Design and modular synthesis of dimeric skeletons of indole alkaloids

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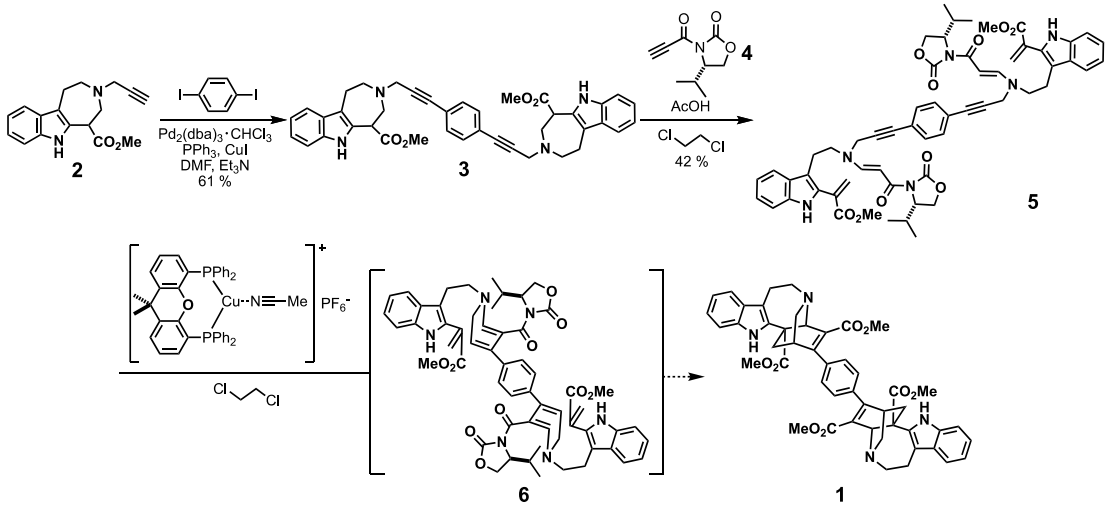
Naturally occurring dimeric indole alkaloids, represented by anticancer drug vinblastine, exhibit potent and unique biological activities involving modulation of protein-protein interaction. In this study, we are developing a modular and asymmetric synthetic process for dimeric alkaloidal scaffolds based on the previously reported biogenetically inspired [4+2] cycloaddition between vinyl indole and 1,6-dihydropyridine installed with a chiral auxiliary.[1)]

Toward concise synthesis of chiral dimeric scaffolds comprised of a pair of pentacyclic *iboga*-type skeletons and a spacer unit, we designed C_2-symmteric dimeric scaffold **1** bearing a 1,4-benzene linker moiety for modular assembly of left and right-segments. Sonogashira coupling of *N*-propargylated azepinoindole **2** with 1,4-diiodobenzene furnished a dimeric intermediate **3** with a benzene unit as the spacer. Conjugate addition of racemic **3** to **4** bearing a chiral auxiliary and subsequent Hofmann elimination allowed installations of vinyl indole and β-carbonyl enamine moieties to give an enantiomerically pure enyne **5**. Cu(I)-catalyzed cyclization of **5** allowed formation of the key cyclization precursor **6** bearing a pair of 1,6-DHP units. Attempts for the biomimetic intramolecular [4+2] cycloadditions of the C_2-symmteric precursors with different spacer units will be reported.



1) Mizoguchi, H.; Oikawa, H.; Oguri, H. *Nat. Chem.* **2014**, *6*, 57.