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A general strategy for the synthesis of azapeptidomimetic lactams

Robert L. Broadrup, Bei Wang and William P. Malachowski*

Department of Chemistry, Bryn Mawr College, Bryn Mawr, PA 19010-2899, USA

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Abstract—A selection of azapeptidomimetics containing constraining lactam rings have been prepared by Mitsunobu cyclization of serine/homologated serine-azaalanine derivatives. These include sterically-congested β-lactams, as well as γ-butyrolactam and δ-valerolactam analogs. A novel azaamino acid acylation method was developed to prepare the sterically demanding α-benzyl-serine-azaalanine precursor. In all cases, the Mitsunobu conditions were highly efficient in forming the desired azapeptidomimetic lactams. The reported process represents a general strategy for the synthesis of peptidomimetic structures with a constraining lactam ring.

1. Introduction

Peptidomimetic structures are the frequent focus of synthetic efforts because they mimic or enhance biologically relevant properties of proteins, but avoid the normal metabolic liabilities.[1] Lactam rings have been a common peptidomimetic target since the seminal work of Freidinger.[1f,2] γ-Butyro-, δ-valero- and ε-caprolactam containing peptidomimetics have been synthesized[2] with a variety of techniques to generate conformationally constrained peptidomimetics. Subsequent research has demonstrated a variety of peptidomimetic lactam applications, many with important biological activity.[3] Recently, even the smaller β-lactam peptidomimetic structures have been synthesized and shown to mimic the β-turn secondary structure and biological activity of melanostatin.[4] Peptidomimetic β-lactams have also shown activity as protease inhibitors.[5]

Similarly, azapeptides or related derivatives have been used as peptide surrogates. They usually create structurally analogous, but metabolically stable peptide mimics, which retain the biological activity of their peptide analogs.[6] Recent reports have demonstrated their unique conformational effects[7] and potent enzyme inhibition.[8]

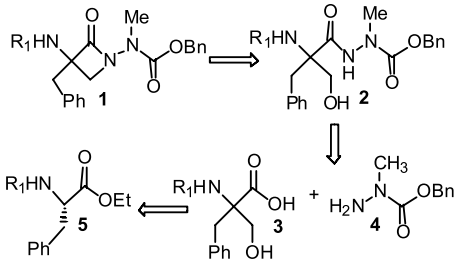
With the goal of extending our previously described synthetic process[9] to a greater array of peptidomimetic lactam structures, we focused on demonstrating that the method would apply to γ-butyrolactams, δ-valerolactams and more complex β-lactams. Described herein are successful strategies to accomplish this goal. The results demonstrate the utility of the intramolecular Mitsunobu reaction of acyl hydrazides for the synthesis of peptidomimetic structures containing a variety of lactam rings embedded in the peptide backbone.

2. Results and discussion

2.1. Azapeptidomimetic quaternary β-lactams

Recent research from Palomo and co-workers[4] has shown the utility of α-alkyl-α-amino-β-lactam peptidomimetics, which contain a quaternary carbon at C-3 of the β-lactam. Use of an α-alkyl-serine derivative with our previously reported method[9] would permit the efficient synthesis of structurally related azapeptidomimetic lactams. We chose to demonstrate this process with α-benzyl-serine, as the aromatic side chain would facilitate chromatographic methods.

A retrosynthetic analysis of β-lactam **1** (Scheme 1) begins with the cyclization of acyl hydrazide **2** under Mitsunobu



Scheme 1. Retrosynthetic analysis for azapeptidomimetic quaternary lactams.

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* Corresponding author. Tel.: +1 610 526 5016; fax: +1 610 526 5086; e-mail: wmalacho@brynmawr.edu

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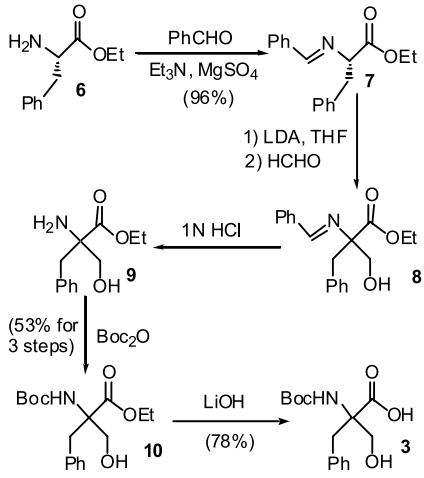
conditions. The acyl hydrazide could be obtained by coupling α-benzyl-serine derivative **3** and azaalanine derivative **4**. Compound **3** could be prepared by hydroxymethylation of *N*-protected phenylalanine ethyl ester **5**. The benzyl ester of azaalanine **4** could arise from the reaction between methyl hydrazine and benzyl chloroformate.

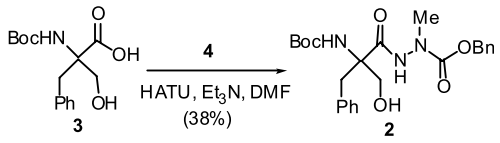
The α-benzyl-serine derivative **3** was synthesized via modification of a reported α-hydroxymethylation protocol (Scheme 2).[10] *N*-Benzylidene-phenylalanine ethyl ester **7** was prepared by the reaction of phenylalanine ethyl ester **6** with benzaldehyde. Hydroxymethylation of **7** occurred by deprotonation with lithium diisopropylamide (LDA) and reaction of the resulting enolate with sublimed formaldehyde. The hydrolytically labile imine group made purification difficult, so the crude product was immediately hydrolyzed to the α-benzyl serine ethyl ester **9** with 1 N HCl. The hydrophilic nature of **9** also made purification difficult, so the most effective procedure was to immediately protect the amine of **9** as a *tert*-butoxycarbonyl (Boc) carbamate. Isolation and purification of **10** was more easily accomplished and the three step process afforded **10** in 53% yield. Finally, hydrolysis of the ethyl ester with lithium hydroxide in ethanol and water gave *N*-Boc-α-benzyl-serine **3**.



Scheme 2. Synthesis of α-benzyl-serine derivative **3**.

The benzyl ester of azaalanine **4** (Scheme 1) was synthesized from methyl hydrazine and benzyl chloroformate as previously described.[9] In our earlier report, 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ) was determined to be the most efficient coupling agent for joining azaalanine and serine derivatives. However, attempts to couple the weakly nucleophilic azaalanine with the more hindered serine derivative **3** proved unsucccessful. After screening a variety of coupling agents, the best, albeit modest, yield was obtained by employing *O*-(benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU), which afforded the desired hydrazide **2** in 38% yield (Scheme 3).

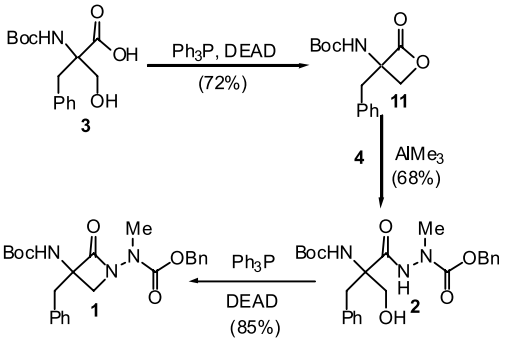
Unsatisfied with a modest coupling yield, we explored an alternative approach, which activated the acid group to nucleophilic acyl substitution via a β-lactone. Over the last decade, β-lactone derivatives have been elegantly exploited



Scheme 3. Coupling of **3** and **4**.

as versatile intermediates.[11] The work of Vederas[12] has permitted the efficient synthesis of β-lactones from serine, however, the vast majority of recent reports with serine β-lactones have focused on reactions at the β-carbon.[12,13] Although there are a few reports that describe reactions at the carbonyl,[14] to the best of our knowledge, there are no reports that describe β-lactones as useful acylating agents for the synthesis of hindered peptides.[15]

Nevertheless, we converted **3** into the corresponding β-lactone **11** (Scheme 4) using triphenylphosphine (Ph_3P) and diethyl azodicarboxylate (DEAD) in 72% yield.[12] Although no reaction occurred when the β-lactone was combined with **4**, pre-activation of **4** by reaction with trimethyl aluminum afforded a dimethylaluminum–hydrazide complex, which efficiently reacted at the acyl group of β-lactone **11** to afford a 68% yield of the desired azapeptide **2**.



Scheme 4. Synthesis of azadipeptide β-lactam **1**.

With an improved procedure for the synthesis of the serine-azaalanine derivative, **2** was then subjected to Mitsunobu conditions (Ph_3P, DEAD) to afford the desired C-3 benzyl β-lactam azapeptidomimetic **1** in high yield. Elaboration of the azapeptide on the amino and carboxy terminal ends mirrored procedures already described[9] with the exception that the more active coupling agent HATU was used to couple at the hindered amino group to make **12** (Scheme 5). The tetrapeptidomimetic **13** was synthesized in an overall yield of 11% from **6** with the longest linear sequence being 12 steps. This process could be made stereoselective if asymmetric methods of α-alkyl-serine synthesis were applied.[16]

2.2. Azapeptidomimetic γ-butyrolactams and δ-valerolactams

A unified strategy for the synthesis of larger lactams was envisioned in the retrosynthetic plan shown in Scheme 6. Briefly, homologues of serine **16** would be coupled with azaamino acids **4** and the product **15** subjected to Mitsunobu conditions to afford the azapeptidomimetic lactams **14**. The