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Synthesis and conformational analysis of 18-membered Aib-containing cyclohexapeptides

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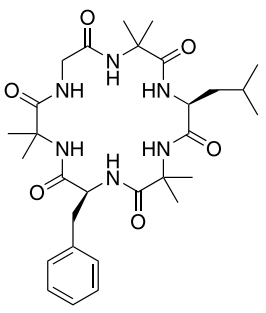
Abstract—The synthesis and conformational analysis of two Aib-containing cyclic hexapeptides, *cyclo*(Gly-Aib-Leu-Aib-Phe-Aib) **1** and *cyclo*(Leu-Aib-Phe-Gly-Aib-Aib) **2**, is described. The linear precursors of **1** and **2** were prepared using solution phase techniques, and the cyclization efficiency of three different coupling reagents (HATU, PyAOP, DEPC) was examined. The success of the cyclization was found to be reagent dependent. Solid-state conformational analysis of **1** and **2** was performed by X-ray crystallography and has revealed some unusual features as all three Aib residues of **1** assume nonhelical conformations. Furthermore, the residue Aib^4 adopts an extended conformation ($\phi = -175.9(3)°$, $\psi = +178.6(2)°$), which is, to the best of our knowledge, the first observation of an Aib residue adopting an extended conformation in a cyclopeptide. The structure of **1** is also a rare example in which an Aib residue occupies the $(i+1)$ position of a type II′ β-turn, stabilized by a bifurcated hydrogen bond. The cyclic peptide **2** adopts a more regular conformation in the solid state, consisting of two fused β-turns of type I/I′, stabilized by a pair of intramolecular hydrogen bonds. In addition, the conformational study of the cyclic peptide **1** in DMSO-d_6 by NMR spectroscopy and molecular dynamics simulations revealed a structure, which is very similar to its structure in the crystalline state.

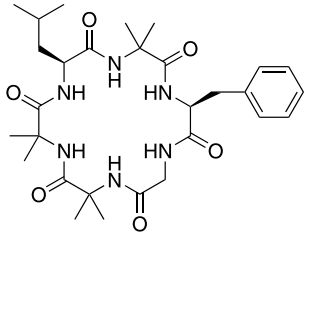
1. Introduction

Cyclic peptides continue to be challenging targets for chemical synthesis.[1] As the synthesis of linear peptides generally proceeds well, the key step for the chemical synthesis of cyclic peptides is usually the cyclization reaction. In particular, the cyclization of small peptides of less than seven amino acid residues is often difficult.[2] Incorporation of turn-inducing elements such as Gly, Pro, D-amino acids and *N*-alkylated amino acids into the peptide backbone is known to improve cyclization yields.[3] Although conformational constraints are usually introduced into peptides through cyclization, cyclic peptides can still possess a remarkable flexibility.[4,5] Thus, the incorporation of sterically hindered C(2)-tetrasubstituted α-amino acids into the peptide backbone leads to more rigid compounds. In addition, cyclic penta- and hexapeptides are often chosen for the synthesis of model cyclopeptides, since larger cyclic peptides already exhibit greater flexibility.[6] Conformation-constrained cyclic peptides may have enhanced metabolic stability, receptor selectivity, and bioavailability, all of which may lead to useful medicinal properties.

Our previous successful synthesis of cyclic hexapeptides containing several Aib (α-aminoisobutyric acid) residues and two Gly residues in positions 1 and 4 of the peptide backbone[7,8] prompted us to investigate the cyclization of hexapeptides containing only one Gly residue as the turn-inducing element. Here, we describe the synthesis of two cyclic hexapeptides *cyclo*(Gly-Aib-Leu-Aib-Phe-Aib) (**1**) and *cyclo*(Leu-Aib-Phe-Gly-Aib-Aib) (**2**), composed of three protein amino acids, i.e. Gly, Leu, Phe and three α-aminoisobutyric acids. The crystal structures of both cyclic peptides were examined by X-ray diffraction in order to study the influence of the Aib residues on the conformation of the backbone of the cyclic hexapeptides. A NMR-based structure determination of **1** in solution was also performed in the present study.



1



2

Keywords: Cyclic peptides; Peptide synthesis; α-Aminoisobutyric acid; Peptide conformation.
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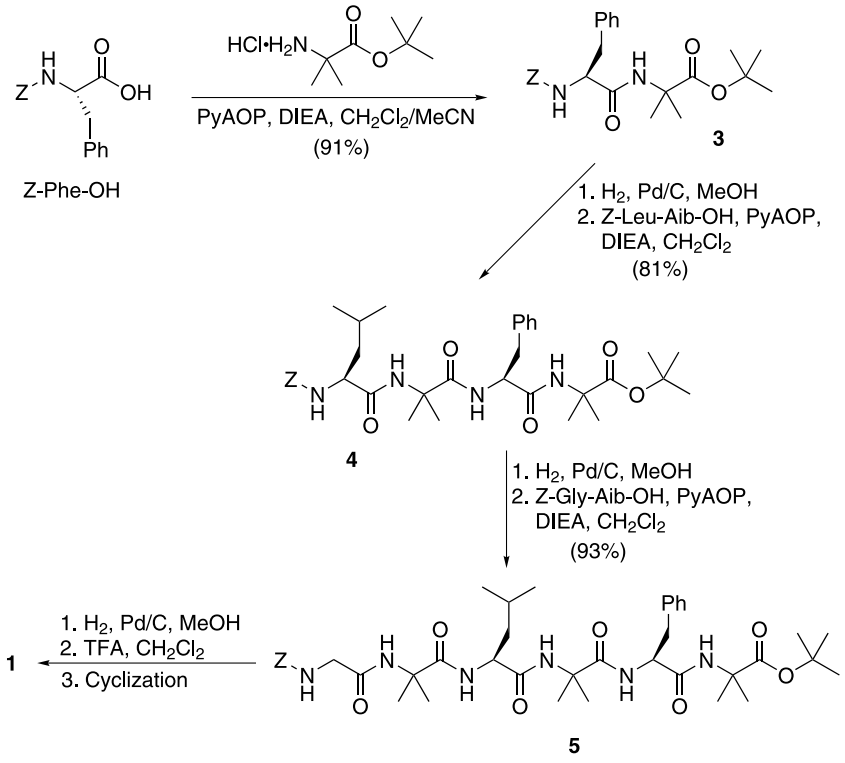
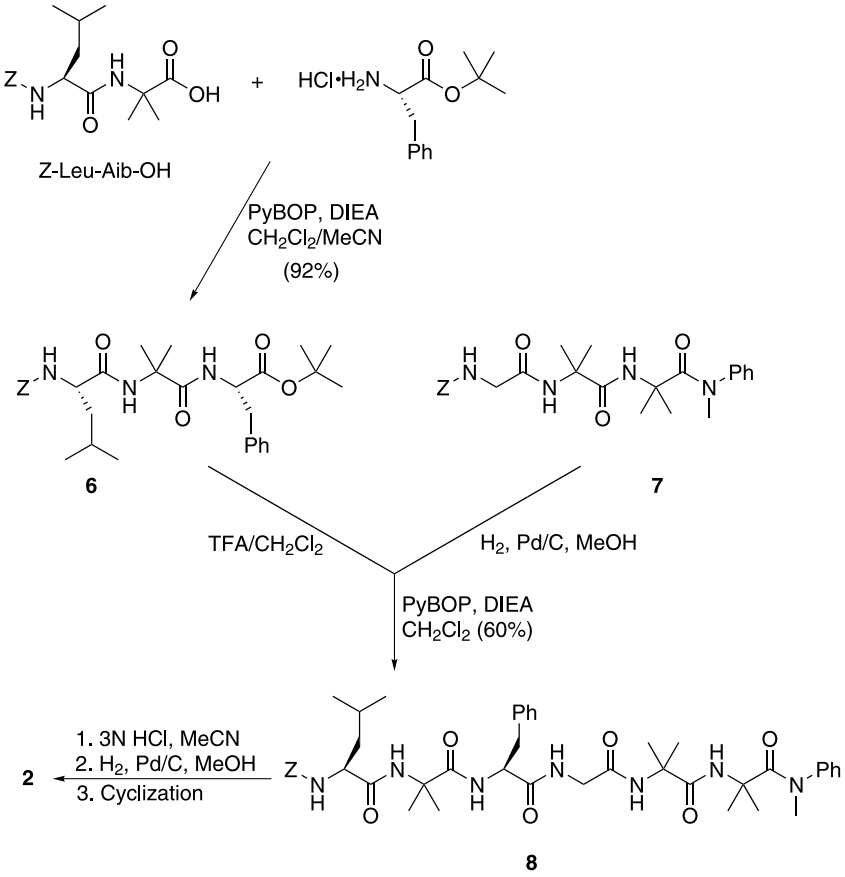


Scheme 1.



Scheme 2.