Synthetic Study of Lycoperdic Acid and Analogs by Asymmetric Hydrogenation of α–Dehydroamino Acid Ester

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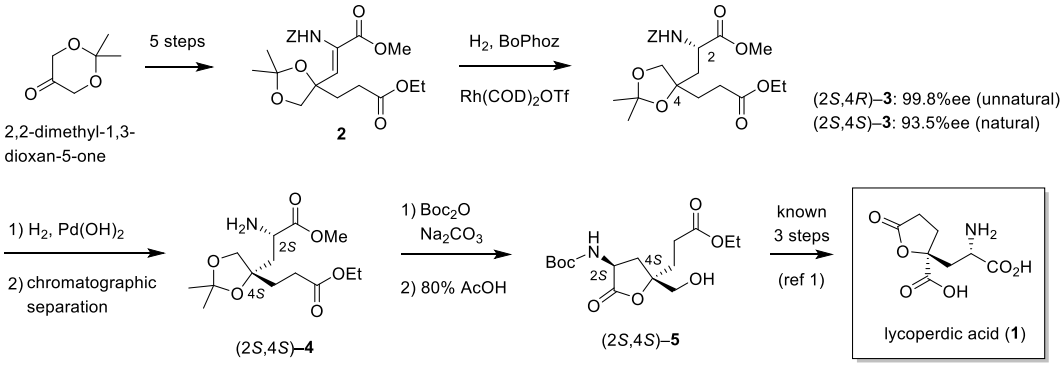
Ionotropic glutamate receptors (iGluRs) mediate the majority of the fast excitatory neurotransmission in the mammalian central nervous system to play a pivotal role in the higher brain functions such as learning, memory, and nociception. Many of the naturally occurring ligands for iGluR typically contain glutamic acid motif fused to five-membered heterocycle such as tetrahydrofuran and pyrrolidine. Here, we planned to develop artificial glutamate analogs as a novel ligand for iGluR, inspired by mushroom-derived lycoperdic acid bearing glutamic acid motif on the γ–butyrolactone core which shows only weak affinity to iGluRs.

Our synthesis plan features diverted synthesis of the analogs via common intermediate **2**, which was prepared in 5 steps from commercially available 2,2–dimethyl–1,3–dioxin–5–one. Thus, asymmetric hydrogenation (H_2, Rh/BoPhoz) of enamide **2** provided (2*S*,4*S*)–**3** with natural configuration (93.5% ee) accompanying formation of unnatural (2*S*,4*R*)–isomer (99.8% ee). The diastereomers were successfully separated after deprotection of the Z group to give (2*S*,4*S*)–**4**. Reprotection (Boc_2O, Na_2CO_3) followed by acidic hydrolysis of isopropylidene group spontaneously facilitated lactonization to furnish γ–butyrolactone (2*S*,4*S*)–**5**, whose spectroscopic data were identical to those reported.[1] Our efforts toward synthesis of lycoperidic acid from (2*S*,4*S*)–**5**, as well as the synthesis of 4–*epi*–lycoperdic acid from (2*S*,4*R*)–**3** will be presented.



1) O. Tamura et al, *J. Org. Chem.* **2005**, *70*, 4569-4577.