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Synthesis of lactam-bridged cyclic peptides using sequential olefin metathesis and diimide reduction reactions

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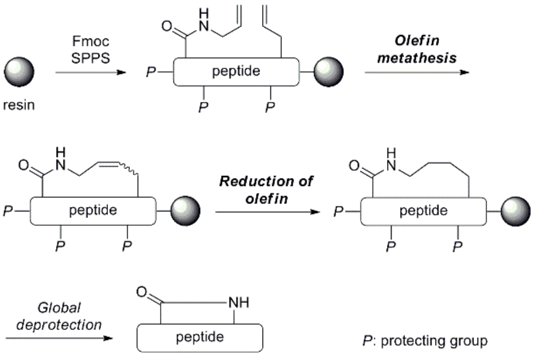
ABSTRACT

A new approach has been developed for the synthesis of lactam-bridged cyclic peptides. Following the introduction of *N*-allyl glutamine and α-allylglycine into the peptide backbone, the side chains of these residues were subjected to a cyclization reaction by ring-closing metathesis (RCM). Reduction of the resulting peptide bearing olefin moiety was achieved using diimide, which was generated *in situ* from *o*-nitrobenzenesulfonyl hydrazine and piperidine, gave the corresponding saturated cyclic peptides.

1. Introduction

Protein-protein interactions (PPIs) play important roles in numerous biological signaling networks, including cell cycle, proliferation and metabolism activities, and the effective regulation of these interactions could allow us to develop a deeper understanding of their role in biological phenomena and discover novel molecular targets for therapeutic systems.[1] PPIs can be controlled using a variety of different ligands, which can interact with the surfaces involved in the formation of the PPIs and prevent the proteins from coming together. Among the ligands used in this context, peptides possessing an analogous amino acid sequence to that of the site of PPI are appropriate candidates.[2] Peptide ligands of this type can be readily prepared by solid-phase peptide synthesis (SPPS) and purified by standard reverse phase HPLC. Furthermore, chemical modifications such as the attachment of a fluorophore[3] or post-translational modifications that effectively mimic the actions of biological systems[4] can be installed at the intended site. Compared with small molecule ligands, peptide ligands have a much wider molecular surface, and are therefore better suited to modulating PPIs. However, the stability profiles of peptide ligands are generally lower than those of small molecule ligands.[5] Furthermore, the three-dimensional structures of peptide fragments do not always reflect the structures of the protein surfaces involved in PPIs because of the flexibility of short peptides. One potential solution to these problems would involve the use of a cyclized peptide, which would allow for the fixation of the active conformer. Furthermore, it was envisaged that the use of unnatural cyclized bonding would prevent these compounds from being degraded by endogenous enzymes. Over the years, a wide variety of methodologies have been reported for the preparing cyclic peptides using side-to-side chain bridging techniques, as evidenced by reports pertaining to disulfide formation,[6] lactamization,[7] all-hydrocarbon linkage (stapled peptide).[8] Among the route already reported for the construction of cyclic peptides, we decided to focus on lactam-bridged cyclic peptides. It was envisaged that lactam-bridged peptides would exhibit much longer periods of activity than the corresponding disulfide peptides because the chemical stability of a lactam bond is generally superior to that of a disulfide.



Scheme 1. Synthetic route to the lactam-bridged cyclic peptide.

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