"Studies towards the total synthesis of skyllamycin A"

by Alexander Denisiuk

Abstract

This work is concerned with studies towards the total synthesis of cyclic depsipeptide skyllamycin A. This natural product was isolated from *Streptomyces* sp. Acta 2897 and shows a potent activity with respect to inhibition of growth factor PDGF BB with an IC_{50} = 11 µM. The 34-membered macrolactone skyllamycin A possesses a scaffold of 11 amino acids, whilst simultaneously showing a high degree of hydroxylations. Additional to the three β-hydroxylations, one glycine bears an unusual α-hydroxyl group. This has only been reported previously in the immunosuppressive peptides spergualin and desoxyspergualin. Due to its inherent instability as an amino acid, its direct incorperation into a peptidic structure is not possible and cannot be used as analytical standard for chiral GC-MS analysis. Additionally a rarely found 2-[1-(*Z*)-propenyl]-cinnamoyl moiety is bound to the *N*-terminus of the molecule which has only been described for the tachykinin antagonist WS9326A8 and the farnesyl transferase inhibitor group of pecticinnamins. Further structural characteristics of the complex diversity of the peptide are different methylations such as those of tyrosine and aspartic acid. To confirm the structure of the natural product this work could establish the synthesis of each building block. Furthermore, the synthetic peptide could be synthesized by a convergent strategy. The protecting group limitations could be circumvented by specific fragment synthesis, and through the careful choice of the cyclization-site, this provided the cyclic peptide. The subsequent global deprotection did not lead to the formation of skyllamycin A, which was effected by the strong acid conditions. However, the presented synthetic route enabled the synthesis of the peptide structure and establishes a basis to the synthesis of skyllamycin A after an exchange of the protecting group strategy.