Accepted Manuscript

Title: Development of aspartic acid ligation for peptide cyclization derived from serine/threonine ligation

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PII: S1001-8417(18)30115-3
DOI: https://doi.org/10.1016/j.cclet.2018.03.012
Reference: CCLET 4473

To appear in: *Chinese Chemical Letters*

Received date: 13-2-2018
Revised date: 24-2-2018
Accepted date: 8-3-2018

Please cite this article as: Ci Xu, Jianchao Xu, Han Liu, Xuechen Li, Development of aspartic acid ligation for peptide cyclization derived from serine/threonine ligation, Chinese Chemical Letters https://doi.org/10.1016/j.cclet.2018.03.012

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ACCEPTED MANUSCRIPT

Communication

Development of aspartic acid ligation for peptide cyclization derived from serine/threonine ligation

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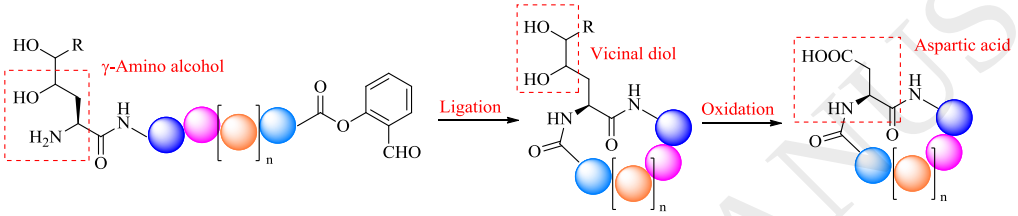
Graphical Abstract



Based on a mechanism analogous to the serine/threonine ligation, the aspartic acid ligation, which is facilitated by the γ-amino alcohol based ligation and oxidation, is developed and applied to the synthesis of cyclic peptides. The γ-hydroxyl group triggers the ring-chain tautomerization *via* a 6-*endo-trig* process, while the δ-hydroxyl group facilitates the oxidative cleavage of the vicinal diol to give carboxylic acid.

ARTICLE INFO

Article history:
Received 13 February 2018
Received in revised form 24 February 2018
Accepted 3 March 2018
Available online

Keywords:
Aspartic acid ligation
Peptide cyclization
Serine/threonine ligation
Ring-chain tautomerization
Acyl transfer
Selective oxidation

ABSTRACT

Based on a mechanism analogous to the serine/threonine ligation, the aspartic acid ligation, which is facilitated by the γ-amino alcohol based ligation and oxidation, is developed and applied to the synthesis of cyclic peptides. The γ-hydroxyl group triggers the ring-chain tautomerization *via* a 6-*endo-trig* process, while the δ-hydroxyl group facilitates the oxidative cleavage of the vicinal diol to give carboxylic acid.

As an important class of molecular constructs from both natural and synthetic sources, cyclic peptides attract the attention of the researchers from synthetic chemistry and medicinal chemistry. Compared with the corresponding linear peptides, cyclic peptides are prone to show improved binding affinity to protein targets and higher stability against degradation, benefiting from the restricted conformations [1-3]. Compared with the linear peptides which can be readily and even automatically assembled *via* solid phase peptide synthesis (SPPS), the syntheses of cyclic peptides pose additional challenges in the head-to-tail macrolactamization of the linear precursors with protected side chains [4]. These challenges include racemization of the C-terminal amino acid residues in the linear

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