Studies Towards the Total Synthesis of Griseoviridin

C. Caso[1], A. Perera[1], K. H. Altmann[1]*

[1]Department of Chemistry and Applied Biosciences, Institute of Pharmaceutical Sciences, ETH Zürich

Griseoviridin (**1**) is a natural product of mixed polyketide-non-ribosomal peptide origin, which was first isolated from culture broths of *Streptomyces griseus* in 1955 by Bartz and co-workers. The compound belongs to the streptogramin A class of antibiotics and exerts its antibacterial activity through binding to the ribosome and the inhibition of protein synthesis. Among the various type A streptogramins, griseoviridin (**1**) is the structurally most complex, featuring an additional thio-vinyl ether containing 9-membered lactone ring, and the one whose chemistry and biology has been least studied. Only a single total synthesis has been reported in the literature. Furthermore, no SAR studies on griseoviridin (**1**) have been reported to date. Its challenging chemical structure combined with its antibacterial activity prompted us to embark on the total synthesis of griseoviridin (**1**). We envision to access the natural product via late-stage construction of the macrolactone domain by an intramolecular HWE reaction; we hypothesize that conducting this key step with the macrolactam system already installed could provide a favorable pre-organization effect for the closure of the strained 9-membered ring. The macrocycle **2** is traced back to the two major building blocks **3** and **4** via a Pd-catalyzed cross-coupling / amide coupling sequence. Herein, we present the current state of our efforts towards the total synthesis of griseoviridin (**1**), including the successful synthesis of vinyl iodide **4** and phosphonate **3**, the results of model studies investigating the feasibility of the envisioned intramolecular HWE reaction, and our attempts directed at forging the macrocyclic backbone.