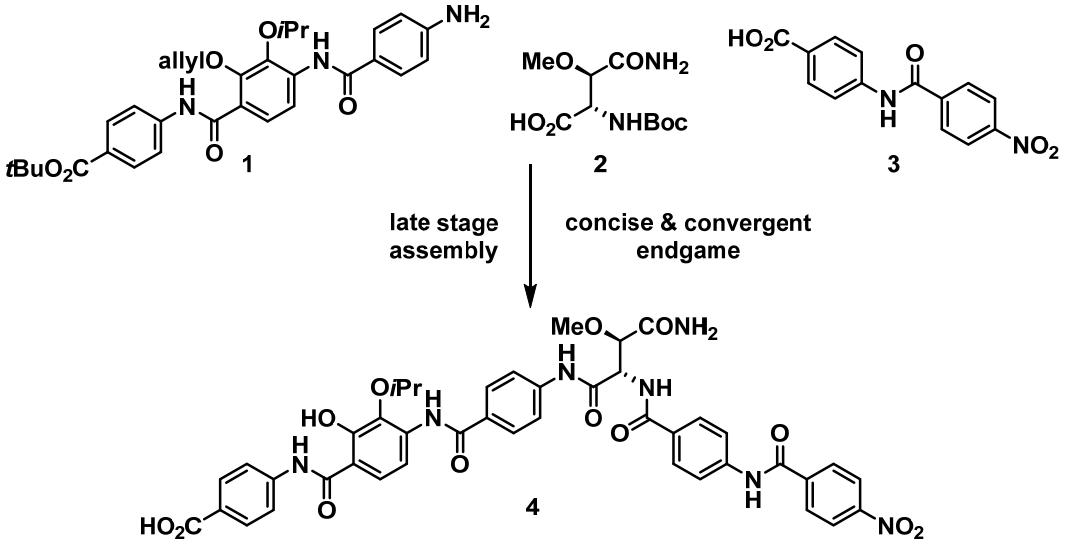
IMPROVED SYNTHESIS OF CYSTOBACTAMID 861-2 AND ANALOGS

Malte Moeller, Matthew D. Norris, Therese Planke and Andreas Kirschning

Institute of Organic Chemistry and Centre of Biomolecular Drug Research (BMWZ), Leibniz Universität Hannover, Schneiderberg 1B, 30167 Hannover, Germany

The cystobactamids are a family of nonribosomal peptides that were first isolated from extracts of the myxobacterium *Cystobacter* sp. (Cbv34) by Müller and co-workers in 2014.[1] Later, cystobactamid 861-2 (**4**) was identified as one of the more potent compounds with inhibitory effects in the low $\mu g\ mL^{-1}$ range against a broad panel of Gram-negative bacteria; thus showing similar therapeutic potential to that of the quinolones, which have been exhausted as a template for the development of new antibiotics.[2] We have previously described the total synthesis of **4**[2] and the related compound cystobactamid 920-1.[3] Despite the success of our existing approach, performing the synthesis on a larger scale has remained a significant challenge. Here, we present an improved and more highly convergent strategy, which is amenable to access both natural and novel cystobactamid analogues in larger quantities (50-100 mg) by linking different polyaromatic fragments to the β-methoxyasparagine "hinge" at a later stage.



Scheme 1: Improved synthesis of cystobactamid 861-2 *via* a convergent approach.

[1] S. Baumann *et al.*, *Angew. Chem., Int. Ed.* **2014**, *53*, 14605-14609.

[2] T. Planke *et al., Org. Lett.* **2019**, *21*, 1359-1363.

[3] S. Hüttel *et al.*, *Angew. Chem., Int. Ed.* **2017**, *56*, 12760-12764.