Design and Synthesis of Indole-fused Saframycin-like Skeletons Towards Modulation of DNA Alkylation Ability

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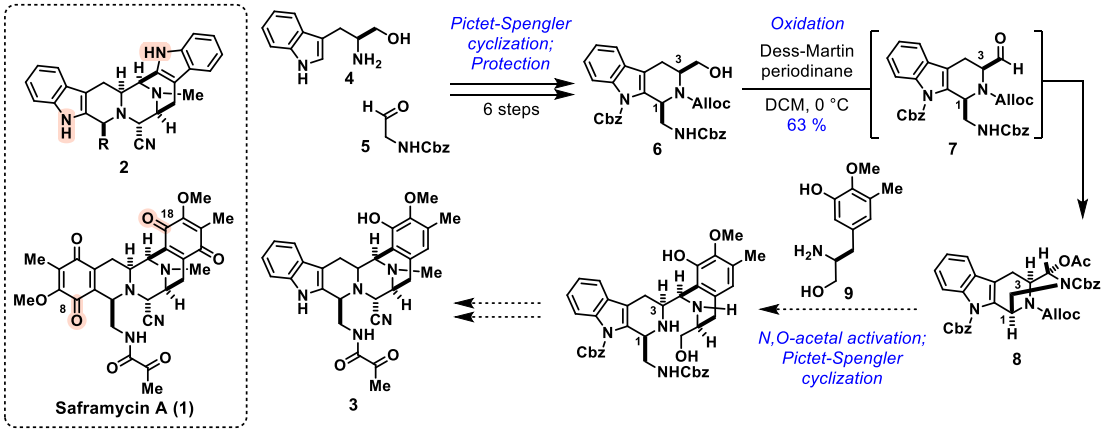
Bis-tetrahydroisoquinoline (THIQ) alkaloids represented by saframycins (**1**) share a densely functionalized pentacyclic scaffold composed of two THIQ units. According to recent reports from both Stoltz and our group, phenolic hydroxyl groups at 8 and 18 positions are likely to play pivotal roles on interaction with DNA,[1,2] while Liu designed heptacyclic scaffold **2** bearing indole NH groups in places of the two hydroxyl groups.[3] In this study, we designed a hexacyclic skeleton **3** with replacement of the left THIQ segment with an indole-fused tetrahydro-β-carboline moiety to modify the mode of interaction with DNA.

Pictet-Spengler reaction of L-tryptophanol **4** with aldehyde **5** and subsequent protecting group manipulations produced **6** as a left segment. While oxidation of the primary alcohol **6** to form the corresponding aldehyde **7** turned out to be challenging under conventional conditions, we alternatively found that treatment of **6** with Dess-Martin periodinane in dichloromethane at 0 ºC resulted in the rapid formation of a stable tetracyclic intermediate **8** bearing an *N*, *O*-acetal moiety in good yield (63%) with nearly complete controls of diasteroselectivities. Further efforts toward assembly of **8** with amino alcohol **9** to construct right segment of **3** will be presented.



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