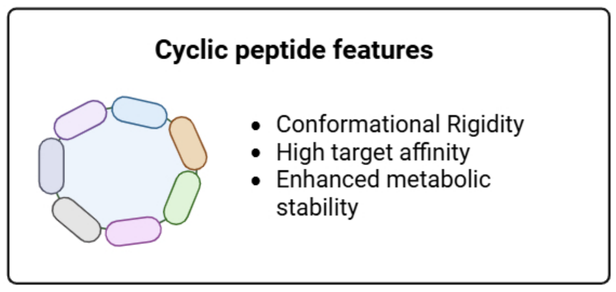
Enantioselective synthesis of antiplasmodial cyclic tetrapeptide Koshidacin A

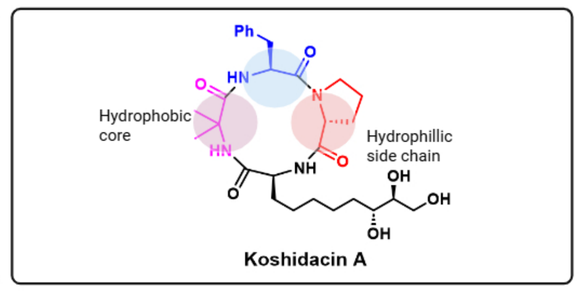
Preeti Kapri, Devki Nandan, Ramesh Ramapanicker*
Department of Chemistry, Indian Institute of Technology Kanpur, Kanpur- 208016, India
Email: preetik21@iitk.ac.in, rameshr@iitk.ac.in
https://doi.org/10.17952/38EPS.2026.P293

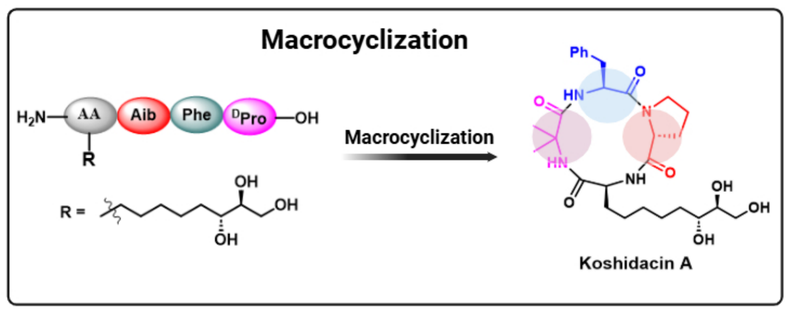
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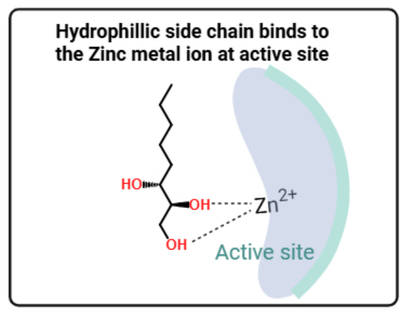
Introduction

- Cyclic peptides offer promising therapeutic scaffolds owing to their conformational rigidity, high target affinity, and enhanced metabolic stability.
- Natural cyclic tetrapeptides often feature a hydrophobic core and a hydroxyl-rich side chain capable of coordinating Zn^{2+} at the HDAC active site.
- Iwatsuki et al. isolated two cyclic tetrapeptides, Koshidacins A and B, from *Pochonia boninensis* FKR-0564, both showing antiplasmodial activity against the *Plasmodium falciparum* FCR3 strain (IC_{50}: 17.1–0.89 μM).
- The synthesis of Koshidacin A features a stereoselective approach to the side-chain triol unit via Sharpless asymmetric epoxidation followed by Payne rearrangement.
- Herein, we developed the synthesis of the antiplasmodial cyclic tetrapeptide Koshidacin A from Homo-Garner aldehyde as the key starting material.



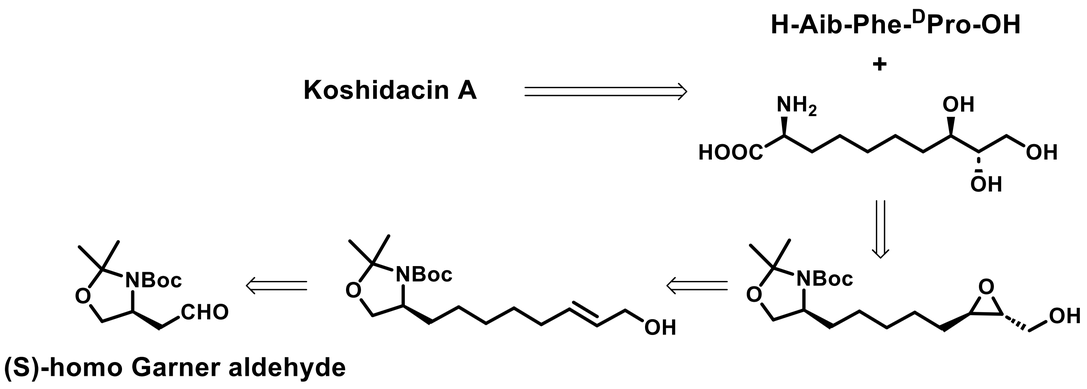




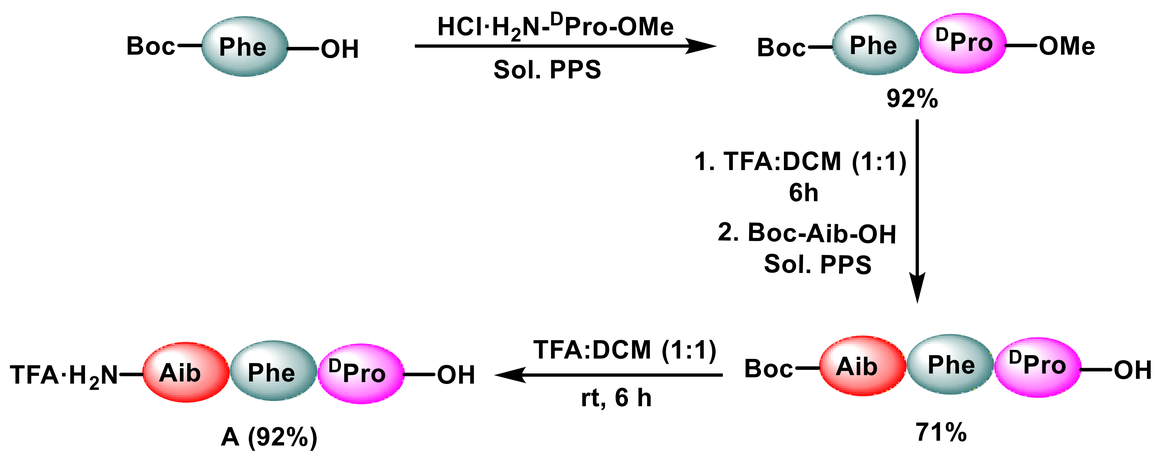


Retrosynthetic Approach

The synthetic route involves Sharpless asymmetric epoxidation followed by a Payne rearrangement, enabling the introduction of a trihydroxy-substituted lipophilic side chain within a specific amino acid fragment.

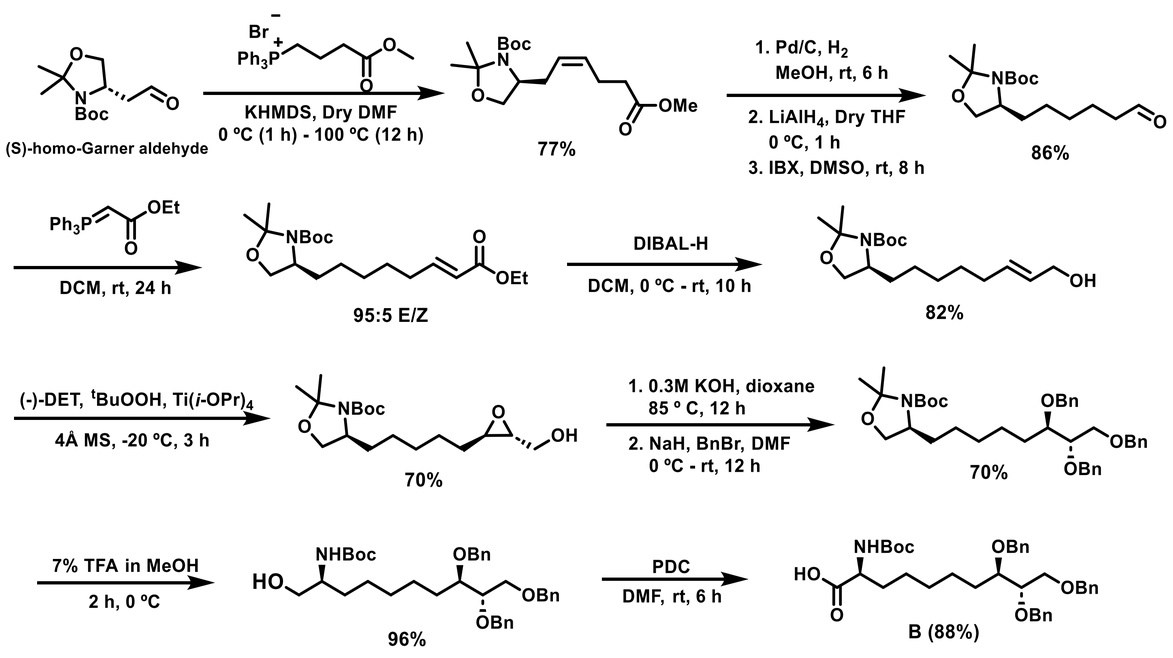


Synthesis of tripeptide fragment A

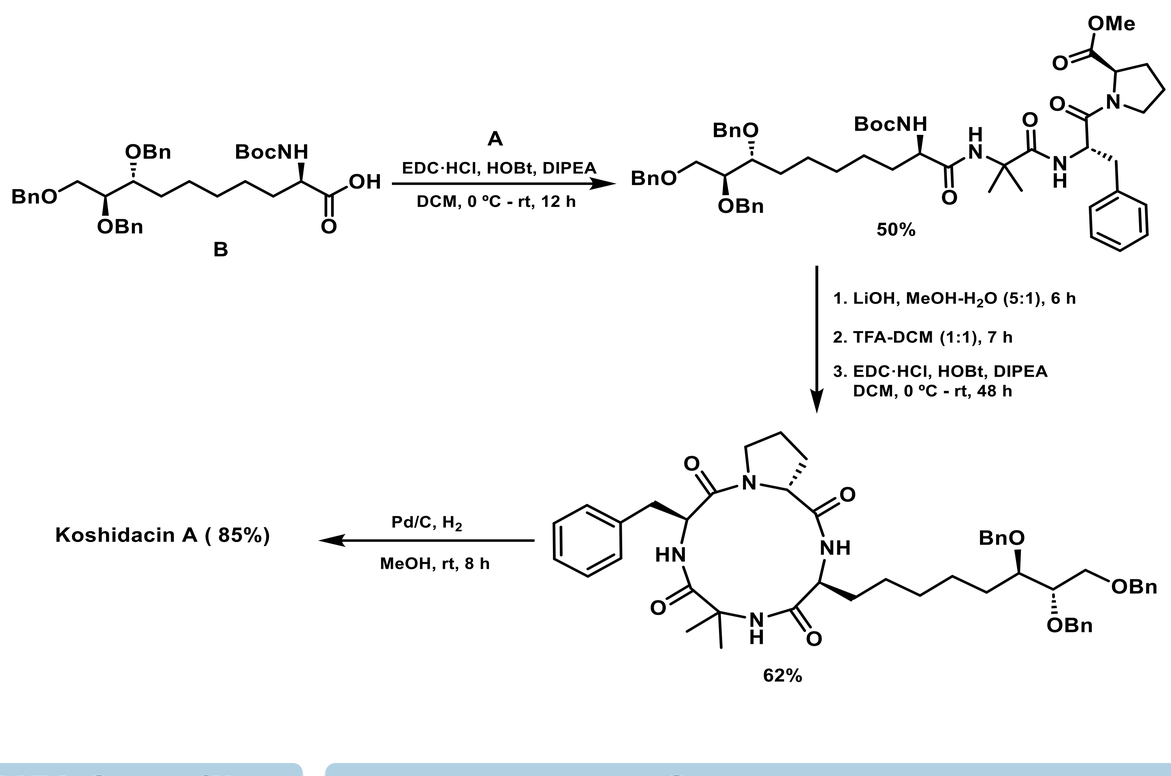


Synthesis of lipophilic amino acid fragment B

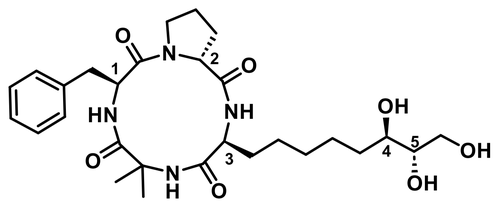
Using (S)-homo-Garner aldehyde as the key starting material to enantioselectively construct the side chain.



Synthesis of Koshidacin A



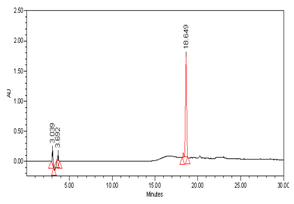
NMR comparison: Natural vs Synthetic Koshidacin A and HPLC profile



	^{1}H NMR data of Koshidacin A	^{1}H NMR data of Synthetic 1	^{13}C NMR data of Koshidacin A	^{13}C NMR data of Synthetic 1
1	5.14 (ddd, 10.0, 10.0, 5.8)	5.12 (td, 10.0, 5.8)	53.4	53.4
2	4.67 (d, 6.3)	4.65 (d, 7.1)	57.8	57.8
3	4.20 (ddd, 10.0, 7.5, 7.4)	4.20 (ddd, 10.0, 7.5, 7.6)	54.5	54.5
4	3.75 (m)	3.75 (m)	73.6	73.6
5	3.61 (m)	3.66-3.57 (m)	73.8	73.9

HPLC Analysis

- **Column:** XTerra® RP-C18 (250 × 4.6 mm, 3.5 μm)
- **Mobile phase:** ACN/H_2O + 0.1% TFA
- **Flow rate:** 1.0 mL min^{-1}
- **Detection:** UV 215 nm
- **tR:** 18.649 min
- **Purity:** 86.14%



Summary

- Developed a concise, efficient method for synthesizing the cyclic tetrapeptide Koshidacin A.
- Established a stereoselective route to the unusual trihydroxy side chain through Sharpless asymmetric epoxidation followed by Payne rearrangement.
- Achieved good yield and reproducibility with the current synthetic strategy.
- The modular synthetic strategy provides a promising platform for the synthesis of Koshidacin A analogues and related cyclic tetrapeptides, enabling future studies of their biological and supramolecular properties.

Acknowledgement

I gratefully acknowledge Prof. Ramesh Ramapanicker for his guidance and Dr. Devki Nandan for valuable discussions. I thank CSIR-UGC for the fellowship and IIT Kanpur for the research facilities.

Reference

Kapri *et al.*, *Eur. J. Org. Chem.* **2026**, *29*, e202500975.