TOWARDS THE TOTAL SYNTHESIS OF VIOPROLIDES A-D

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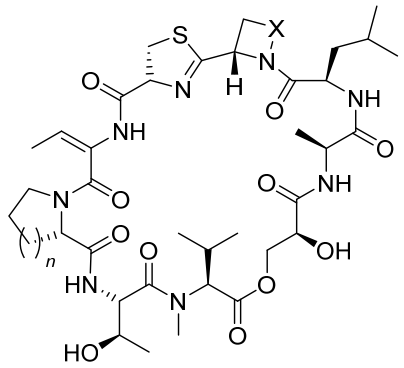
In 1996, a group of peptolides was isolated from the myxobacterium *cystobacter violaceus* (strain Cb vi35) that revealed potent cytotoxicity (LD_{50} up to 2 $ng \cdot ml^{-1}$) and antifungal effects [1]. These metabolites, called vioprolides A-D, were shown to be structurally closely related and only differ regarding two amino acid units. Vioprolides A and C contain the unusual (2*S*,4*R*)-4-methylazetidine carboxylic acid (L-Maz), while vioprolides B and D incorporate L-proline at the same position. The other varying building block is occupied by L-pipecolic acid (vioprolides A and B) or L-proline (vioprolides C and D). Due to their potent biological activity and their unknown mode of action, these natural products have been attractive synthetic targets to the chemical community, but still, their total synthesis remains an unsolved challenge [2].



n = 2, X =  vioprolide A

n = 2, X = —CH_2CH_2— vioprolide B

n = 1, X =  vioprolide C

n = 1, X = —CH_2CH_2— vioprolide D

So far, our synthetic work has focused on vioprolide D. As previous reports by other groups showed the difficulty of synthesizing the strained (*E*)-dehydrobutyrine [2b], our efforts were concentrated on the (*Z*)-configured epimer of vioprolide D, a molecule with unstudied biological properties whose synthesis is therefore worthwhile in its own right. We will present the convergent synthesis of different linear precursor molecules that were applied in alternative macrocyclization approaches. The presentation will be completed by our most recent studies of the final transformations in the synthesis of (*Z*)-vioprolide D and our plans as well as preliminary results concerning its isomerization to the (*E*)-configured natural product itself.

[1] D. Schummer, E. Forche, V. Wray, T. Dimke, H. Reichenbach, G. Höfle, *Liebigs Ann.* **1996**, 971-978.
[2] a) N. Chopin, F. Couty, G. Evano, *Lett. Org. Chem.* **2010**, *7*, 353-359. b) E. Butler, D. Cornut, G. Gomez-Campillos, H. Liu, A. C. Regan, L. F. Rico, E. J. Thomas, *Org. Biomol. Chem.* **2018**, *16*, 6935-6960.