Chemical Synthesis and Rational Design of Ion Channel Functions

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Polytheonamide B (**1**) is a potent cytotoxic natural product isolated from the marine sponge, *Theonella swinhoei*, and is by far the largest nonribosomal peptide known to date. The 48 amino acid residues including a variety of nonproteinogenic amino acids have the sequence of alternating D- and L-chirality. These structural features permit the formation of a single stranded helix of 6.5 residues per turn, which forms a pore of approximately 4 Å in diameter. In the biological setting, cations can be transported across lipid bilayer of cells through the pore to exert its bioactivity. The unique and synthetically challenging structure of **1** together with the potent cytotoxicity motivated us to launch a project for their chemical construction. Here we report the first total synthesis of polytheonamide B.

The containing nonproteinogenic amino acids were prepared by multi-step syntheses from readily available starting materials. Then, four peptide fragments (A, B, C, and D) were synthesized on solid phase under the carefully optimized conditions. Next, A, B, and C were derivatized to the corresponding thioesters, and the union of these fragments was performed using $AgNO_3$ in the presence of HOOBt in a stepwise fashion, delivering the protected polytheonamide B. The last global deprotection was realized under the acidic conditions to provide polytheonamide B. The present versatile synthetic strategy should be useful for synthesizing the variable analogs that may provide valuable structural insight into its channel function and dynamic behavior.