Towards the total syntheses of Variecolorin D and K from the halotolerant fungus *Aspergillus variecolor*

A. Dierks,[a] T. Lindel[a]
TU Braunschweig, Hagenring 30, 38106 Braunschweig, Germany
a.dierks@tu-braunschweig.de

The isoechinulin-type alkaloids variecolorin A−L (D: **1**, K: **2**) from the fungus *Aspergillus variecolor* display radical scavenging, UV-A-protecting, immunosuppressive, and anti-bacterial activity. The variecolorins share a prenyl-derived side chain at C5, that may be oxygenated and chlorinated in various ways. As in the structurally related echinulins, a *tert*-prenyl group is present at C2 and the tryptophan head forms an alkylidene diketopiperazine unit with alanine.[1]

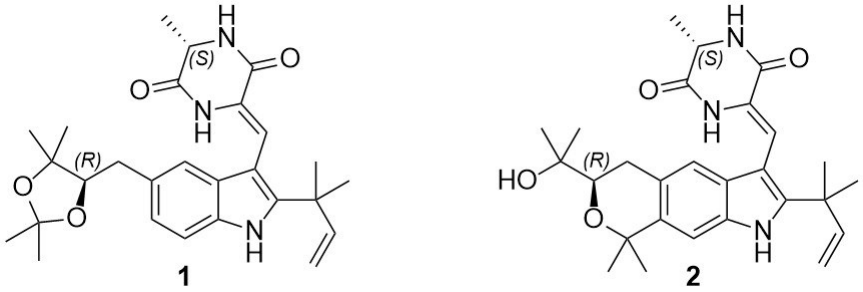

Figure 1. Variecolorin D (**1**) and K (**2**)

The first target was the synthesis of 6-iodo-5-prenylindoline by an aza-Claisen rearrangement from a *tert*-prenylated amine. The more direct strategy involving a reductive iodonio-Claisen rearrangement, which would follow an S_N2' attack of allyl or prenyl silane at an λ^3-iodane was found to be inferior. The main goal of this synthesis was to determine if the sterically crowded dihydropyran ring of **2** could be assembled. Sharpless AD of the prenyl group, followed by protection of the resulting diol as an acetonide, and subsequent hydroxyisopropylation of C6 through iodine/lithium exchange afforded the required cyclization precursor for variecolorin K (**2**) and the deiodonaited starting material, provides a precursor for variecolorin D (**1**). The subsequent deprotection and cyclization under acidic conditions established the dihydropyran ring of **2** for the first time. The total yield over eleven steps starting from indoline was 6.9% (*ee* = 69%). Elimination of *p*-toluenesulfinic acid, followed by *tert*-prenylation with boronic acid[2] at C2, formylation at C3, and condensation with *N,N'*-diacetyl-*c*[Ala-Gly], could give variecolorin D (**1**) and K (**2**).

1 W.-L. Wang, Z.-Y. Lu, H.-W. Tao, T.-J. Zhu, Y.-C. Fang, Q.-Q. Gu, W.-M. Zhu, *J. Nat. Prod*. **2007**, *70*, 1558. 2 M. Ghosh, S. Sahu, S. Saha, M. S. Maji, *Chem. Sci.* **2024**, *15*, 1789.