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Design-Oriented Synthesis of Melanostatin Derivatives: Exploring Structural and Functional Diversity

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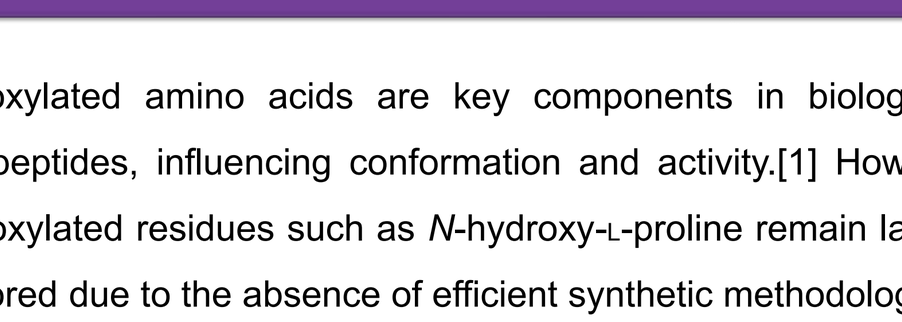
INTRODUCTION & AIM

Hydroxylated amino acids are key components in biologically active peptides, influencing conformation and activity.[1] However, *N*-hydroxylated residues such as *N*-hydroxy-L-proline remain largely unexplored due to the absence of efficient synthetic methodologies.

This work presents a new approach for the on-site *N*-hydroxylation of prolyl-containing peptides via Cope elimination, using the cyanoethyl group as both a protecting and leaving group. Melanostatin (MIF-1), a neuropeptide with activity as a positive allosteric modulator of the dopamine D_2 receptors,[2] was selected as a model peptide to demonstrate this strategy. The aim was to develop a robust, high-yielding method for the assembly of *N*-hydroxy-MIF-1, expanding access to *N*-hydroxyprolyl peptides.



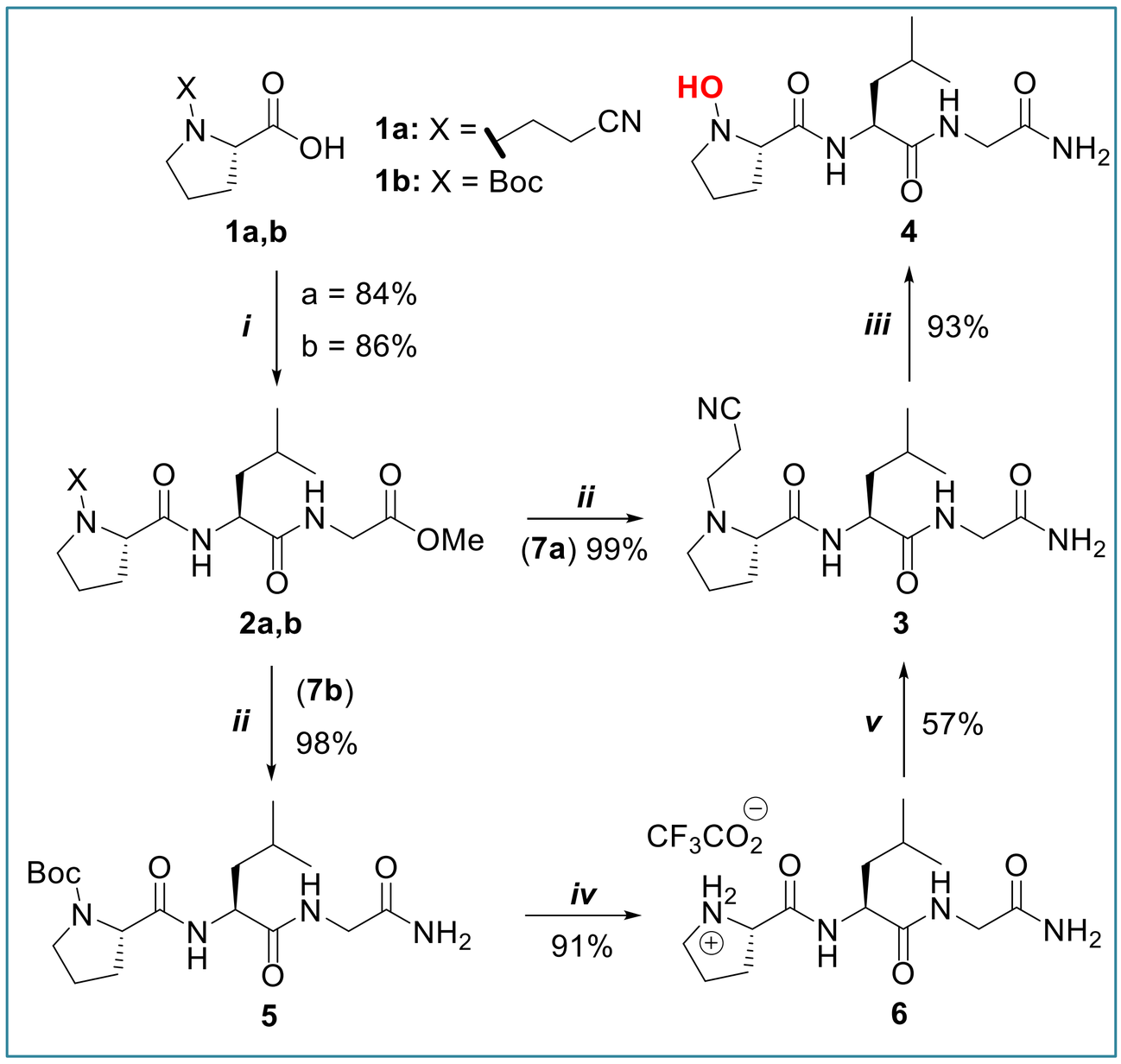
N-Hydroxy-L-proline — *N*-Hydroxy-MIF-1

Figure 1. Structure of *N*-hydroxy-L-proline and *N*-hydroxy-MIF-1

METHOD

Starting from *N*-(cyanoethyl)-L-proline, the peptide sequence was assembled through TBTU-mediated coupling. The cyanoethyl group served as a temporary *N*-protection during synthesis and as a leaving group during the oxidative step. On-site *N*-hydroxylation was achieved by Cope elimination upon oxidation with *m*-chloroperbenzoic acid (*m*-CPBA) in methanol, affording *N*-hydroxy-MIF-1 in high yield. Comprehensive spectroscopic characterization (1D and 2D NMR) together with HRMS analyses confirmed the structure. Comparative optimization of early versus late cyanoethyl installation identified the most efficient route for *N*-hydroxy-MIF-1 synthesis.

RESULTS & DISCUSSION



Scheme 1. On-site assembly of *N*-hydroxy-MIF-1. Reagents and conditions: ***i.*** TBTU, DIPEA, methyl L-leucylglycinate trifluoroacetate, CH_2Cl_2. ***ii***. 7 M NH_3 solution in MeOH. ***iii.*** *m*-CPBA, MeOH. ***iv.*** TFA, CH_2Cl_2. ***v.*** acrylonitrile, DIPEA.

CONCLUSION

A novel on-site *N*-hydroxylation protocol for prolyl-containing peptides was developed, exploiting the cyanoethyl group as a bifunctional protecting and leaving group. This method enabled the synthesis of *N*-hydroxy-MIF-1 in excellent yield without requiring additional protecting-deprotecting steps. The approach proved mild, efficient, and broadly applicable to other peptide systems. This work establishes a new route for preparing *N*-hydroxyprolyl peptides with potential in organic and medicinal chemistry.

REFERENCES

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