THE SYNTHESIS OF AN ARTIFICIAL, BACKBONE MODIFIED ENTEROBACTIN ANALOGUE

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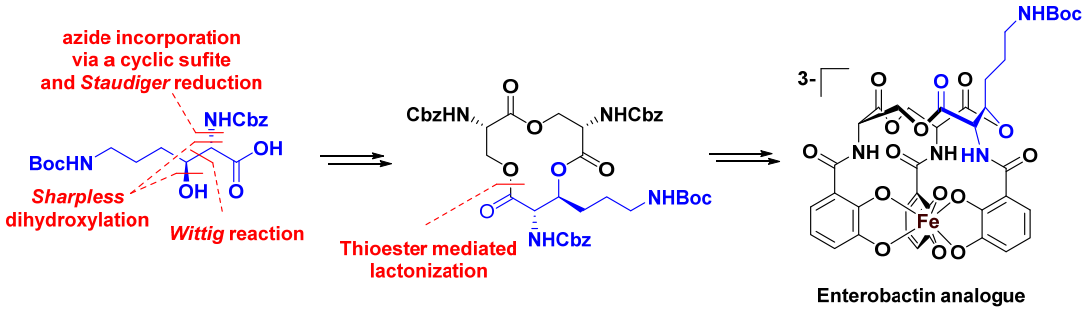
Enterobactin is a *tris*-catechol siderophore displaying a high affinity for Fe(III)-ions ($K_D=10^{52}$)[1], which is utilized by several Gram-negative pathogens, such as *E. coli* and *P. aeruginosa*, to ensure their supply with iron. Especially, during human host infection high-affinity iron binders such as Enterobactin play an important role in bacterial iron acquisition to compete with host iron binders such as transferrin and hem. To counteract growing bacterial resistance to market antibiotic, there is a strong need for the development of novel anti-microbials against bacterial pathogens. In this context, especially, Gram-negative bacteria are hard to tackle as their asymmetric cell envelope provides an effective permeation barrier rendering multiple compounds, showing activity against Gram-positive bacteria, inactive against Gram-negative ones. A smart approach to translocate drugs over this barrier and accumulate them in Gram-negative bacteria is the development of siderophore-drug conjugates. We want to develop novel siderophore-drug conjugates based on a backbone modified Enterobactin analogue. Here, we report about the synthesis and evaluation of this analogue.[2] Retro synthetically, we wanted to assemble the analogue by cyclization of a linear trimer precursor, bearing a γ-modified *L-allo*-threonine derivative. This building block was supposed to place a functional handle for drug conjugation at the opposite face of the catechol units at the backbone, in order not to interfere with the siderophore recognition. Furthermore, an elaborated protective group strategy was necessary for the assembly of the intrinsically labile linear precursor. Finally, the formation of the 12-membered *tris*-lactone backbone and decoration with siderophore units led to the desired Enterobactin analogue.



Scheme 1: Retrosynthesis of backbone modified Enterobactin.

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[1] Harris, W. R.; Carrano, C. J.; Cooper, S. R.; Sofen, S. R.; Avdeef, A.; McArdle, J. V.; Raymond, K. N, *J. Am. Chem. Soc.* **1979**, *101*, 6097.

[2] Zscherp, R.; Klahn, P. **2019**, unpublished results.