Synthesis of Darobactin Analogues for SAR Studies

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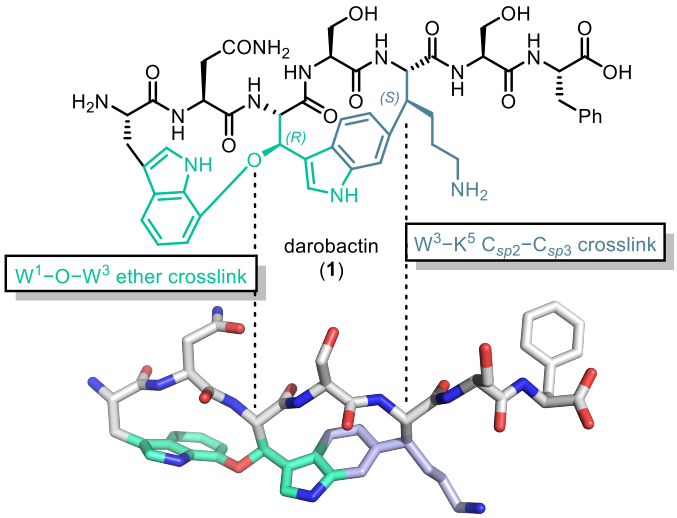
Isolated from *Photorhabdus khanii* found in entomopathogenic nematodes,[1] darobactin (**1**) represents the first member of the novel daropeptide class, characterized by its unique side-chain cyclized structure. The rigidity of these indole-bridged macrocycles bestows a β-strand-like structure to darobactin,[2] allowing for the inhibition of the β-barrell BamA,[1,2]a peptide-folding chaperone found in the outer membrane of Gram-negative bacteria. BamA binding of darobactin and derivatives from the outside of the bacterial cell is bactericidal,[3,4] and therefore elevates darobactins to high-interest candidates for antibiotics with a novel mode of action.



Synthetically, darobactin's indole-bridged structure bears challenges like enantioselective synthesis of building blocks and their atroposelective macrocyclization. Enantiopure β-hydroxytryptophans were prepared as scaffold to tackle these challenges and pave the way to diverse derivatives. While two small-scale total syntheses have been recently reported,[5,6] easily accessible darobactin analogues might facilitate the way to extensive SAR studies and development of therapeutically useful antibiotics. A first set of analogues was prepared and tested for minimum inhibitory concentrations (MIC).

[1] Lewis *et al.*, *Nature* **2019**, *576*, 459-464.
[2] Hiller *et al.*, *Nature* **2021**, *593*, 125-129.
[3] Schäberle *et al.*, *Microbiol. Spectrum* **2021**, *9*, e01535-01521.
[4] Müller *et al.*, *Angew. Chem. Int. Ed.* **2023**, *62*, e202214094.
[5] Sarlah *et al.*, *J. Am. Chem. Soc.* **2022**, *144*, 14026-14030.
[6] Baran *et al.*, *J. Am. Chem. Soc.* **2022**, *144*, 14458-14462.