protection or deprotection steps.

Experimental Section

Materials. (*S*)-2-Pyrrolidone-5-carboxylic acid ((*S*)-pyroglutamic acid) was purchased from ICN Biomedicals, Inc. Methanol was purified by distillation from magnesium and iodine and stored over 3 Å molecular sieves. Propylamine, benzylamine, isopropylamine, and dipropylamine were distilled from CaH_2. TFE was treated with $NaHCO_3$ and distilled before use. DMF and $CHCl_3$ were dried and stored over activated 4 Å molecular sieves. All other materials were purchased from Aldrich Chemical Co. or Acros Organics and used as received.

Instrumentation. ^{13}C NMR and ^{1}H NMR were obtained on a Bruker AC-300 spectrometer using standard acquisition parameters and DMSO-d_6 containing 0.1% TMS as internal reference. Thermogravimetric analyses were performed on a TA Instruments SDT 2960 module (TA 2100 controller) at a heating rate of 20 °C/min in a nitrogen environment. Melting points were obtained on a Mel-Temp hot block melting point apparatus. Elemental Analyses were performed by Qualitative Technologies, Inc., Whitehouse, NJ.

(51) Bon, E.; Bigg, D. C. H.; Betrand, G. *Synlett* **1992**, 747−748.

1,7-Diazatricyclo[7.3.0.0]dodecane-2,6,8,12-tetrone (Pyroglutamic Diketopiperazine) (3). To a 1000 mL round-bottom flask were added acetic anhydride (345 mL), pyridine (64 mL), and a magnetic stirring bar. A reflux condenser was attached, and the flask was lowered into an oil bath preheated to 110 °C. *S*-Pyroglutamic acid (77.4 g) was added to the solvent mixture when the temperature reached 110 °C. Pyroglutamic diketopiperazine began to precipitate from solution as a white solid after 5 min. Heating was continued for an additional 15 min. The reaction mixture was cooled in an ice bath, and the product was collected by vacuum filtration and washed with cold methanol. The product was transferred to an Erlenmeyer flask, covered with methanol, and collected by filtration. This was repeated with distilled water. The product was dried overnight under vacuum: yield 39.7 g (60%); mp 290 °C dec; ^{1}H NMR (DMSO-d_6 with TMS) δ 4.84 (dd, J = 8.86, 7.87 Hz, 2H), 2.84−2.11 (m, 8H); ^{13}C NMR (DMSO-d_6 with TMS) δ 172.7, 165.7, 58.4, 31.2, 18.9. Anal. Calcd for $C_{10}H_{10}N_2O_4$: C, 54.05; H, 4.54; N, 12.61; O, 28.80. Found: C, 54.10; H, 4.57; N, 12.62; O, 28.99.

Dipropyl-2,5-diketopiperazine-3,6-dipropanamide (4a) and *N*-Propylpyroglutamide (5a). To a 50 mL round-bottom flask were added pyroglutamic diketopiperazine (1.00 g, 0.0045 mol), $CHCl_3$ (10 mL), and a magnetic stir bar. Propylamine (0.59 g, 0.0099 mol) was added, and the reaction mixture was stirred for 4 h. The white solid was collected by filtration and dried in vacuo to give **4a**: yield 0.078 g (5.1%); mp 290 °C dec; ^{1}H NMR (DMSO-d_6 with TMS) δ 7.97 (s, 1H), 7.64 (s, 1H), 3.82 (t, J = 5.15 Hz, 2H), 3.03−2.96 (m, 4H), 2.27−2.10 (m, 4H), 1.46−1.34 (m, 4H), 0.84 (t, J = 7.35 Hz, 6H); ^{13}C NMR (DMSO-d_6 with TMS) δ 171.1, 167.5, 53.5, 40.1, 30.9, 30.5, 22.0, 11.0. Anal. Calcd for $C_{16}H_{28}N_4O_4$: C, 56.45; H, 8.29; N, 16.46. Found: C, 56.39; H, 8.23; N, 16.46.

$CHCl_3$ was removed from the filtrate in vacuo to give **5a** as a white solid: yield 1.424 g (92.7%); mp 103−106 °C; ^{1}H NMR (DMSO-d_6 with TMS) δ 7.93 (s, 1H), 7.77 (s, 1H), 3.98−3.93 (m, 1H), 3.06−2.99 (m, 2H), 2.30−2.05 (m, 3H), 1.89−1.78 (m, 1H), 1.48−1.36 (m, 2H), 0.84 (t, J = 7.35 Hz, 3H); ^{13}C NMR (DMSO-d_6 with TMS) δ 177.4, 172.2, 55.9, 40.6, 29.3, 25.4, 22.5, 11.2. Anal. Calcd for $C_8H_{14}N_2O_2$: C, 56.45; H, 8.29; N, 16.46. Found: C, 56.00; H, 8.27; N, 16.27.

Dibenzyl-2,5-diketopiperazine-3,6-dipropanamide (4b) and *N*-Benzylpyroglutamide (5b). To a 50 mL round-bottom flask were added pyroglutamic diketopiperazine (0.989 g, 0.0045 mol), $CHCl_3$ (20 mL), and a magnetic stir bar. Benzylamine (1.00 g, 0.0093 mol) was added and the reaction mixture was stirred for 12 h. The white precipitate was collected by vacuum filtration, mixed with DMF, and filtered once more. The white solid was dried in vacuo to give **4b**: yield 0.132 g (6.8%); mp 264 °C dec; ^{1}H NMR (DMSO-d_6 with TMS): δ: 8.33 (s, 2H), 8.16 (s, 2H), 7.33−7.23 (m, 10H), 4.26 (d, 4H), 3.87 (m, 2H), 2.32−2.17 (m, 4H), 2.03−1.88 (m, 4H); ^{13}C NMR (DMSO-d_6 with TMS) δ 171.5, 167.7, 139.5, 128.3, 127.2, 126.7, 53.5, 42.1, 30.8, 29.1. Anal. Calcd for $C_{24}H_{28}N_4O_4$: C, 66.04; H, 6.47; N, 12.84. Found: C, 65.92; H, 6.35; N, 12.71.

$CHCl_3$ and DMF were removed in vacuo from the combined filtrates obtained above to give **5b** as a white solid: yield 1.671 g (86%) white solid; mp 134−137 °C; ^{1}H NMR (DMSO-d_6 with TMS) δ 8.51 (s, 1H), 7.87 (s, 1H), 7.35−7.25 (m, 5H), 4.30 (d, 2H), 4.07−4.038 (m, 1H), 2.34−1.86 (m, 4H); ^{13}C NMR (DMSO-d_6 with TMS) δ 177.6, 172.6, 139.3, 127.3, 127.1, 126.9, 56.1, 42.2, 29.4, 25.5. Anal. Calcd for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47; N, 12.84. Found: C, 65.83; H, 6.55; N, 12.72.

Bis(2-hydroxyethyl)-2,5-diketopiperazine-3,6-dipropanamide (4c) and *N*-(2-Hydroxyethyl)pyroglutamide (5c). To a 50 mL round-bottom flask were added pyroglutamic diketopiperazine (2.115 g, 0.0095 mol), $CHCl_3$ (20 mL), and a magnetic stir bar. Ethanolamine (1.16, 0.0190 mol) was added and the reaction mixture was stirred for 12 h. Chloroform was removed in vacuo and methanol added to the resulting white solid. The insoluble white solid was collected by filtration and was identified as **4c**: yield 0.123 g (3.76%); mp 257 °C dec; ^{1}H NMR (DMSO-d_6 with TMS) δ 8.17 (s, 1H), 7.85 (s, 1H), 4.66 (t, J = 4.41 Hz, 2H), 3.83 (s, 2H), 3.87 (m, 4H), 3.09 (q, 4H), 2.25−2.08 (m, 4H), 1.98−1.80 (m, 4H); ^{13}C NMR (DMSO-d_6 with TMS) δ 171.6, 167.7, 53.6, 41.5, 30.9, 29.3. Anal. Calcd for $C_{14}H_{24}N_4O_6$: C, 48.83; H, 7.02; N, 16.27. Found: C, 48.57; H, 7.19; N, 16.05.

Methanol was removed in vacuo from the filtrate obtained above to give **5c** as a white solid: yield 3.086 g (94.3%); mp 165−169 °C; ^{1}H NMR (DMSO-d_6 with TMS): δ: 7.91 (s, 1H), 7.75 (s, 1H), 4.68 (s, 1H), 3.98 (m, 1H), 3.41 (t, J = 5.88 Hz, 2H), 3.17−3.11 (m, 2H), 2.27−1.84 (m, 4H); ^{13}C NMR (DMSO-d_6 with TMS) δ 177.1, 172.4, 60.0, 55.9, 41.6, 29.4, 25.4.

Pyroglutamylglycine (5d). To a 50 mL round-bottom flask were added pyroglutamic diketopiperazine (2.07 g, 0.0093 mol), glycine (1.43 g, 0.0191 mol), 2,2,2-trifluoroethanol (20 mL), and a stir bar. The reaction vessel was purged with nitrogen gas and cooled to 0 °C in an ice bath, and triethylamine (1.98 g, 0.0196 mol) was added via syringe. The reaction was allowed to warm slowly to room temperature and stirred for 12 additional h. The reaction flask was capped with a reflux condenser and placed in an 80 °C oil bath for 2 h. The solvent was removed in vacuo to give a milky white liquid. Methanol was added, and the insoluble white solid was removed by gravity filtration. Methanol was removed from the filtrate in vacuo to give a viscous yellow oil. The oil was dissolved in 2 M NaOH (10 mL) and stirred for 1 h. The aqueous solution was transferred to a separatory funnel and washed twice with $CHCl_3$ (10 mL). HCl (5 M, 3.9 mL) was added, and the solvent was then removed in vacuo. Ethanol was added to the resulting white slurry and the salt that formed was removed by vacuum filtration. The solvent was removed in vacuo to give **5d** as a white solid: yield 2.74 g (81%); mp 168−171 °C; ^{1}H NMR (DMSO-d_6 with TMS) δ 8.23 (t, J = 5.88 Hz, 1H), 7.88 (s, 1H), 4.05 (q, 1H), 3.73 (d, 2H), 2.34−1.84 (m, 4H); ^{13}C NMR (DMSO-d_6 with TMS) δ 177.6, 173.0, 171.2, 55.6, 40.7, 29.2, 25.4.

Diisopropyl-2,5-diketopiperazine-3,6-dipropanamide (4e) and *N*-Isopropylpyroglutamide (5e). To a 100 mL round-bottom flask were added pyroglutamic diketopiperazine (1.02 g, 0.0048 mol), $CHCl_3$ (25 mL), and a magnetic stir bar. Isopropylamine (1.95 mL, 0.0229 mol) was added and the reaction mixture was stirred for 12 h at room temperature. An insoluble white solid was collected by gravity filtration and was identified as **4e**: yield 0.034 g (2.2%); mp 274 °C dec; ^{1}H NMR (DMSO-d_6 with TMS) δ 8.15 (s, 2H), 7.69 (d, 2H), 3.86−3.78 (m, 4H), 2.17−2.05 (m, 4H), 1.92−1.85 (m, 4H), 1.02 (d, 12H); ^{13}C NMR (DMSO-d_6 with TMS) δ 170.3, 167.7, 167.6, 53.5, 31.0, 30.5, 29.2, 28.5, 22.4. Anal. Calcd for $C_{16}H_{28}N_4O_4$: C, 56.45; H, 8.29; N, 16.46. Found: C, 55.89; H, 8.10; N, 16.32.

Chloroform and excess isopropylamine were removed in vacuo from the filtrate obtained above to give **5e** as a white solid: yield 1.516 g (97%); mp 126−130 °C; ^{1}H NMR (DMSO-d_6 with TMS) δ 7.80 (m, 2H), 3.95−3.91 (m, 1H), 3.83 (m, 1H), 2.25−2.04 (m, 3H), 1.89−1.79 (m, 1H), 1.06 (dd, 6H); ^{13}C NMR (DMSO-d_6 with TMS) δ 177.4, 171.3, 55.8, 40.4, 29.3, 25.3, 22.3, 22.2. Anal. Calcd for $C_8H_{14}N_2O_2$: C, 56.45; H, 8.29; N, 16.46. Found: C, 56.48; H, 8.42; N, 16.63.

(*S*)-1-Phenylethyl-(*S*)-pyroglutamide (5f). To a 50 mL round-bottom flask were added pyroglutamic diketopiperazine (0.50 g, 0.0023 mol), $CHCl_3$ (10 mL) and a magnetic stir bar. (*S*)-(−)-1-Phenylethylamine (1.36 g, 0.0113 mol) was added and the reaction mixture was stirred for 12 h. A condenser was attached to the flask and the reaction mixture was heated at reflux for 3 h. The solution was cooled and then filtered through Celite. The solvent was removed from the filtrate in vacuo to give a clear oil. The oil was triturated with ether which resulted in the formation of a white solid. This material was washed with excess ether and dried under vacuum to give **5f** as a white solid: yield 0.88 g (84%); mp 135−138 °C; ^{1}H NMR (DMSO-d_6 with TMS) δ 8.41 (d, 1H), 7.82 (s 1H), 7.32−7.27 (m, 5H), 4.92 (m, 1H), 4.06−4.02 (q, 1H), 2.31−2.06 (m, 3H), 1.85−1.74 (m, 1H), 1.36 (d, 3H); ^{13}C NMR (DMSO-d_6 with TMS) δ 177.4, 171.4, 144.4, 128.3, 126.7, 125.9, 55.6, 47.8, 29.3, 25.2, 22.4. Anal. Calcd for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 67.14; H, 7.11; N, 12.16.

(*R*)-1-Phenylethyl-(*S*)-pyroglutamide (5g). Preparation was similar to that of (*S*)-1-phenylethyl-(*S*)-pyroglutamide (**5f**) above: yield (87%); mp 151−152 °C; ^{1}H NMR (DMSO-d_6 with

TMS) δ 8.41 (d, 1H), 7.83 (s 1H), 7.33−7.26 (m, 5H), 4.91 (m, 1H), 4.06−4.00 (q, 1H), 2.30−2.07 (m, 3H), 1.95−1.82 (m, 1H), 1.36 (d, 3H); ^{13}C NMR (DMSO-d_6 with TMS) δ 177.5, 171.5, 144.4, 128.3, 126.7, 126.0, 55.7, 48.0, 29.3, 25.4, 22.4.

1-Pyroglutamyl-3-methyl-1,3-diaminopropane (5h). To a 250 mL round-bottom flask were added pyroglutamic diketopiperazine (2.72 g, 0.0122 mol), CH_3OH (60 mL) and a magnetic stir bar. The suspension was cooled to −15 °C followed by the addition of 1-ethyl-1,3-diaminopropane (2.20 g, 0.025 mol). The reaction mixture was stirred for 12 h and allowed to gradually warm to room temperature. The clear solution was filtered and the solvent removed in vacuo to give a viscous oil which crystallized upon standing: yield 4.89 g (93%); mp 95−98 °C; ^{1}H NMR (DMSO-d_6 with TMS) δ 8.00 (t, 1H), 7.82 (s, 1H), 3.97−3.93 (m, 1H), 3.10 (q, 2H), 2.44 (t, 2H), 2.24−2.05 (m, 6H), 1.90−1.81 (m, 1H), 1.53 (m, 2H); ^{13}C NMR (DMSO-d_6 with TMS) δ 177.5, 172.3, 55.9, 49.0, 36.9, 36.1, 29.3, 29.0, 25.5.

2,2,2-Trifluoroethyl Pyroglutamate (6). To a 50 mL round-bottom flask were added pyroglutamic diketopiperazine (2.00 g, 0.0090 mol), 2,2,2-trifluorethanol (10 mL), and a magnetic stir bar. The flask was capped with a septa, purged with N_2 gas, and cooled to 0 °C in an ice bath. Triethylamine (0.181 g, 0.0018 mol) was added, and the reaction was stirred for 12 h while warming to room temperature. A condenser was attached to the flask, and the reaction mixture was heated at reflux for 2 h. Upon cooling the reaction mixture was concentrated in vacuo. Diethyl ether was added and with cooling **6** crystallized as a white solid: yield 3.91 g (41%); mp 72−73 °C; ^{1}H NMR (DMSO-d_6 with TMS) δ 8.10 (s, 1H), 4.83 (q, 2H), 4.33 (dd, J = 2.94, 3.68 Hz, 1H), 2.40 (m, 1H), 2.16 (m, 2H), 2.00 (m, 1H); ^{13}C NMR (DMSO-d_6 with TMS) δ 177.1, 171.8, 125(q), 60.5(q), 54.5, 28.7, 24.5. Anal. Calcd for $C_7H_8F_3NO_3$: C, 39.82; H, 3.82; N, 6.63. Found: C, 39.84; H, 3.81; N, 6.58.

Ethyl Pyroglutamate (7). To a 25 mL round-bottom flask were added pyroglutamic diketopiperazine (0.20 g, 9×10^{-4} mol), KCN (0.024 g, 1.8×10^{-4} mol), and ethanol (10 mL). The reaction flask was purged with N_2, capped with a septum, and the reaction mixture was stirred for four h until it became clear. The solvent was removed in vacuo to give the product as a clear, viscous oil in quantitative yield: ^{1}H NMR (DMSO-d_6 with TMS) δ 7.97 (s, 1H), 4.14 (m, 3H), 2.40−2.27 (m, 1H), 2.16−2.10 (m, 2H), 2.01−1.91 (m, 1H), 1.20 (t, 3H); ^{13}C NMR (DMSO-d_6 with TMS) δ 177.1, 172.9, 60.7, 54.8, 28.9, 24.6, 14.1.

***N,N′*-Diacetyl-2,5-diketopiperazine (8).** 2,5-Diketopiperazine (5.00 g, 0.0438 mol), acetic anhydride (100 mL), and a magnetic stir bar were placed together in a 250 mL round-bottom flask with an attached refluxed condenser. The reaction mixture was heated to 130 °C for 4 h and cooled, and then the majority of the liquid was removed in vacuo. The remaining solution was poured into ethanol, and the resulting white solid was collected by vacuum filtration. Additional crops of product were obtained from the filtrate upon standing. The fractions were combined and dried in vacuo to give **8** as a white solid: yield 5.54 g (64%); mp 100−102 °C; ^{1}H NMR (DMSO-d_6 with TMS) δ 4.53 ppm (s, 4H), 2.43 (s, 6H); ^{13}C NMR (DMSO-d_6 with TMS) δ 170.4, 166.8, 47.0, 26.3.

1,4-Diazabicyclo[4.3.0]nonane-2,5,9-trione (Cyclo(pyroglutamylglycine)) (12). Pyroglutamyl glycine **5d** (1.00 g, 0.0054 mol) was weighed into a 50 mL round-bottom flask. A magnetic stir bar and trifluoroacetic anhydride (15 mL) were added. A reflux condenser was attached, and the reaction mixture was then placed in a 50 °C oil bath and refluxed for 1 h. The reaction mixture was cooled to 0 °C. The yellow solid was collected by vacuum filtration and washed with ether to give **12** as a white solid: yield 0.723 g (80%); ^{1}H NMR (DMSO-d_6 with TMS) δ 9.00 (b, 1H), 4.54−4.48 (dd, 1H J = 7.35, 9.56 Hz), 3.98−3.79 (m, 2H), 2.75−2.62 (m, 1H), 2.36−2.27 (m, 2H), 1.97−1.82 (m, 1H); ^{13}C NMR (DMSO-d_6 with TMS) δ 173.6, 170.0, 168.2, 59.8, 40.4, 34.0, 24.1.

Propylpyroglutamylglycinamide (13). To a 25 mL round-bottom flask were added 1,4-diaazbicyclo[4,3,0]nonane-2,5,9-trione (**12**) (0.106 g, 0.0006 mol), $CHCl_3$ (3 mL), and a magnetic stir bar. Propylamine (0.078 g, 0.0013 mol) was added, and the reaction mixture was stirred for 30 min. The solvent was removed in vacuo to give **13** as a viscous oil: yield 0.138 g (97%); ^{1}H NMR (DMSO-d_6 with TMS) δ 8.16 (s, 1H), 7.80 (s, 2H), 4.08−4.03 (m, 1H), 3.67 (m, 2H), 3.02 (q, 2H), 2.29−2.06 (m, 3H), 1.95−1.87 (m, 1H), 1.39 (m, 2H), 0.83 (t, 3H); ^{13}C NMR (DMSO-d_6 with TMS) δ 177.48, 172.75, 168.43, 55.82, 42.01, 40.87, 29.29, 25.94, 22.41, 11.28.

Glutamic Diketopiperazine (14). To a 100 mL round-bottom flask were added pyroglutamic diketopiperazine (2.015 g, 0.0091 mol), ice-cold H_2SO_4, and a magnetic stir bar. The reaction mixture was stirred until the DKP dissolved. The flask was cooled in an ice bath and distilled H_2O (50 mL) added. The resulting precipitate was collected by filtration and dried to give **14**. Additional product precipitated from the filtrate and was collected and combined with the first batch: yield 1.77 g (76%); mp 245 °C dec; ^{1}H NMR (DMSO-d_6 with TMS) δ 12.13 ppm (s, 2H), 8.18 (s, 2H), 3.88 (dd, J = 6.62, 5.15 Hz, 2H), 2.40−2.23 (m, 4H), 2.01−1.80 (m, 4H); ^{13}C NMR (DMSO-d_6 with TMS) δ 173.9, 167.9, 53.3, 29.4, 28.2. Anal. Calcd for $C_{10}H_{14}N_2O_6$: C, 46.51; H, 5.46; N, 10.85. Found: C, 46.54; H, 5.54; N, 10.73.

Glutamic Diketopiperazine Dimethyl Ester (15a). To a 250 mL round-bottom flask were added pyroglutamic diketopiperazine (7.00 g, 0.0315 mol), benzene (100 mL), methanol (5.54 g, 0.1733 mol), sulfuric acid (10 drops), and a magnetic stir bar. The reaction mixture was refluxed for 4 h until the DKP dissolved. The reaction flask was cooled and the solvent removed in vacuo. The resulting white solid was recrystallized from methanol to give **15a**: yield 3.154 g (35%); mp 185−187 °C; ^{1}H NMR (DMSO-d_6 with TMS) δ 8.22 (s, 2H), 3.89 (dd, J = 5.89, 6.62 Hz, 2H), 3.59 (s, 6H), 2.44−2.37 (m, 4H), 2.05−1.84 (m, 4H); ^{13}C NMR (DMSO-d_6 with TMS) δ 172.8, 167.8, 53.1, 51.4, 29.1, 28.0. Anal. Calcd for $C_{12}H_{18}N_2O_6$: C, 50.35; H, 6.34; N, 9.79. Found: C, 50.25; H, 6.48; N, 9.70.

Glutamic Diketopiperazine Diethyl Ester (15b). To a 100 mL round-bottom flask were added pyroglutamic diketopiperazine (2.023 g, 0.0091 mol), benzene (40 mL), ethanol (2.303 g, 0.0500 mol), sulfuric acid (five drops), and a magnetic stir bar. The reaction mixture was refluxed for 6 h until the DKP dissolved. The reaction flask was cooled and the solvent removed in vacuo. The resulting white solid was recrystallized from ethanol to give **15b**: yield 0.672 g (23.5%); mp 166−169 °C; ^{1}H NMR (DMSO-d_6 with TMS) δ 8.19 (s, 2H), 4.05 (q, 4H), 3.88 (dd, J = 5.15, 6.62 Hz, 2H), 2.41−2.35 (m, 4H), 2.04−1.83 (m, 4H), 1.18 (t, J = 7.35 Hz, 6H); ^{13}C NMR (DMSO-d_6 with TMS) δ 172.3, 167.7, 59.9, 53.1, 29.3, 28.0, 14.1. Anal. Calcd for $C_{14}H_{22}N_2O_6$: C, 53.49; H, 7.05; N, 8.91. Found: C, 53.49; H, 7.12; N, 8.85.

Glutamic Diketopiperazine Dipropyl Ester (15c). To a 100 mL round-bottom flask were added pyroglutamic diketopiperazine (2.025 g, 0.0091 mol), benzene (40 mL), propanol (3.07 g, 0.0501 mol), sulfuric acid (5 drops), and a magnetic stir bar. The reaction mixture was refluxed for six h until the DKP dissolved. The reaction flask was cooled and the solvent removed in vacuo. The resulting white solid was recrystallized from ethanol to give **15c**: yield 0.593 g (19%); mp 149−152 °C; ^{1}H NMR (DMSO-d_6 with TMS) δ 8.20 (s, 2H), 3.96 (t, J = 6.62 Hz, 4H), 3.89 (m, 2H), 2.43−2.36 (m, 4H), 2.04−1.85 (m, 4H), 1.64−1.52 (m, 4H), 0.88 (t, J = 7.35 Hz, 6H); ^{13}C NMR (DMSO-d_6 with TMS) δ 172.4, 167.8, 62.5, 53.2, 29.3, 28.1, 21.5, 10.3. Anal. Calcd for $C_{16}H_{26}N_2O_6$: C, 56.13; H, 7.65; N, 8.18. Found: C, 55.84; H, 7.59; N, 8.27.

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Supporting Information Available: Complete X-ray cyrstallographic data for **3** and ^{1}H and ^{13}C NMR of **3**, **4a**,**c**,**e**, **5a**,**c**−**g**, a mixture of **5f** and **5g**, **6**, **13**, and **15c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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