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1,2-Cyclic Sulfamidates as Versatile Precursors to Thiomorpholines and Piperazines

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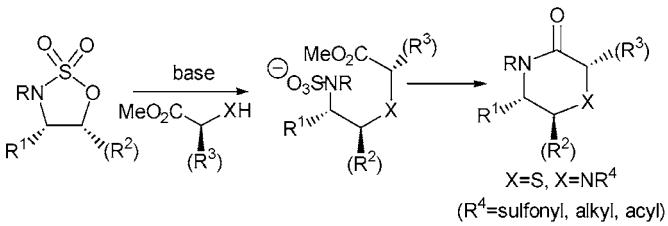
ABSTRACT

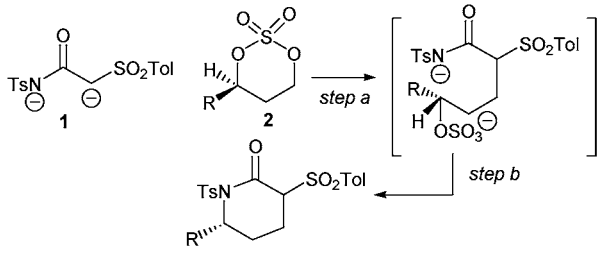


1,2-Cyclic sulfamidates undergo regiospecific nucleophilic displacement with either methyl thioglycolate or α-amino esters, followed by lactamization (thermal, base-mediated, or cyanide-catalyzed), to give thiomorpholin-3-ones and piperazin-2-ones.

Cyclic sulfates and cyclic sulfamidates represent a versatile class of functionalized and enantiomerically pure electrophiles. As a result, these reactive alkylating agents are finding increasing synthetic applications across a range of areas.[1]

We previously reported the use of 1,3-cyclic sulfates as components of a [3 + 3] annulation approach to piperidines.[2] *C,N*-Bis nucleophiles, e.g., enolate **1**, enable a stepwise, double displacement of a cyclic 1,3-cyclic sulfate **2** to be achieved in a regio- and stereocontrolled manner, providing functionalized piperidines (Scheme 1).

Scheme 1. Functionalized Piperidines via 1,3-Cyclic Sulfates



However, there are issues with the second (intramolecular) displacement (step b, Scheme 1), such as the ease of reaction and the degree of enantiospecificity observed.[3]

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(1) Byun, H.-S.; He, L.; Bittman, R. *Tetrahedron* **2000**, *56*, 7051−7091. Lohray, B. B.; Bhushan, V. *Adv. Heterocycl. Chem.* **1997**, *68*, 89−180. For recent methods of synthesis of cyclic sulfamidates, see: Lowe, G.; Reed, M. A. *Tetrahedron: Asymmetry* **1990**, *1*, 885−894. Espino, C. G.; Wehn, P. M.; Chow, J.; Du Bois, J. *J. Am. Chem. Soc.* **2001**, *123*, 6935−6936. Nicolaou, K. C.; Huang, X.; Snyder, S. A.; Rao, P. B.; Bella, M.; Reddy, M. V. *Angew. Chem., Int. Ed.* **2002**, *41*, 834−838. Posakony, J. J.; Grierson, J. R.; Tewson, T. J. *J. Org. Chem.* **2002**, *67*, 5164−5169. Duran, F.; Leman, L.; Ghini, A.; Burton, G.; Dauban, P.; Dodd, R. H. *Org. Lett.* **2002**, *4*, 2481−2483.

(2) Littler, B. J.; Gallagher, T.; Boddy, I. K.; Riordan, P. D. *Synlett* **1997**, 22−26. Eskici, M.; Gallagher, T. *Synlett* **2000**, 1360−1362.

(3) Step b (Scheme 1) can be achieved by direct thermal displacement of a secondary *O*-sulfate, or by hydrolysis and subsequent Mitsunobu reaction. Thermal cyclization did lead to some loss of stereochemical integrity (up to 10% ee), the extent of which depended on the substrate involved. The chemistry in Scheme 1 has also been applied to the synthesis of substituted pyrrolidines using enolate **1** and enantiomerically pure 1,2-cyclic sulfates.

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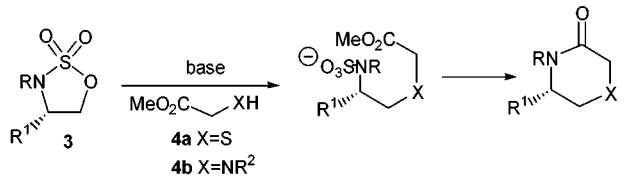
1,2-Cyclic sulfamidates **3**[4] provide an attractive alternative entry to *N*-heterocycles by allowing the key C−N bond stereochemistry to be defined at the outset and retained. Our approach is outlined in Scheme 2, using **4** as the other

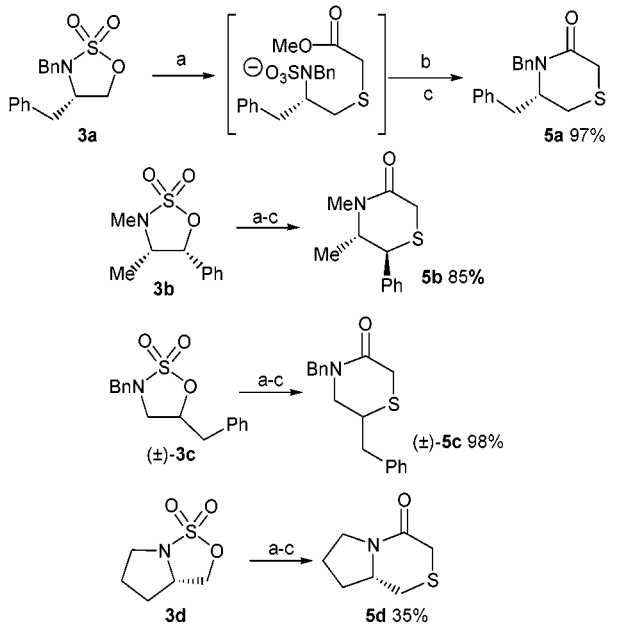
Scheme 2



component, where a heteroatom nucleophile is adjacent to an acetate moiety. This combination would allow a regioselective nucleophilic displacement to occur on **3** (C−O bond cleavage always being favored over C−N bond cleavage), followed by lactamization (involving the adjacent acetate fragment) to give a six-ring *N*-heterocycle.

This chemistry has been explored using both methyl thioglycolate **4a** and a range of α-amino esters (cf **4b**), which leads to thiomorpholine and piperazine derivatives, respectively. The synthesis of thiomorpholin-3-ones **5** is outlined in Scheme 3.[5] Base-mediated reaction of methyl thioglycolate **4a** with cyclic sulfamidate **3a**[6] gave the thiomorpholin-3-one **5a** in 97% yield. The optimized procedure used either $NaHCO_3$ or Cs_2CO_3 as a base, and after initial nucleophilic

Scheme 3. Synthesis of Substituted Thiomorpholin-3-ones[a]



[a] Reagents and conditions: (a) $NaHCO_3$, 1:1 THF/H_2O or Cs_2CO_3, THF; (b) 5 M HCl, rt, then $NaHCO_3$; (c) PhMe, reflux, 3 h.

displacement, acidic hydrolysis (of the intermediate *N*-sulfate) was followed by neutralization and thermolysis to achieve lactamization.

Similarly, the ephedrine-derived sulfamidate **3b**[7] gave the trans 5,6-disubstituted thiomorpholin-3-one **5b**[8] in 85% yield, the structure of which was confirmed by X-ray crystallographic analysis (Figure 1). We were also interested in the ability of a 3-substituted cyclic sulfamidate **3c** (the regioisomer of **3a**) to participate in this process. In the event, the

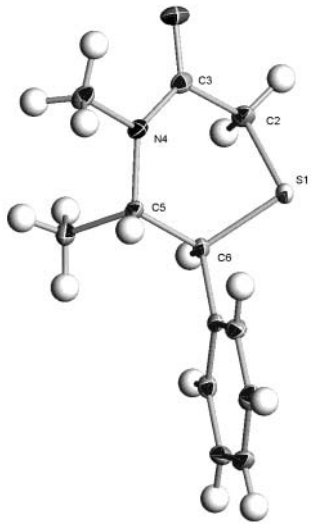


Figure 1. Structure of **5b**.

(4) For general nucleophilic displacements of 1,2- and 1,3-cyclic sulfamidates, see: (a) Meunier, N.; Veith, U.; Jäger, V. *Chem. Commun.* **1996**, 331−332. (b) Pound, M. K.; Davies, D. L.; Pilkington, M.; Sousa, M.; Wallis, J. D. *Tetrahedron Lett.* **2002**, *43*, 1915−1918. Synthesis of fluoroamines: (c) Posakony, J. J.; Tewson, T. J. *Synthesis* **2002**, 766−770. (d) Posakony, J. J.; Tewson, T. J. *Synthesis* **2002**, 859−864. (e) Ok, D.; Fisher, M. H.; Wyvratt, M. J.; Meinke, P. T. *Tetrahedron Lett.* **1999**, *40*, 3831−3834. (f) Lyle, T. A.; Magill, C. A.; Pitzenberger, S. M. *J. Am. Chem. Soc.* **1987**, *109*, 7890−7891. (g) Thompson, W. J.; Anderson, P. S.; Britcher, S. F.; Lyle, T. A.; Thies, J. E.; Magill, C. A.; Varga, S. L.; Schwering, J. E.; Lyle, P. A.; Christy, M. E.; Evans, B. E.; Colton, C. D.; Holloway, M. K.; Springer, J. P.; Hirshfield, J. M.; Ball, R. G.; Amato, J. S.; Larsen, R. D.; Wong, E. H. F.; Kemp, J. A.; Tricklebank, M. D.; Singh, L.; Oles, R.; Priestly, T.; Marshall, G. R.; Knight, A. R.; Middlemiss, D. N.; Woodruff, G. N.; Iversen, L. L. *J. Med. Chem.* **1990**, *33*, 789−808. (h) Van Dort, M. E.; Jung, Y.-W.; Sherman, P. S.; Kilbourn, M. R.; Wieland, D. M. *J. Med. Chem.* **1995**, *38*, 810−815. Synthesis of chiral ether ligands: (i) Okuda, M.; Tomioka, K. *Tetrahedron Lett.* **1994**, *35*, 4585−4586. In manipulating carbohydrates: (j) Aguilera, B.; Fernández-Mayoralas, A. *Chem. Commun.* **1996**, 127−128. (k) Aguilera, B.; Fernández-Mayoralas, A.; Jaramillo, C. *Tetrahedron* **1997**, *53*, 5863−5876. (l) Aguilera, B.; Fernandez-Mayoralas, A. *J. Org. Chem.* **1998**, *63*, 2719−2723. Manipulation of α-amino acids, including serine derivatives: (m) Baldwin, J. E.; Spivey, A. C.; Schofield, C. J. *Tetrahedron: Asymmetry* **1990**, *1*, 881−884. (n) Boulton, L. T.; Stock, H. T.; Raphy, J.; Horwell, D. C. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1421−1429. (o) Wei, L.; Lubell, W. D. *Org. Lett.* **2000**, *2*, 2595−2598. (p) Wei, L.; Lubell, W. D. *Can. J. Chem.* **2001**, *79*, 94−104. (q) Atfani, M.; Wei, L.; Lubell, W. D. *Org. Lett.* **2001**, *3*, 2965−2968. (r) Cohen, S. B.; Halcomb, R. L. *Org. Lett.* **2001**, *3*, 405−407. (s) Cohen, S. B.; Halcomb, R. L. *J. Am. Chem. Soc.* **2002**, *124*, 2534−2543. Synthesis of 2-substituted pyrrolidines: (t) Cooper, G. F.; McCarthy, K. E.; Martin, M. G. *Tetrahedron Lett.* **1992**, *33*, 5895−5896.

(5) Thiomorpholin-3-ones, including **5d**, have also been prepared efficiently by reaction of oxazolinidin-2-ones with ethyl thioglycolate. Ishibashi, H.; Uegaki, M.; Sakai, M. *Synlett* **1997**, 915−916. Ishibashi, H.; Uegaki, M.; Sakai, M.; Takeda, Y. *Tetrahedron* **2001**, *57*, 2115−2120.

(6) Sulfamidate **3a** was prepared from the corresponding (*S*)-amino alcohol using a modification[4q] of the procedure reported by Garst (White, G. J.; Garst, M. E. *J. Org. Chem.* **1991**, *56*, 3177−3178).

racemic 6-substituted thiomorpholin-3-one **5c**, which is the regioisomer of **5a**, was isolated in excellent yield.

The method is also applicable to bicyclic sulfamidates, such as **3d**, which provided the corresponding bicyclic thiomorpholinone **5d** in 35% yield. The synthesis of **5d** was problematic because hydrolysis of the initially formed *N*-sulfate was very slow under our standard reaction conditions, and extended reactions times may have contributed to the lower yield observed in this case.

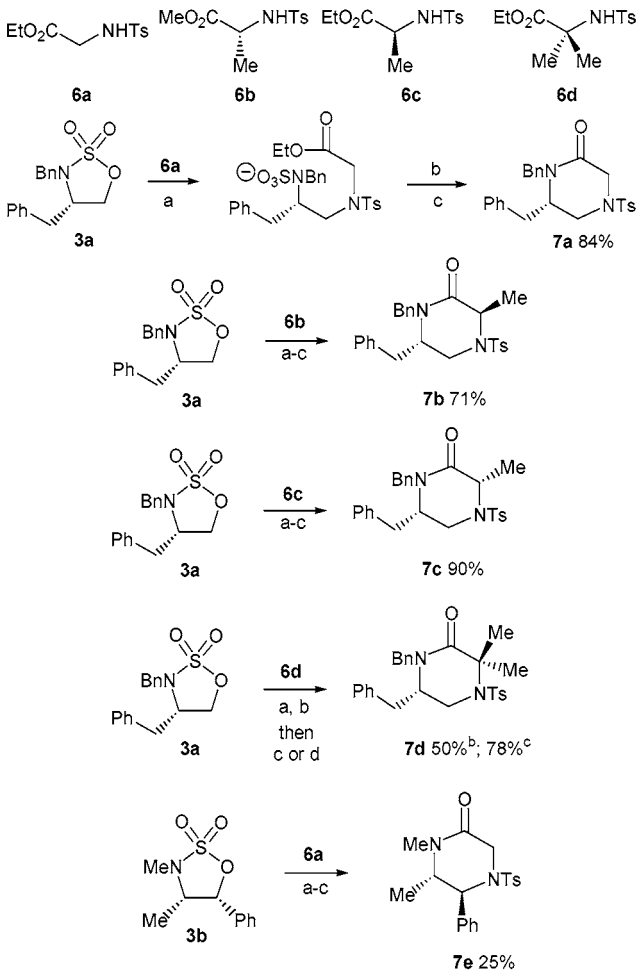
α-Amino esters are also reactive toward 1,2-cyclic sulfamidates, and this provides a flexible entry to piperazine derivatives[9] (Scheme 4). Use of the (*S*)-phenylalanine-derived 1,2-sulfamidate **3a** as a prototype in reaction with *N*-tosyl glycine ethyl ester **6a** gave the differentially protected piperazin-2-one **7a** in 84% yield.

It was important to validate the ability of a base-sensitive stereocenter to withstand the conditions used in this chemistry. This was established using amino esters **6b** and **6c** derived from (*R*)- and (*S*)-alanine, respectively. Reaction of each amino ester with **3a** gave the corresponding *trans*- and *cis*-3,6-disubstituted piperazin-2-ones **7b** and **7c**, respectively. In neither case was the other diastereomer detected, thus demonstrating the stability of these epimerizable substrates to the particular conditions used (however, see below).

A more hindered variant, such as **6d**, gave piperazinone **7d**, and in this case, lactamization was successfully carried out under both thermal and base-mediated conditions in 50 and 78% yields, respectively. The ephedrine-derived sulfamidate **3b**, which now requires the amino ester to displace at a secondary center, did react with **6a** to give the 5,6-disubstituted piperazin-2-one **7e** in 25% yield.[10] While azide ion is known to react well with secondary cyclic sulfamidates, amine nucleophiles do require significantly more forcing conditions.[11]

An important issue associated with this approach to the synthesis of substituted piperazines became apparent with

Scheme 4. Synthesis of Substituted Piperazin-2-ones[a]



[a] Reagents and conditions: (a) NaH or Cs_2CO_3, DMF; (b) 5 M HCl, rt, then $NaHCO_3$; (c) PhMe, reflux, 18 h; (d) NaOEt, EtOH, reflux. [b]Yield using thermal lactamization. [c]Yield under base-mediated lactamization conditions.

(*S*)-proline ethyl ester **6e** and ethyl (*S*)-pyroglutamate **6f**. Reaction of **3a** with **6e** gave, after hydrolysis, the initial adduct **8**. Thermal lactamization (xylene, reflux) was slow and very inefficient, but **7f** was isolated without epimerization at C(8a) being detected. More rapid (and essentially quantitative) lactamization of **8** was achieved using NaOMe (in MeOH); however, under these conditions, **7f** was obtained as a 1:1 mixture of diastereomers, epimeric at C(8a) (Scheme 5).

These problems (slow lactamization vs facile epimerization) were overcome by using catalytic sodium cyanide[12] to promote the final ring-closure step (of **8**), which gave **7f** as a single diastereomer in 50% yield.

Analogous problems were encountered when ethyl (*S*)-pyroglutamate **6f** was employed and were also solved using catalytic cyanide to achieve lactamization, and under these

(7) Sulfamidates **3b**,[4h] **3c**, and **3d** were prepared from the corresponding amino alcohols using essentially the same procedures as those used for **3a**. In the case of **3c**, racemic amino alcohol was used.

(8) The cis and trans morpholine analogues of **5b** are known (Spassov, S. L.; Stefanovsky, J. N.; Kurtev B. J.; Fodor, G. *Chem. Ber.* **1972**, *105*, 2467−2475), but the coupling constants associated with H(5) and H(6) that were reported did not correlate well to those observed for **5b**. For this reason, the relative configuration of **5b** was established by X-ray crystallographic analysis.

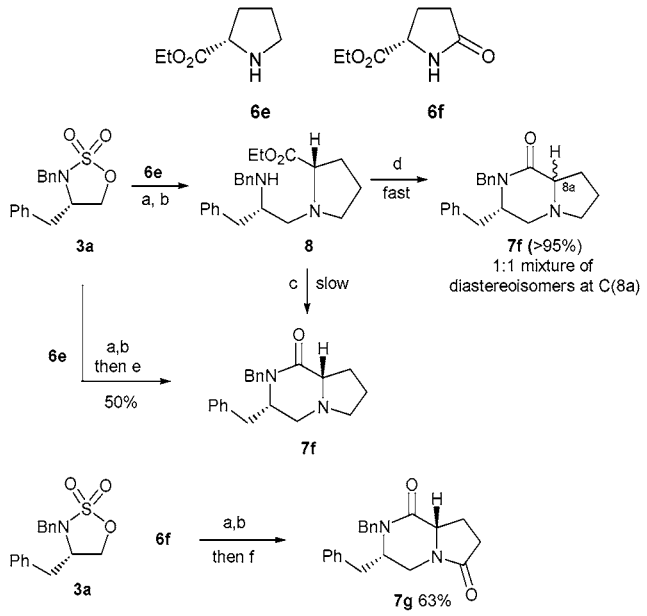
(9) For the synthesis of C-substituted piperazines and piperazinones, see: Jung, M. E.; Rohloff, J. C. *J. Org. Chem.* **1985**, *50*, 4909−4913. Shono, T.; Kise, N.; Shirakawa, E.; Matsumoto, H.; Okazaki, E. *J. Org. Chem.* **1991**, *56*, 3063−3067. Schanen, V.; Riche, C.; Chiaroni, A.; Quirion, J.-C.; Husson, H.-P. *Tetrahedron Lett.* **1994**, *35*, 2533−2536. Mickelson, J. W.; Belonga, K. L.; Jacobsen, E. J. *J. Org. Chem.* **1995**, *60*, 4177−4183. Schanen, V.; Cherrier, M. P.; de Melo, S. J.; Quirion, J.-C.; Husson, H.-P. *Synthesis* **1996**, 833−837. Nefzi, A.; Giulianotti, M. A.; Houghten, R. A. *Tetrahedron Lett.* **1999**, *40*, 8539−8542. Dinsmore, C. J.; Zartman, C. B. *Tetrahedron Lett.* **2000**, *41*, 6309−6312. Rubsam, F.; Mazitschek, R.; Giannis, A. *Tetrahedron* **2000**, *56*, 8481−8487. González-Gómez, J. C.; Uriarte-Villares, E.; Figueroa-Pérez, S. *Synlett* **2002**, 1085−1088. Viso, A.; de la Pradilla, R. F.; López-Rodríguez, M. L.; García, A.; Tortosa, M. *Synlett* **2002**, 755−758. Beshore, D. C.; Dinsmore, C. J. *Org. Lett.* **2002**, *4*, 1201−1204.

(10) The stereochemistry of **7e** is based on comparison with **5b**, the structure of which was unambiguously assigned (see Figure 1).

(11) Azide displacement: Li, G.; Chang, H. T.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 451−454. Amine nucleophiles require 125 °C in a steel bomb: Zubovics, Z.; Toldy, L.; Varro, A.; Rabloczky, G.; Kurthy, M.; Dvortsak, P.; Jerkovich, G.; Tomori, E. *Eur. J. Med. Chem.* **1986**, *21*, 370−378.

(12) Mori, K.; Tominaga, M.; Takigawa, T.; Matsui, M. *Synthesis* **1973**, 790−791. Högberg, T.; Ström, P.; Ebner, M.; Rämsby, S. *J. Org. Chem.* **1987**, *52*, 2033−2036.

Scheme 5. Synthesis of Bicyclic Piperazinones. Base vs Thermal vs Cyanide-Mediated Lactamization[a]



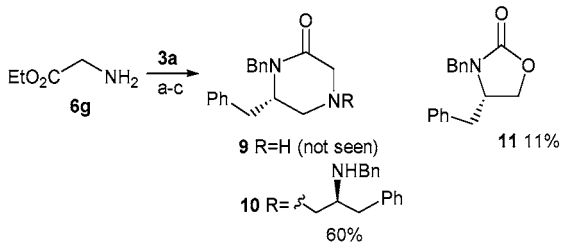
[a] Reagents and conditions: (a) NaH, DMF, rt; (b) 5 M HCl, rt, then $NaHCO_3$; (c) xylene, reflux, >24 h (<10%); (d) NaOMe, MeOH; (e) NaCN (5−10 mol %), MeOH, reflux; (f) NaCN (5−10 mol %), EtOH, 50 °C.

conditions, the bicyclic adduct **7g** was isolated as a single diastereomer in 63% overall yield.[13]

The use of primary amino ester **6g** failed to react with **3a** to give the desired piperazine product **9**. In this case, a facile double N-alkylation of **6g** occurred, which could not be suppressed. This led to the 2:1 adduct **10** in 60% yield (based on **3a**) (Scheme 6). In this case, formation of oxazolidinone **11** (11%) was observed, which arises from the use of $NaHCO_3$.[14]

(13) In the case of **7f**, NaCN in MeOH at reflux was more efficient than use of EtOH at 50 °C. Formation of **7g** via thermal lactamization (xylene, 5 days, reflux) proceeded in 48% yield, and no stereochemical scrambling at C(8a) was observed. Piperazine **7g** was also isolated in 50% yield using NaCN (10 mol %) in MeOH at reflux. Cyanide may mediate lactamization via transesterification when MeOH is used as a solvent, but **7g** was formed efficiently using EtOH as a solvent.

Scheme 6. Use of Primary Amino Ester Nucleophiles[a]



[a] Reagents and conditions: (a) DIPEA, EtOH, rt; (b) 5 M HCl, rt, then $NaHCO_3$.

In summary, 1,2-cyclic sulfamidates, which are easily prepared from the corresponding 1,2-amino alcohols, provide a flexible and generally efficient entry to a range of *N*-heterocycles based on thiomorpholines and piperazines, the scope of which is reflected by the range of sulfamidates used. It is important to appreciate the advantages that 1,2-cyclic sulfamidates offer over related electrophiles such as aziridines. Sulfamidates readily undergo a regiospecific displacement (compare **3a** and **3c**, Scheme 3), and application of this chemistry to provide other classes of *N*-heterocycles is currently underway.

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Supporting Information Available: Experimental details and characterization data for all new compounds, including crystallographic details for **5b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) This is a known process,[4c] but attempts to prevent production of **11** (a major byproduct under our standard conditions) using NaOH led to low mass recovery. Also, lactamization to give **10** occurred directly following neutralization.