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Efficient, Stereoselective Synthesis of Oxazolo[3,2-*a*]pyrazin-5-ones: Novel Bicyclic Lactam Scaffolds from the Bicyclocondensation of 3-Aza-1,5-ketoacids and Amino Alcohols

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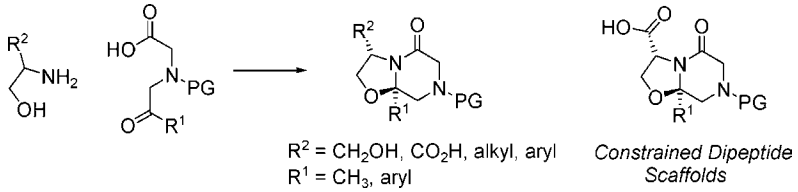
ABSTRACT



The bicyclocondensation of 3-aza-1,5-ketoacids and amino alcohols furnished novel oxazolo[3,2-*a*]pyrazin-5-one scaffolds possessing angular, ring junction substituents in high yield with excellent levels of substrate-based diastereocontrol. Mild oxidation of serinol-derived scaffolds provided access to a new class of constrained dipeptide surrogates. Deprotection of the endocyclic amine contained within these scaffolds allows for further diversification via *N*-functionalization.

The use of peptides as drugs has generally been compromised by several biological liabilities including poor permeability and absorption, rapid metabolism, high clearance, and low oral availability. This has led to the emergence of the field of peptidomimetics[1] in which peptide-like activity is preserved while circumventing many of the aforementioned liabilities through minimized rotational freedom, lower molecular weight, and incorporation of features that enhance selectivity and profit the biological profile.

Recently, amino acid motifs constrained within a bicyclo-[*X*,*Y*,0]lactam architecture have been applied to the design of modified peptides and peptidomimetics in an effort to discover new therapeutics and gain an improved understanding of the interactions of ligands with target enzymes and receptors.[2−6] These compounds have displayed structural variations with respect to ring size, degree of heteroatom incorporation, and relative stereochemical configuration (Figure 1).

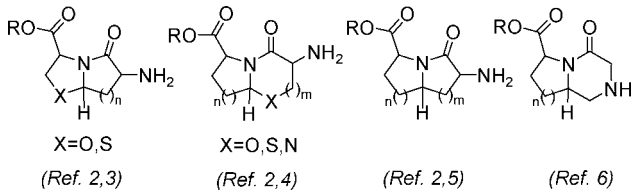


Figure 1. Constrained, bicyclic-lactam dipeptide scaffolds.

None of the syntheses for these scaffolds, however, have enabled either the installation of angular, ring-junction substituents or endo heteroatom incorporation within both rings

(1) For recent reviews see: (a) Hruby, V. J. *Nature Rev. Drug Discov.* **2002**, *1*, 847. (b) Ripka, A. S.; Rich, D. H. *Curr. Opin. Chem. Biol.* **1998**, *2*, 441. (c) Giannis, A.; Kolter, T. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1244.

(2) For a recent review see: Hanessian, S.; McNaughton-Smith, G.; Lombart H.-G.; Lubell, W. D. *Tetrahedron* **1997**, *53*, 12789.

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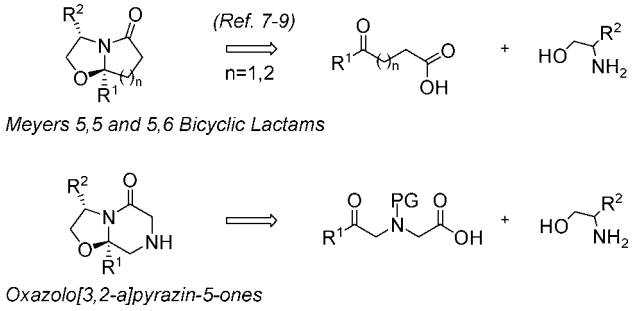
of the bicyclic system. These features were considered worthy of investigation from both a synthetic and a biological perspective in the discovery of new conformationally constrained, lactam-based amino acid scaffolds and peptidomimetics. Specifically, the introduction of these structural elements would provide additional sites of diversification enabling modulation for the probing of binding interactions (i.e. hydrophobic and donor−acceptor interactions) not possible in the structures of Figure 1. Furthermore, the development of a flexible synthetic route that yields a collection of lactam scaffolds bearing manipulatable functional handles would facilitate diversification via combinatorial methods, thus generating libraries of compounds based on the bicyclic lactam core structure. We disclose herein an efficient synthetic approach to oxazolo[3,2-*a*]pyrazin-5-ones, a novel class of bicyclic lactam scaffolds for which ring-junction substitution is accessed in a stereoselective fashion and an amine functional handle is poised for exploitation in rapid and diversity-oriented library synthesis.

It was quickly recognized that the cyclocondensation of amino alcohols and ketoacids developed by Meyers[7] could in theory be applicable to analogous 3-aza-1,5-keto acids (Scheme 1). Moreover, it was conceived that the rigid

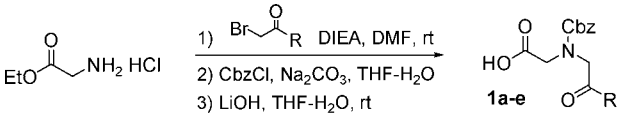
Scheme 1. Retrosynthetic Analysis

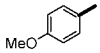
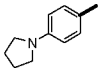


stereocontrol observed in the formation of Meyers' 5,5-bicyclic[8] lactams and specific 5,6 versions[9] might be preserved in the formation of our 5,6-aza bicyclic lactams. This route would allow rapid, convergent incorporation of diversity elements from both components of the cyclocondensation, and angular substitution would be installed at the previously unexplored ring junction.

Our efforts were initiated by developing a reliable route to the requisite 3-aza-1,5-ketoacids. We avoided a previously reported route[10] to these intermediates in favor of a novel, more direct approach that began with alkylation of ethyl glycinate with a variety of commercially available bromoacetophenones (Table 1). Under the developed conditions, products arising from dialkylation of ethyl glycinate were not observed. This is presumably the result of an inductive decrease in nucleophilicity of the product amine. Subsequent Cbz protection of the crude mono *N*-alkylated glycine esters under standard conditions followed by saponification furnished the desired 3-aza-1,5-ketoacids **1a**−**e** in 67−79% over 3 steps.

Table 1. Synthesis of *N*-Protected 3-Aza-1,5-ketoacids



entry	R	product	3-step yield (%)
1		**1a**	73
2		**1b**	67
3		**1c**	79
4		**1d**	70
5		**1e**	72

Anticipating strong acid lability of the bicyclic cyclocondensation products, the Cbz protecting group was chosen for its easy removal under nonacidic conditions.[11] In addition, Cbz-protected substrates were predicted to be both stable and soluble in the Meyers cyclocondensation conditions (refluxing toluene).[7]

To achieve substituent diversity beyond arenes, the corresponding methyl-substituted aza ketoacid was also synthesized. Optimal synthesis was achieved by alkylation of *N*-Cbz ethyl glycinate with methallyl bromide to give ester **2** (Scheme 2). Oxidative cleavage of the olefin under Johnson−Lemieux[12] conditions provided methyl ketone **3**, which upon ester hydrolysis gave the target ketoacid **1f** in good overall yield.

(3) (a) Gu, X.; Tang, X.; Cowell, S.; Ying, J.; Hruby, V. J. *Tetrahedron Lett.* **2002**, *43*, 6669. (b) Qiu, W.; Gu, X.; Soloshonok, V. A.; Carducci, M. D.; Hruby, V. J. *Tetrahedron Lett.* **2001**, *42*, 145. (c) Estiarte, M. A.; Rubiralta, M.; Diez, A.; Thormann, M.; Giralt, E. *J. Org. Chem.* **2000**, *65*, 6992.

(4) (a) Mizutani, N.; Chiou, W.-H.; Ojima, I. *Org. Lett.* **2002**, *4*, 4575. (b) Sun, H.; Moeller, K. D. *Org. Lett.* **2002**, *4*, 1547.

(5) (a) Hanessian, S.; Buckle, R.; Bayrakdarian, M. J. *Org. Chem.* **2002**, *67*, 3387. (b) Wang, W.; Yang, J.; Ying, J.; Xiong, C.; Zhang, J.; Cai, C.; Hruby, V. J. *J. Org. Chem.* **2002**, *67*, 6353. (c) Beal, L. M.; Liu, B.; Chu, W.; Moeller, K. D. *Tetrahedron*, **2000**, *56*, 10113.

(6) (a) Tong, Y.; Fobian, Y. M.; Wu, M.; Boyd, N.; Moeller, K. D. *J. Org. Chem.* **2000**, *65*, 2484. (b) Maison, W.; Kuntzer, D.; Grohs, D. *Synth. Lett.* **2002**, *11*, 1795.

(7) For reviews see: (a) Romo, D.; Meyers, A. I. *Tetrahedron* **1991**, *47*, 9503. (b) Groaning, M. D.; Meyers, A. I. *Tetrahedron* **2000**, *56*, 9843.

(8) In contrast to 5,5-bicyclic lactams, Meyers has reported that analogous 5,6-lactams bearing angular, alkyl substituents (R^1 = alkyl, Scheme 1) are formed with diminished levels of diastereomeric control (see ref 7a).

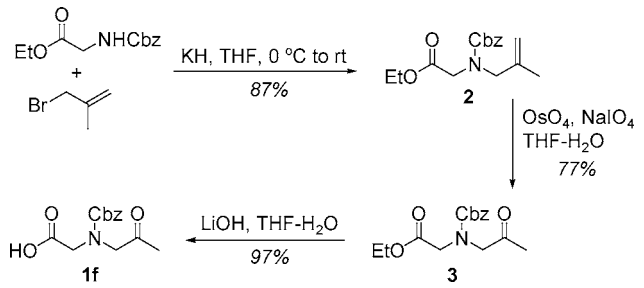
(9) For recent precedence of complete diastereoselectivity in the formation of an angular, phenyl-substituted Meyers 5,6-bicyclic lactam (R^1 = Ph, Scheme 1) see: Amat, M.; Margalida, C.; Llor, N.; Bosch, J. *Chem. Commun.* **2002**, 526.

(10) Cheng, S.; Comer, D. D.; Williams, J. P.; Myers, P. L.; Boger, D. L. *J. Am. Chem. Soc.* **1996**, *118*, 2567.

(11) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley and Sons: New York, 1999; pp 531−537.

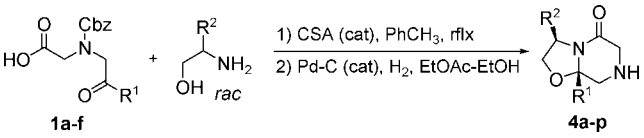
(12) Pappo, R.; Allen, D. S., Jr.; Lemieux, R. U.; Johnson, W. S. *J. Org. Chem.* **1956**, *21*, 478.

Scheme 2. Synthesis of Methyl-Substituted 3-Aza-1,5-ketoacid



The pivotal bicyclocondensation was next explored. Gratifyingly, it was found that heating the prepared aza ketoacids and 1,2-amino alcohols in toluene in the presence of catalytic camphor sulfonic acid resulted in complete condensation−bicyclization to furnish the desired Cbz-protected oxazolo-[3,2-*a*]pyrazin-5-ones (Table 2). Water formed during the course of the reaction was removed azeotropically by aid of a Dean−Stark apparatus. Liberation of the amine from Cbz protection was smoothly carried out by hydrogenolysis catalyzed by Pd on carbon providing bicyclic lactam scaffolds **4a**−**p** in good yield over the two-step sequence.

Table 2. Results of Bicyclocondensation of 3-Aza-1,5-ketoacids



entry	R^1	R^2	product	2-step yield (%)[a]
1	Ph (**1a**)	CH_3	**4a**	76
2	Ph (**1a**)	Ph	**4b**	77
3	Ph (**1a**)	Bn	**4c**	80
4	Ph (**1a**)	CH_2OH	**4d**	87[b]
5	4-MeOPh (**1d**)	CH_3	**4e**	78
6	4-MeOPh (**1d**)	Ph	**4f**	83
7	4-FPh (**1b**)	CH_3	**4g**	83
8	4-FPh (**1b**)	Bn	**4h**	74
9	4-Cl (**1c**)	Ph	**4i**	65
10	4-PyPh (**1e**)	CH_3	**4j**	49
11	4-PyPh (**1e**)	Ph	**4k**	49
12	4-PyPh (**1e**)	Bn	**4l**	50
13	CH_3 (**1f**)	CH_3	**4m**	45[c]
14	CH_3 (**1f**)	Ph	**4n**	72[d]
15	CH_3 (**1f**)	Bn	**4o**	58[e]
16	CH_3 (**1f**)	CH_2OH	**4p**	55[b,f]

[a] Isolated yield of pure, single diastereomer over two steps. [b] Yield of Cbz intermediate. [c] 25/1.0 dr as determined by 400-MHz ^{1}H NMR analysis. [d] 8.3/1.0 dr as determined by 400-MHz ^{1}H NMR analysis. [e] 9.1/1.0 dr as determined by 400-MHz ^{1}H NMR analysis. [f] 25/1.0 dr as determined by 400-MHz ^{1}H NMR analysis.

Drawing from the commercial pool of 1,2-amino alcohols, a select subset was chosen that was comprised of alaninol, phenylgylcinol, phenylalaninol, and serinol. This selection enabled the degree of steric bulk to be varied and, in the serinol case, an additional functional handle to be incorporated. Racemic mixtures of the amino alcohols were employed to provide access to both antipodes of final products for biological testing. Attempts to use serine as the amino alcohol component failed to produce the desired carboxyl analogue ($R^2 = CO_2H$) apparently due to poor solubility. Carboxyl installation was eventually achieved through mild oxidation of the serinol adducts (vide infra).

For cyclization substrates bearing aryl substituents (entries 1−12), the bicyclocondensation was observed to occur with complete syn diastereoselectivty in accord with the results obtained in Meyers' 5,5-bicyclic lactam systems[8] and the angular phenyl 5,6-lactam reported by Amat and Bosch.[10] Assignment of the syn stereochemical orientation was based on gradient NOESY experiments for which a strong NOE interaction between the angular bridgehead and amino alcohol substituents was found to be most diagnostic (Figure 2). In cyclizations involving methyl substrate **1f** (entries 13−16), the reaction generally proceeded with high diastereocontrol but formation of the minor diastereomer was detected in levels as high as 11% (entry 14). The observed syn diastereochemical outcome for the formation of the oxazolo[3,2-*a*]pyrazin-5-ones may be adequately explained via the mechanistic rationale applied to the 5,*n* Meyers cyclodehydrations.[13]

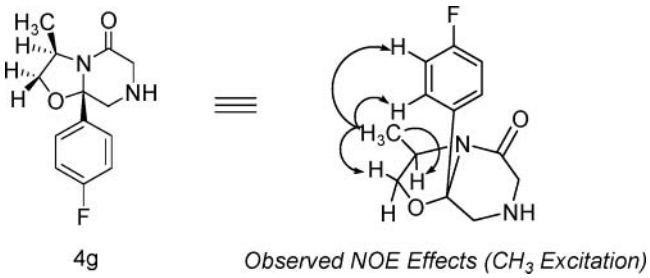


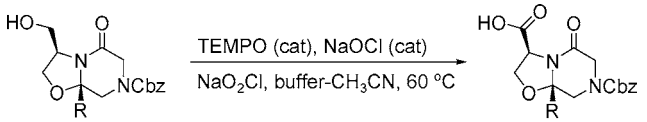
Figure 2. Gradient NOESY results for **4g**.

The successful inclusion of serinol (entries 4 and 16) in the bicyclocondensation was particularly interesting as it introduced a point of diversification through *O*-functionalization. Along these lines, we found that the Cbz-protected bicycles **4d** and **4p** could be readily *O*-alkylated, *O*-arylated, and converted to carbamate derivatives thus increasing the diversity of our scaffold collection.

Of greatest significance, the serinol-derived scaffolds **4d** and **4p** could be transformed into constrained dipeptide surrogates as follows. TEMPO-catalyzed oxidation of alco-

(13) (a) Meyers, A. I.; Downing, S. V.; Weiser, M. J. *J. Org. Chem.* **2001**, *66*, 1413. (b) Amat, M.; Llor, N.; Bosch, J. *Tetrahedron Lett.* **1994**, *35*, 2223. Unlike the more flexible 5,6 Meyers lactams described in the above citations, an even greater degree of conformational rigidity is believed to reside within the Cbz-protected products **4a**−**p**, thus strongly disfavoring the formation of a highly strained and sterically compressed anti product.

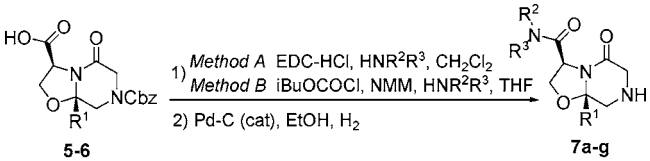
Scheme 3. Oxidation of Serinol-Derived Scaffolds



4d R=Ph
4p R=CH_3

5 R=Ph 92%
6 R=CH_3 94%

Table 3. Constrained, Modified Peptide Scaffolds via Amidation



5-6 **7a-g**

entry	product	R^1	R^2R^3NH	method	2-step yield (%)
1	**7a**	Ph	H_3C-NH_2	A	72
2	**7b**	Ph		A	65
3	**7c**	Ph		A	50
4	**7d**	Ph		B	74
5	**7e**	Ph		A	58
6	**7f**	CH_3		A	75
7	**7g**	CH_3		B	90

hols **4d** and **4p** under mild, buffered conditions[14] proceeded in excellent yield to provide the desired *N*-protected amino acids **5** and **6** (Scheme 3). Coupling of these acids with amines, using carbodiimide (method A) or mixed anhydride activation (method B), and subsequent Cbz deprotection furnished a diverse set of constrained modified dipeptides **7a**−**g** in good yield (Table 3). Complete preservation of stereochemical fidelity during the oxidation and subsequent coupling was verified by NMR analysis in all cases.

In summary, we have developed an efficient and highly stereoselective route to a new class of heterocyclic scaffolds bearing the oxazolo[3,2-*a*]pyrazin-5-one core structure. The key cyclocondensation of prepared 3-aza-1,5-ketoacids and amino alcohols enabled single-step formation of both rings with high diastereochemical control of angular substituents. The efficient preparation of constrained dipeptide scaffolds **5** and **6** derived from serinol enables future investigation as new bicyclic lactam-based peptidomimetics.

This synthetic approach is potentially applicable to other suitably functionalized ketoacids (i.e. aspartic and glutamic acid derivatives) to form additional classes of constrained bicyclic peptide scaffolds in either racemic or enantio-enriched form. In addition, oxazolo[3,2-*a*]pyrazin-5-ones prepared from enantio-pure amino alcohols could quite readily serve as chiral templates for the preparation of stereo-defined, substituted piperazines and piperazinones.

Acknowledgment. The authors thank Andrew Allen for gradient NOESY NMR studies, Carolina Vong for analytical support, and Nick Neitzel for sample preparation.

Supporting Information Available: General experimental procedures for the preparation of **1a**−**e**, **1f**, and **4a**−**p** and representative ^{1}H NMR and gradient NOESY spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL030065H

(14) Zhao, M.; Li, J.; Mano, E.; Song, Z.; Tschaen, D. M.; Grabowski, E. J. J.; Reider, P. J. *J. Org. Chem.* **1999**, *64*, 2564.