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# Modular Synthesis of Cyclic Peptidomimetics Inspired by γ-Turns†

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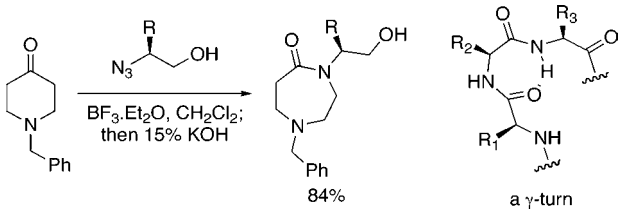
## ABSTRACT

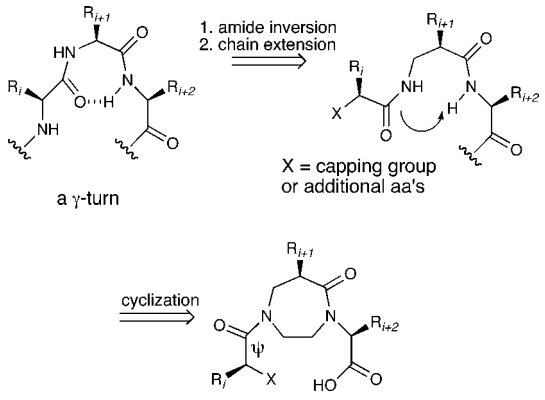



**A series of peptidomimetics based on a γ-turn motif were synthesized using a modular approach, in which N-protected piperidones were reacted with a selection of 2-hydroxyalkyl azides derived from common L-amino acids. Hydrolysis of the initially formed iminium ethers afforded the targeted series of substituted 1,4-diazepin-5-ones.**

The peptidomimetic concept continues to inspire medicinal chemists seeking potential drug leads or pharmacological tools.[1] One valuable approach is to synthesize heterocycles devised to resemble common features of peptide secondary structures. Although this strategy has been dominated by the multitudinous approaches to β-turn mimicry,[2] there has been a steady undercurrent of work directed toward γ-turns as well.[3]

A γ-turn features a hydrogen bond between the carbonyl of a residue *i* with the amide proton of residue *i* + 2 (Scheme 1). We wanted to synthesize mimics based on a simple, readily synthesized heterocycle that would accommodate side

**Scheme 1**




† Dedicated to the memory of Professor Murray Goodman, who epitomized the phrase "a scholar and a gentleman".

(1) (a) Goodman, M.; Chorev, M. *Acc. Chem. Res.* **1979**, *12*, 1−7. (b) Huffman, W. F.; Callahan, J. F.; Eggleston, D. S.; Newlander, K. A.; Takata, D. T.; Codd, E. E.; Walker, R. F.; Schiller, P. W.; Lemieux, C.; Wire, W. S.; Burks, T. F. In *Peptides, Chemistry and Biology, Proceedings of the 10th Annual American Peptide Symposium*; Marshall, G. R., Ed.; ESCOM: Leiden, 1988; pp 105−108. (c) Giannis, A.; Kolter, T. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1244−1267. (d) Marshall, G. R. *Tetrahedron* **1993**, *49*, 3547−3558. (e) Olson, G. L.; Bolin, D. R.; Bonner, M. P.; Bös, M.; Cook, C. M.; Fry, D. C.; Graves, B. J.; Hatada, M.; Hill, D. E.; Kahn, M.; Madison, V. S.; Rusiecki, V. K.; Sarabu, R.; Sepinwall, J.; Vincent, G. P.; Voss, M. E. *J. Med. Chem.* **1993**, *36*, 3039−3049. (f) Aubé, J. In *Advances in Amino Acid Mimetics and Peptidomimetics*; Abell, A., Ed.; JAI Press: Greenwich, CT, 1997; Vol. 1, pp 193−232. (g) Hanessian, S.; McNaughton-Smith, G.; Lombart, H.-G.; Lubell, W. D. *Tetrahedron* **1997**, *53*, 12789−12854. (h) MacDonald, M.; Aubé, J. *Curr. Org. Chem* **2001**, *5*, 417−438.

(2) For leading reviews on β-turns and their mimics, see: Rose, G. D.; Gierasch, L. M.; Smith, J. A. In *Advances in Protein Chemistry*; Anfinsen, C. B., Edsall, J. T., Richards, F. M., Eds.; Academic: Orlando, 1985; Vol. 37, pp 1−109. See also ref 1 above.

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chains corresponding to residues *i* through *i* + 2 at readily modified positions.

The natural amino acid sequence was morphed into a heterocyclic platform by first changing the directionality of an amide bond and adding a methylene group into the backbone.[4] Conformational restriction was then carried out by cyclization into a seven-membered ring. The resulting 1,4-diazepin-5-one ring system was attractive because it readily accommodated potential side chains/points of diversity α to the carbonyl group, on the lactam nitrogen, and in the guise of an amino acid attached to N-1. In the last case, flexibility of the $\psi$ bond of the amino acid permits the side chain to act as a credible mimic of the parent *i* substituent. Ab initio calculations of the proposed turn analogues showed reasonable overlap of the side chains with those of a standard $\gamma$-turn (see Figure 1).

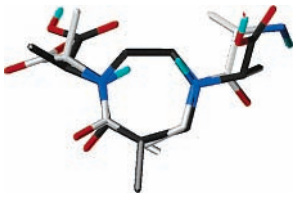
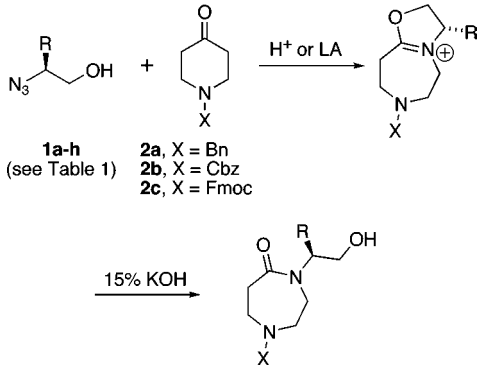


**Figure 1.** Overlay of an idealized $\gamma$-turn (grey) with the proposed mimetic (black), both containing alanine side chains.

Another goal was for the proposed turns to be synthesized in a modular manner. Recent work in these laboratories has established that the Lewis acid-promoted reaction of a ketone with a hydroxyalkyl azide permits a ring-expansive route to lactams.[5] To apply this reaction to the present problem, a sublibrary of hydroxyalkyl azides with side chains corresponding to naturally occurring amino acids **1** were reacted with N-protected piperidones **2** (Scheme 2). The reaction

**Scheme 2**




proceeds by hemiketal formation followed by azide insertion into the heterocycle, affording iminium ethers as the primary product.[5a,c] Hydrolysis of the latter species was expected to form the desired 1,4-diazepin-5-ones. The advantage of this technique is that it permits ready incorporation of enantiomerically pure, prefabricated amino acid equivalents into existing ketones. Herein, we demonstrate the concept using the parent piperidone system. We have previously shown that the ring expansion reaction readily accommodates substituted carbocyclic ketones, which bodes well for systems wherein $R_{i+1} \neq H$.[5e]

The desired hydroxyalkyl azides were made from the corresponding amino acids by reduction and conversion of the α-amino group to an azide. When necessary, appropriate protecting groups were incorporated into the products. The amino acids were reduced using TMSCl/$NaBH_4$ and the resulting amino alcohols converted to the corresponding azides via treatment with $TfN_3$.[6] In this way, a variety of azides derived from various amino alcohols were obtained. Note that **1h** was prepared by direct azidation of serine benzyl ester, resulting in an azidoalkyl alcohol having the opposite absolute configuration relative to the rest of the series (Table 1).

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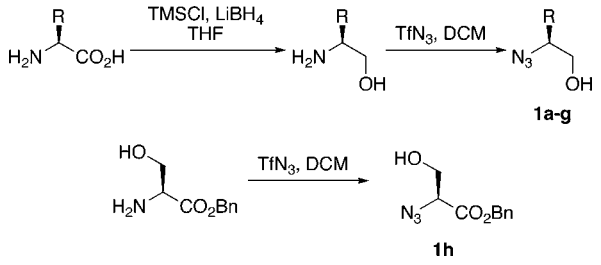
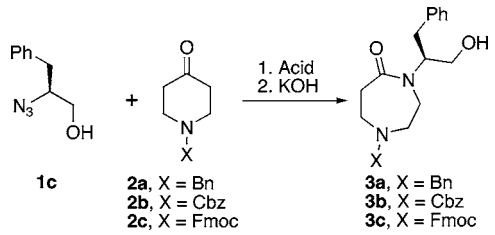
**Table 1.** Synthesis of Hydroxyalkyl Azides




| entry | starting amino acid | R | azido alcohol | overall yield (%) |
|---|---|---|---|---|
| 1 | valine | $-CHMe_2$ | **1a** | 90 |
| 2 | leucine | $-CH_2CHMe_2$ | **1b** | 86 |
| 3 | phenylalanine | $-CH_2Ph$ | **1c** | 93 |
| 4 | *O*-benzyl tyrosine | $-CH_2C_6H_4OBn$ | **1d** | 87 |
| 5 | *N*−Cbz ornithine | $-(CH_2)_3NHCbz$ | **1e** | 71 |
| 6 | *N*−Cbz lysine | $-(CH_2)_4NHCbz$ | **1f** | 93 |
| 7 | methionine | $-(CH_2)_2SMe$ | **1g** | 82 |
| 8 | serine benzyl ester | $-CH_2CO_2Bn$ | **1h** | 90 |

Hydroxyalkyl azide **1c** derived from phenylalanine was reacted with a series of differently N-protected piperidones to determine which protecting groups were compatible with the two-stage sequence involving both acidic and basic conditions. The results, shown in Table 2, indicate that the

**Table 2.** Reactions of **1c** with Piperidinones **2a**−**c**

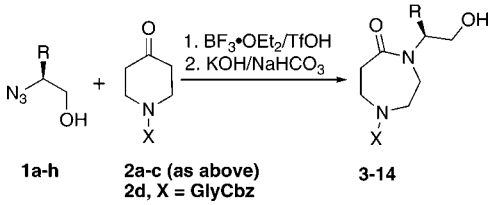



| entry | ketone | acid | yield (%) |
|---|---|---|---|
| 1 | **2a** | $BF_3{\cdot}OEt_2$ | 52 |
| 2 | **2a** | TfOH | 84 |
| 3 | **2b** | $BF_3{\cdot}OEt_2$ | 46 |
| 4 | **2b** | TfOH | 51 |
| 5 | **2c** | $BF_3{\cdot}OEt_2$ | 74 |
| 6 | **2c** | TfOH | 55 |

transformation is compatible with two of the most important nitrogen protecting groups in peptide chemistry as well as an *N*-benzyl substituent, which is useful for other synthetic applications and incidentally serves as a useful model for some kinds of solid-phase attachments. The success of the reaction with a heterocycle containing a basic nitrogen atom was not assured at the outset given that such groups have been problematic with other kinds of acid-promoted azido-Schmidt reactions.[7] It was useful to note that different acidic conditions, needed to enact the initial ring expansion, were more compatible with particular functional groups.

Functional group compatibility was tested by carrying out reactions with several of the piperidinones as depicted in Table 3. In general, excellent yields of products could be

**Table 3.** Syntheses of Substituted 1,4-Diazepin-5-ones

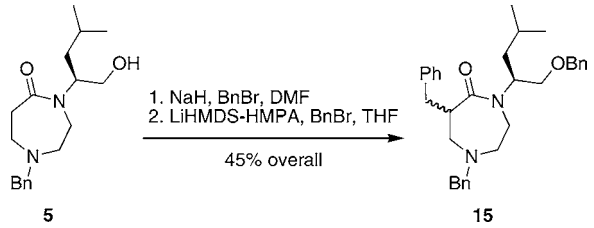



| entry | azide | R | X | lactam | yield (%) |
|---|---|---|---|---|---|
| 1 | **1a** | $-CHMe_2$ | Bn | **4** | 89 |
| 2 | **1b** | $-CH_2CHMe_2$ | Bn | **5** | 87 |
| 3 | **1d** | $-CH_2C_6H_4OBn$ | Bn | **6** | 63 |
| 4 | **1e** | $-(CH_2)_3NHCbz$ | Bn | **7** | 84 |
| 5 | **1f** | $-(CH_2)_4NHCbz$ | Bn | **8** | 88 |
| 6 | **1g** | $-(CH_2)_2SMe$ | Bn | **9** | 55 |
| 7 | **1h** | $-CO_2Bn$ | Bn | **10** | 62 |
| 8 | **1a** | $-CHMe_2$ | Fmoc | **11** | 63 |
| 9 | **1b** | $-CH_2CHMe_2$ | Fmoc | **12** | 68 |
| 10 | **1b** | $-CH_2CHMe_2$ | Cbz | **13** | 52 |
| 11 | **1b** | $-CH_2CHMe$ | GlyCbz | **14** | 79 |

obtained in this way. Moreover, lactams containing both hydrophobic side chains as well as those with basic groups (in protected form) were readily prepared.

Two other synthetic issues were preliminarily investigated in this work. The direct alkylation of lactam **5** afforded a dibenzylated derivative that could be converted to give **15** as a mixture of stereoisomers (Scheme 3). For some

**Scheme 3**

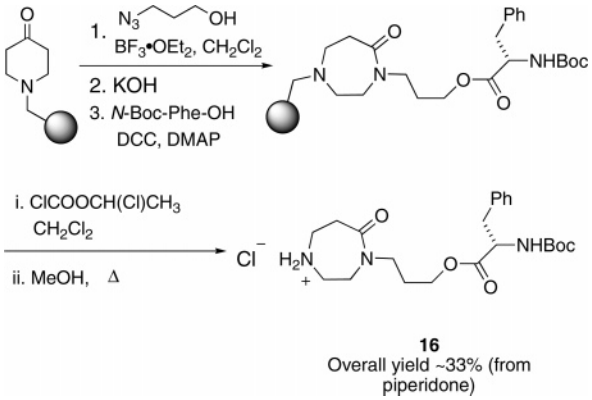



applications, this allows entry into a series of mimics in which the $i + 1$ residue corresponds to something other than glycine (here, phenylalanine). More advanced applications will entail carrying out the ring expansion reaction on a series of piperidones containing previously installed substitution.

Finally, the applicability of this chemistry to solid-state synthesis was briefly investigated (Scheme 4). Thus, piperidone itself was attached to Merrifield resin by normal means and subjected to the ring-expansion protocol using 3-azidopropanol.[5a,c] Extension into the "C-terminal" direction

(7) Wendt, J. A.; Aubé, J. *Tetrahedron Lett.* **1996**, *37*, 1531−1534.

**Scheme 4**




**16**
Overall yield ~33% (from piperidone)

was accomplished by esterification with *N*-Boc phenylalanine on the resin. Compound **16** was obtained in good yield (ca. 80%) by cleavage using a literature method.[8] This simple example suggests that it should be possible to optimize the overall peptidomimetic sequence in a solid-phase format and also provides one demonstration of the addition of further diversity to the central core.

Conformational analysis (Figure 1) suggests that these heterocycles should be good stand-ins for $\gamma$-turns. The main advantage of the approach is its inherently modular nature. In addition, it should be possible to diversify the products through manipulation of the scaffolds and to incorporate these subunits into growing peptide chains with minor modifications of the route presented (see especially entry 11, Table 3). Work in these directions, along with the eventual biological testing of compounds thus obtained, will be reported in future publications.

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

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