

## Synthetic Study of Clickable Dysiherbaine

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Chemical probes are important tools to elucidate functions of target proteins as well as their interactions. Development of chemical probes for ionotropic glutamate receptor (iGluRs), that mediates majority of fast excitatory neurotransmission in the central nervous system (CNS), is highly challenging due to the unique structure of the ligand binding domain.

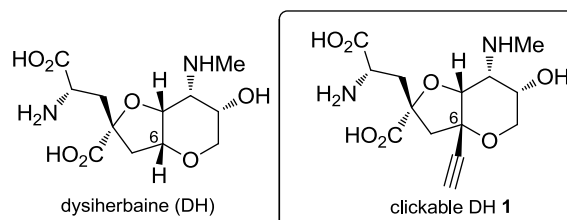


Figure 1

Dysiherbaine (DH, Fig. 1), which was isolated from Micronesian marine sponge *Lendenfeldia chondrodes* in 1997 by Sakai et al, is a potent agonist selective to GluK1- and GluK2-containing subtypes of kainate type iGluR. In the present study, we planned to synthesize clickable DH **1** (Fig. 1) as a precursor for the chemical probe which has ethynyl group at the C6 position. While several total syntheses of DH have been reported, de novo synthetic route was needed to be developed for the clickable DH bearing additional quaternary carbon center at C6.

Herein we report stereoselective synthesis of the vital intermediate, which has three stereocenters, performed in 10 steps starting from D-ribose. The key transformation includes domino aldol-Cannizzaro reaction followed by stereoselective aldol reaction at the ring juncture of the bicyclo[3.3.0]octane skeleton, and stereoselective addition of ethynyl group to the lactol moiety.