Isolated in 2005, gymnocin B is the second largest contiguous marine ladder polyether, comprising one THF, nine THPs, and five oxepanes. Herein, we report the first total synthesis of gymnocin B based on a two-phase strategy. In Phase I, inspired by the proposed biosynthesis, four epoxide-opening cascades assemble 10 out of 15 cyclic ether rings making up the molecular core. In the subsequent Phase II, coalescence elevates the molecular complexity further by coupling of these subunits. As demonstrated by a 45-step longest-linear-sequence synthesis of gymnocin B, our two-phase synthetic approach significantly improved the step efficiency of the synthesis of this class of natural products.

References