Synthesis and Neuroactivity of a Model for Clickable Dysiherbaine

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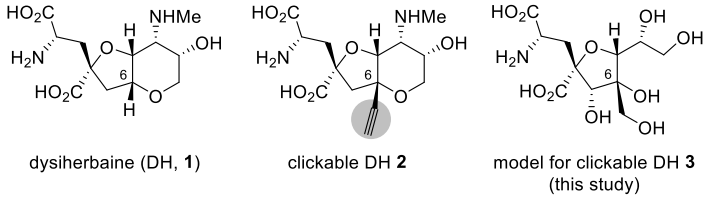
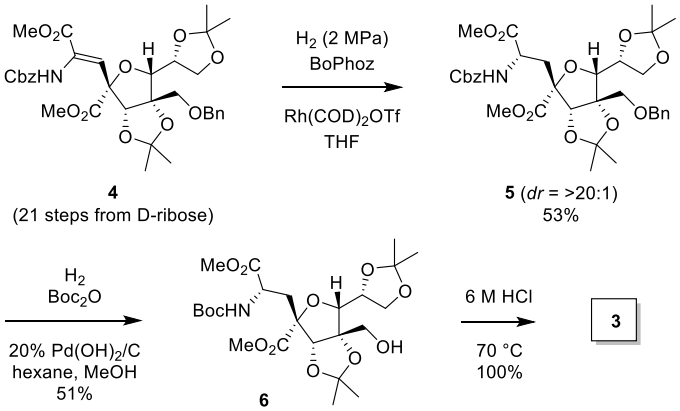
Ionotropic glutamate receptor (iGluR) mediates the majority of excitatory neurotransmission in the central nervous system. We are studying synthetic development of the chemical probe to investigate the biological function of iGluR at a subunit level, based on dysiherbaine (DH) which is a potent agonist for GluK1.[1]



Our design is as follows. From the structure of DH/GluK1 complex (3GBA),[2] C6 position was thought to be suitable for introduction of alkynyl group, which is the key functionality for conjugation with various tags. In this study, model compound **3** was decided to be synthesized prior to **2** to confirm the neuroactivity. The model **3** was expected to be obtained from a synthetic intermediate en route to clickable DH **2**.



Synthesis of dehydroamino acid ester **4** has been already established and reported.[3] Asymmetric hydrogenation of **4** using BoPhoz ligand proceeded stereoselectively to elaborate glutamic acid side chain in 53% yield. Hydrogenolysis of Bn and Cbz groups in the presence of Boc_2O gave **6** in 51% yield. Global deprotection by acidic hydrolysis quantitatively furnished the model for clickable DH **3**. Neuroactivity of **3** is under evaluation and the results will be also presented.

1) Sakai, R. et al *J. Am. Chem. Soc.* **1997**, *119*, 4112. 2) Frydenvang, K. et al *J. Biol. Chem.* **2009**, *284*, 14219. 3) Fukushima, K. et al *The 95th Annual Meeting of The Chemical Society of Japan*, **2015**, 1J1-38 (March 26, 2015).