Total syntheses of (+)-lycoricidine and (+)-narciclasine

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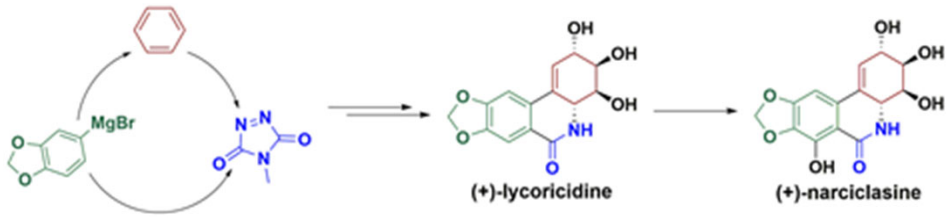
Two of the more potent congeners of the *Amaryllidaceae* isocarbostyril alkaloid class of natural products, (+)-narciclasine and (+)-lycoricidine, have been shown to possess sub-micromolar cytotoxicity that is selective for cancer cells. Despite this activity, in-depth studies of the biological functions of these natural products have been restricted by low isolation yields and limited synthetic access. Here, we describe short and scalable total syntheses of (+)-lycoricidine and (+)-narciclasine. Our approach to these natural products employs a dearomative [4+2] photocycloaddition of the arenophile *N*-methyl-1,2,4-triazolinedione (MTAD) with benzene. The resultant cycloadduct is then subject to a nickel catalyzed asymmetric dearomative *trans*-carboamination to introduce all the carbons of the natural products in a single operation. Subsequent olefin functionalization chemistry followed by a cascade epoxide isomerization, lithium halogen exchange, and intramolecular nucleophilic addition, produces the isocarbostyril core and enables rapid access to (+)-lycoricidine and (+)-narciclasine.



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