Total Synthesis of Isodaphlongamine H

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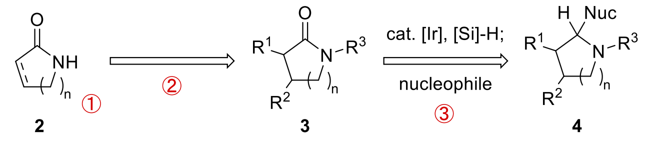
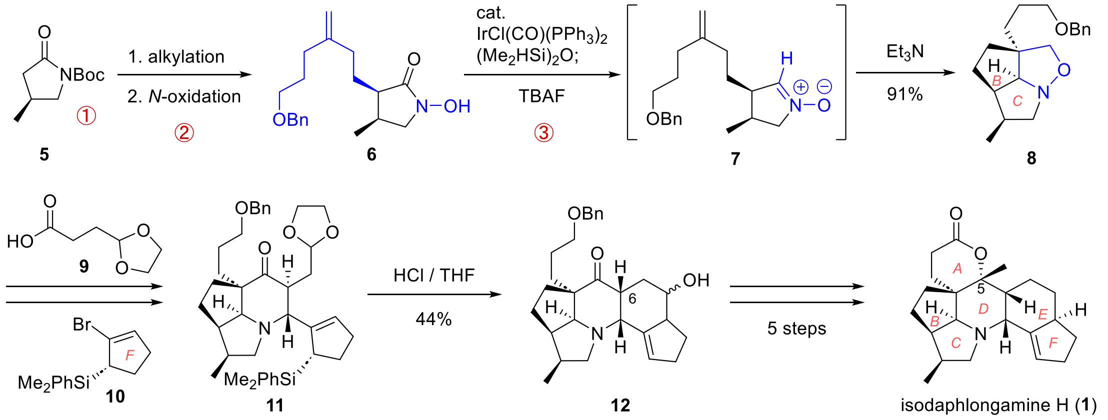
Isodaphlongamine H (**1**) is an unnatural 5-*epi* isomer of daphlongamine H,[1)] but is known to show the comparable cytotoxicity against several human cell lines. Structurally, it features a hexacyclic skelton containing eight stereocenters. In this study, we report the total synthesis of isodaphlongamine H (**1**) based on a lactam strategy to give highly substituted cyclic amines, which involves i) use of easily available lactam **2** as a starting material, ii) lactam functionalization, and iii) amide carbonyl functionalization.

Our synthesis commenced with alkylation and *N*-oxidation of easily available chiral lactam **5** to provide *N*-hydroxylactam **6**.[2)] As a key amide carbonyl functionalization, treatment of **6** with the Vaska complex and tetramethyldisiloxane, followed by addition of TBAF generated cyclic nitrone **7**.[3)] The resulting nitrone **7** was then heated in a one-pot process to promote an intramolecular [3+2] cycloaddition, affording isoxazolidine **8** in 91% yield. After isoxazolidine **8** was transformed to tetracyclic intermediate **11**, intramolecular Hosomi-Sakurai allylation furnished pentacyclic compound **12**, associated with epimerization at C6. The total synthesis of isodaphlongamine H (**1**) was accomplished in 5 steps from **12**.



lactam stategy
① Use of from easily available lactam
② Lactam functionalization
③ Amide carbonyl functionalization



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