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Solid-Phase Synthesis of Constrained Terminal and Internal Lactam Peptidomimetics

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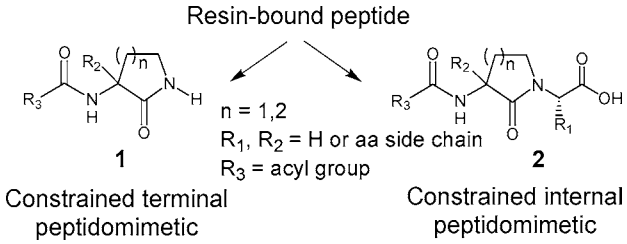
ABSTRACT



Lactams are key components of many peptidomimetic structures. Five- and six-membered lactam peptidomimetics with hydrogen or amino acid side chains at the α-position can be constructed from peptide precursors during a solid-phase synthesis. There is no significant racemization of remote stereocenters during synthesis.

Lactams are important scaffolds in conformationally restricted peptides and peptidomimetics.[1] The *β*-lactam ring present in penicillin derivatives can be regarded as the prototypical example from nature, and there are synthetic examples of four- to eight-membered lactams in conformationally restricted peptidomimetic probes and drugs.

We have been systematically developing solid-phase methodology to make resin-bound α-mono- or α,α-disubstituted unnatural amino acids, for cleavage and direct use, or for further incorporation (using solid-phase chemistry) into peptides or peptidomimetics.[2] Recently, we reported ways to introduce *ω*-halo alkanes at the α-carbon of natural and unnatural amino acids.[3] These resin-bound intermediates provide simple access to a wide variety of conformationally constrained amino acids.[3,4] In this article, we report on the continued development of this methodology to provide, in the course of a normal solid-phase peptide synthesis, ready access to conformationally restricted lactam peptidomimetics.[5−7] When combined with our published methodology to α-substituted unnatural amino acids,[2] there are now available, through solid-phase techniques, large numbers of conformationally constrained lactam peptidomimetics **1** (terminally constrained)[8] and **2** (internally constrained)[5] bearing natural or unnatural amino acid side chains (Figure 1).

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(1) For excellent reviews on peptidomimetic chemistry, see: (a) Giannis, A.; Kolter, T. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1244−1267. (b) Gante, J. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1699−1720. (c) Hanessian, S.; McNaughton-Smith, G.; Lombart, H.-G.; Lubell, W. D. *Tetrahedron* **1997**, *53*, 12789−12854. (d) Gillespie, P.; Cicariello, J.; Olson, G. L. *Biopolym. (Peptide Sci.)* **1997**, *43*, 191−217. (e) Synthesis of Peptides and Peptidomimetics. In *Houben-Weyl, Methods in Organic Chemistry*; Goodman, M., Felix, A., Moroder, L., Toniolo, C., Eds.; Thieme: Stuttgart, New York, 2003; Vol. E22c.

(2) (a) O'Donnell, M. J.; Zhou, C.; Scott, W. L. *J. Am. Chem. Soc.* **1996**, *118*, 6070−6071. (b) Scott, W. L.; Zhou, C.; Fang, Z.; O'Donnell, M. J. *Tetrahedron Lett.* **1997**, *38*, 3695−3698. For a recent short review about UPS chemistry, see: (c) O'Donnell, M. J.; Scott, W. L. Unnatural Amino Acid and Peptide Synthesis (UPS). In *Peptides 2000: Proceedings of the Twenty-Sixth European Peptide Symposium*; Martinez, J., Fehrentz, J.-A., Eds.; EDK: Paris, 2001; pp 31−36.

(3) (a) Scott, W. L.; O'Donnell, M. J.; Delgado, F.; Alsina, J. *J. Org. Chem.* **2002**, *67*, 2960−2969. (b) O'Donnell, M. J.; Alsina, J.; Scott, W. L. *Tetrahedron Lett.* **2003**, *44*, 8403−8406.

(4) Scott, W. L.; Alsina, J.; O'Donnell, M. J. *J. Comb. Chem.* **2003**, *5*, 684−692.

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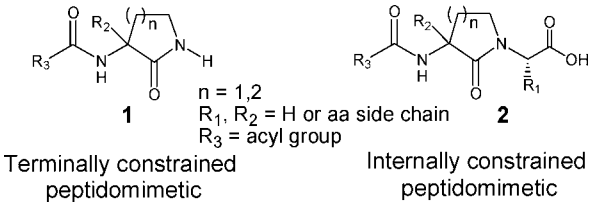
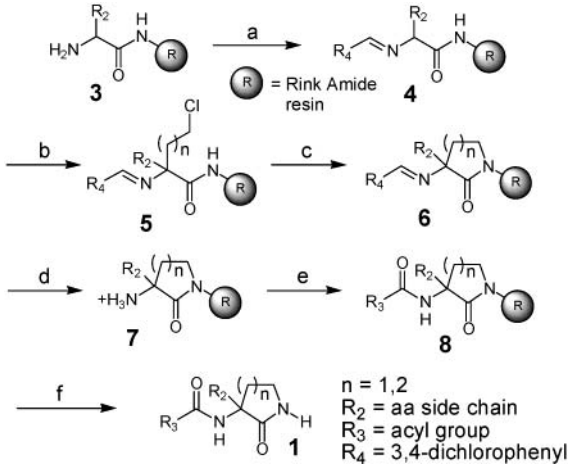


Figure 1. Peptidomimetic lactams.

Examples of five- and six-membered derivatives were prepared for both **1** and **2**. Scheme 1 outlines the synthesis of the terminally constrained α-substituted lactams **1**.

Scheme 1. Synthesis of Terminal γ- and δ-Lactams with α-Substituted Amino Acid Side Chains[a]



[a] Reagents and Conditions: (a) 3,4-dichlorobenzaldehyde (15 equiv), NMP−$(CH_3O)_3CH$ (1:2), 24 h, 25 °C; (b) $Br(CH_2)_nCH_2Cl$ (10 equiv); for n = 1, BEMP (10 equiv), $^nBu_4NI$ (10 equiv); for n = 2, BTPP (10 equiv); NMP, 24 h, 25 °C; (c) for n = 1, BTPP (10 equiv); for n = 2, BTPP (10 equiv), $^nBu_4NI$ (10 equiv); NMP, 24 h, 85 °C; (d) THF−1 N HCl (2:1), 4 h, 25 °C; (e) R_3COCl (10 equiv), DIEA (20 equiv), NMP, 24 h, 25 °C; (f) TFA−Et_3SiH (95:5), 2 h, 25 °C.

Commercially available α-substituted amino acids were attached to Rink amide resin and the α-position activated by conversion to the aldimine-derived Schiff base **4.** Alkylation was accomplished by using the appropriate α,ω-dihalide to give the ω-chloro derivative **5**. Lactams **6** were prepared on resin by a base-catalyzed intramolecular nitrogen alkylation. For both the five- and six-membered rings, heating (85 °C), stronger base (BTPP),[9,10] and, in the case of the six-membered ring, activation with $^nBu_4NI$ were required to obtain complete cyclization. Imine deprotection, N-acylation, and cleavage from the resin provided lactam products **1a**−**c** (Figure 3).[11]

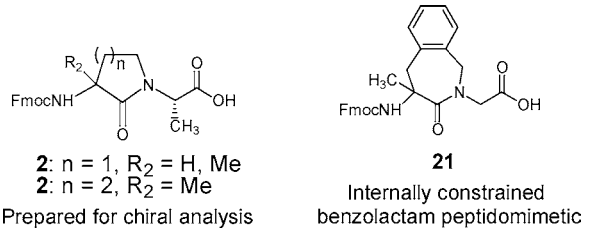


Figure 2. Additional compounds prepared.

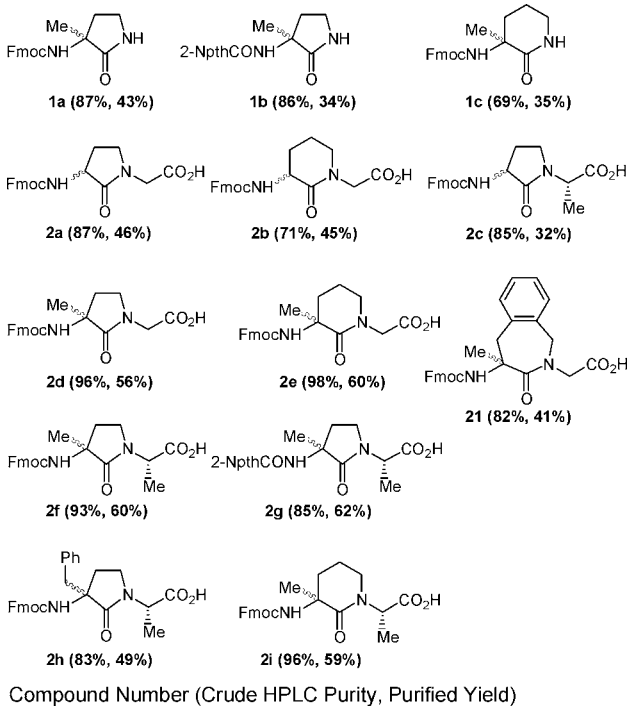


Figure 3. Representative products.

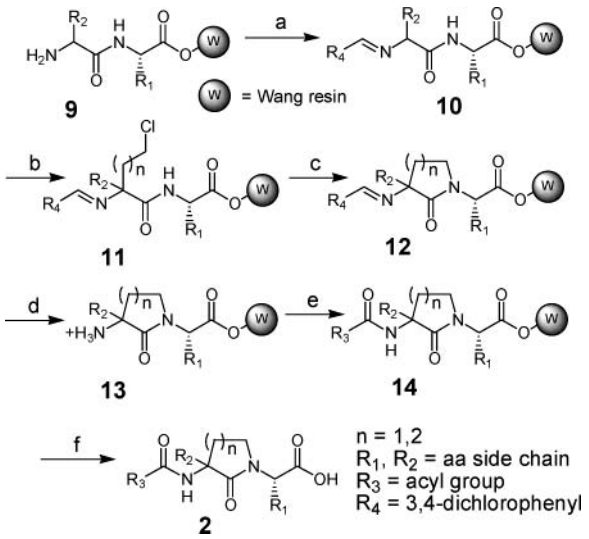
A similar process yielded the internally constrained α-substituted lactam peptidomimetics **2** (Scheme 2). In these examples, amino acid-substituted Wang resins were used as

(5) (a) Freidinger, R. M.; Veber, D. F.; Perlow, D. S.; Brooks, J. R.; Saperstein, R. *Science* **1980**, *210*, 656−658. (b) Freidinger, R. M.; Perlow, D. S.; Veber, D. F. *J. Org. Chem.* **1982**, *47*, 104−109. (c) Aubé, J. Synthetic Routes to Lactam Peptidomimetics. In *Advances in Amino Acid Mimetics and Peptidomimetics*; JAI Press, Inc.: Greenwich, CT, 1997; Vol. 1, pp 193−232. (d) Freidinger, R. M. *J. Med. Chem.* **2003**, *46*, 5553−5566. (e) Dolbeare, K.; Pontoriero, G. F.; Gupta, S. K.; Mishra, R. K.; Johnson, R. L. *J. Med. Chem.* **2003**, *46*, 727−733.

(6) For selected recent references concerning the solution- and solid-phase synthesis of the related β-lactam systems, see: (a) Palomo, C.; Aizpurua, J. M.; Benito, A.; Miranda, J. I.; Fratila, R. M.; Matute, C.; Domercq, M.; Gago, F.; Martin-Santamaria, S.; Linden, A. *J. Am. Chem. Soc.* **2003**, *125*, 16243−16260. (b) Shunk, S.; Enders, D. *Org. Lett.* **2000**, *2*, 907−910. (c) Meloni, M. M.; Taddei, M. *Org. Lett.* **2001**, *3*, 337−340.

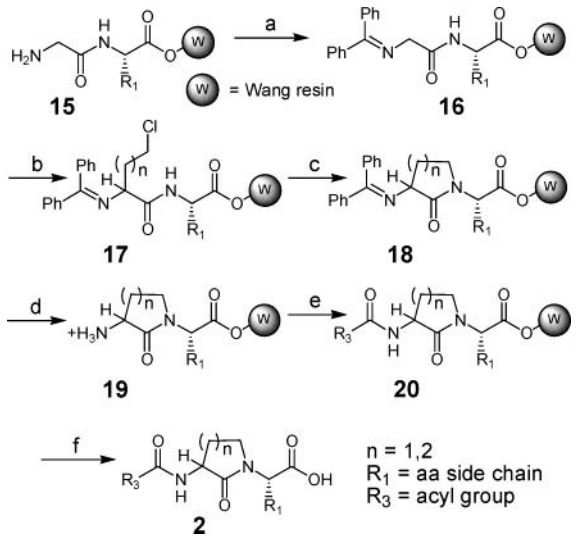
(7) For reports of the solid-phase synthesis of seven-membered dehydro-Freidinger lactams by a ring-closing metathesis strategy, see: (a) Piscopio, A. D.; Miller, J. F.; Koch, K. *Tetrahedron Lett.* **1997**, *38*, 7143−7146. (b) Piscopio, A. D.; Miller, J. F.; Koch, K. *Tetrahedron Lett.* **1998**, *39*, 2667−2670. (c) Piscopio, A. D.; Miller, J. F.; Koch, K. *Tetrahedron* **1999**, *55*, 8189−8198.

Scheme 2. Synthesis of Internal γ- and δ-Lactam Peptidomimetics with α-Substituted Amino Acid Side Chains[a]



[a] Reagents and Conditions: (a) 3,4-dichlorobenzaldehyde (15 equiv), NMP−$(CH_3O)_3CH$(1:2), 24 h, 25 °C; (b) $Br(CH_2)_nCH_2Cl$ (10 equiv), BEMP (10 equiv), $^nBu_4NI$ (10 equiv), NMP, 24 h, 25 °C; (c) for $n = 1$, spontaneous; for $n = 2$, BEMP (10 equiv), $^nBu_4NI$ (10 equiv), NMP, 18 h, 25 °C; (d) THF−1 N HCl (2:1), 4 h, 25 °C; (e) R_3COCl (10 equiv), DIEA (20 equiv), NMP, 24 h, 25 °C; (f) TFA−Et_3SiH (95:5), 2 h, 25 °C.

Scheme 3. Synthesis of Internal γ- and δ-Lactam Peptidomimetics with No Substitution at the α-Position[a]



[a] Reagents and Conditions: (a) benzophenone imine (10 equiv), HOAc (8.7 equiv), NMP, 24 h, 25 °C; (b) $Br(CH_2)_nCH_2Cl$ (10 equiv); for $n = 1$, BEMP (10 equiv), $^nBu_4NI$ (10 equiv); for $n = 2$, BTPP (10 equiv); NMP, 24 h, 25 °C, (c) for $n = 1$, spontaneous; for $n = 2$, BTPP (10 equiv), NMP, 24 h, 85 °C; (d) THF−1 N HCl (2:1), 4 h, 25 °C; (e) R_3COCl (10 equiv), DIEA (20 equiv), NMP, 24 h, 25 °C; (f) TFA−Et_3SiH (95:5), 2 h, 25 °C.

starting materials and converted into the simple dipeptides **9**. These were then carried on to the lactams **12** by an activation, alkylation, and cyclization sequence analogous to the terminally constrained cases described above. However, the more accessible amide reaction site permitted the use of milder cyclization conditions (BEMP and 25 °C). Imine hydrolysis, acylation, and cleavage from the resin gave the desired products **2d**−**i** (Figure 3) with good crude HPLC purities and purified yields.

The internally constrained unsubstituted lactam peptidomimetics (**2**, $R_2 = H$; $n = 1, 2$) were also prepared (Scheme 3; Figure 3, **2a**−**c**). This required a different activating group ($Ph_2C{=}N$) for the alkylation step. In the case of the six-membered lactam, the cyclization step also necessitated a stronger base (BTPP) and heating at 85 °C.[12] These more vigorous conditions (compared to those required for the formation of **2** when R_2 was a group other than hydrogen) are presumably a consequence, in the latter case, of a Thorpe−Ingold accelerated cyclization.[13]

Since optimal alkylation and cyclization conditions required customization of reaction conditions, a summary of the various experimental protocols follows.

(a) For five-membered ring lactam products (**1** or **2**, $n = 1$): Complete alkylation was accomplished by using 10 equiv each of 1-bromo-2-chloroethane, BEMP, and $^nBu_4NI$ in NMP for 24 h at 25 °C. Under these conditions cyclization occurred spontaneously to form the internal lactam constrained peptidomimetics **2** ($R_2 = H$ or aa side chain). To complete the cyclization in the case of the terminal lactam constrained peptidomimetics **1**, a subsequent treatment with BTPP (10 equiv) in NMP for 24 h at 85 °C was necessary due to the lower reactivity of the Rink amide nitrogen.

(b) For six-membered ring lactam products (**1** or **2**, $n = 2$): Complete alkylation was accomplished by using 10 equiv each of 1-bromo-3-chloropropane and BTPP in NMP for 24 h at 25 °C. Under these conditions, cyclization occurred spontaneously to form α-substituted peptidomimetics **2** (R_2 = aa side chain). However, to complete the cyclization in the case of peptidomimetics **1**, or peptidomimetics **2** with no substitution at the α-position ($R_2 = H$), a subsequent treatment with 10 equiv each of BTPP and $^nBu_4NI$ in NMP for 24 h at 85 °C was necessary. Alternatively, α-substituted peptidomimetics **2** (R_2 = aa side chain) can be prepared with

(8) Holladay, M. W.; Nadzan, A. M. *J. Org. Chem.* **1991**, *56*, 3900−3905.

(9) The following abbreviations are used: BEMP, 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine; BTPP, *tert*-butylimino-tri(pyrrolidino)phosphorane; DIEA, *N*,*N*-diisopropylethylamine; Fmoc, 9-fluorenylmethoxycarbonyl; HOAc, acetic acid; LC/MS, liquid chromatography/mass spectrometry; 2-Npth, 2-naphthoyl; UPS, unnatural peptide synthesis.

(10) For a comparison of the basicities of BTPP and BEMP, see footnote 12 in: O'Donnell, M. J.; Delgado, F.; Hostettler, C.; Schwesinger, R. *Tetrahedron Lett.* **1998**, *39*, 8775−8778.

(11) Crude HPLC purity of the six-membered ring lactam product **1c** (Figure 3) was lower because the ω-chloro compound **5** partially cyclized on the relatively unreactive imine nitrogen to form the five-membered ring α-substituted proline (17% by HPLC).

(12) Cleaved product **2b** contained 28% (by HPLC) of the five-membered ring dipeptide Fmoc-Pro-Gly-OH.

(13) Clayden, J.; Greeves, N.; Warren, S.; Wothers, P. *Organic Chemistry*; Oxford University Press: Oxford, 2001; pp 1138−40.

lower levels of C-terminal epimerization (see following stereochemical discussion) by using 10 equiv each of 1-bromo-3-chloropropane, BEMP, and $^{n}Bu_4NI$ in NMP for 24 h at 25 °C for the alkylation, followed by 10 equiv each of BEMP and $^{n}Bu_4NI$ in NMP for 18 h at 25 °C for the cyclization.

The syntheses described in this work all give rise to peptidomimetics with negligible diastereoselectivity at the N-terminal α-site of the lactam. Since our goal is to produce enabling methodology for lead discovery rather than lead optimization, this is not a drawback. Conventional analytical/preparative techniques could be used to separate the isomers and determine their identity.

However, we were concerned that the synthetic protocol might lead to loss of chirality at preexisting remote stereocenters. To assess potential C-terminal epimerization, we carried out chiral HPLC analyses of the five- and six-membered internally constrained peptidomimetics **2** (R_1 = methyl, from (*S*)-alanine; R_2 = methyl or H, Figure 2). In each case, authentic samples of all four possible stereoisomers were also prepared. For five-membered ring lactam products **2c** and **2f**, the combined amount of the two epimerized C-terminal alanine diastereomers was <2%. For the six-membered ring lactam product **2i**, the combined amount of the two epimerized C-terminal alanine diastereomers was <8% (using BTPP) or <6% (using BEMP).

Finally, we examined the possibility of constructing seven-membered lactams with this methodology. Attempted synthesis of **2** ($n = 3$, R_1 = H, R_2 = Me) afforded a mixture of products, and although there was a peak in the LC/MS consistent with the desired lactam, the material was not further characterized. However, the internally constrained seven-membered peptidomimetic **21** could be readily obtained, under mild conditions [α,α′-dichloro-*o*-xylene (10 equiv), BTPP (10 equiv), NMP, 24 h, 25 °C] in a 41% purified yield from the resin-bound alanine−glycine precursor.[14]

Figure 3 shows representative structures and purified yields[15,16] for the terminally and internally constrained peptidomimetics obtained in this work. This figure illustrates the range of lactam peptidomimetics that are available using the solid-phase methodology discussed here. When combined with our published solid-phase synthetic routes to a wide variety of "unnatural" amino acid side chains at R_1 and R_2 in the starting materials **3** (Scheme 1) or **9** (Scheme 2), a rich diversity of these lactam peptidomimetics should now be readily available.

Acknowledgment. We thank the National Institutes of Health and Eli Lilly and Company for financial support of this work and the Analytical Department at Eli Lilly for analytical support.

Supporting Information Available: Experimental procedures and proton NMR spectra of all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) For solution-phase routes to compounds related to **21**, see: (a) de Laszlo, S. E.; Bush, B. L.; Doyle, J. J.; Greenlee, W. J.; Hangauer, D. G.; Halgren, T. A.; Lynch, R. J.; Schorn, T. W.; Siegl, P. K. S. *J. Med. Chem.* **1992**, *35*, 833−846. (b) Casimir, J. R.; Tourwé, D.; Iterbeke, K.; Guichard, G.; Briand, J.-P. *J. Org. Chem.* **2000**, *65*, 6487−6492. (c) Van Rompaey, K.; Van den Eynde, I.; De Kimpe, N.; Tourwé, D. *Tetrahedron* **2003**, *59*, 4421−4432.

(15) Purification of the terminally constrained (**1a**−**c**) and the internally constrained (**2a**−**i** and **21**) crude lactam residues was carried out over silica gel with $CHCl_3$−THF (60:40, or similar solvent composition) and $CHCl_3$−THF−HOAc (80:20:2, or similar solvent composition), respectively, to provide the desired products, generally as amorphous solids. See Supporting Information for specific information for each compound.

(16) Yields of the final compounds, after chromatographic purification (as described above), were calculated on the basis of the initial loading of the starting resins given by the manufacturer and are the overall yields for all reaction steps starting from these resins. Only fractions with excellent HPLC purity were considered in the calculation of the purified yield.