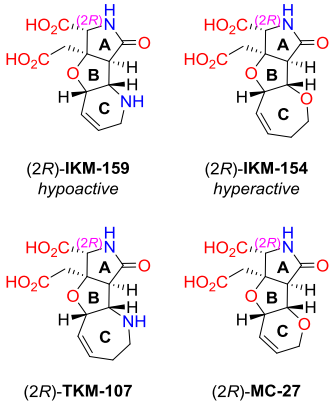
Studies on Asymmetric Synthesis of Artificial Glutamate Analogs Having Opposite Neuronal Activities

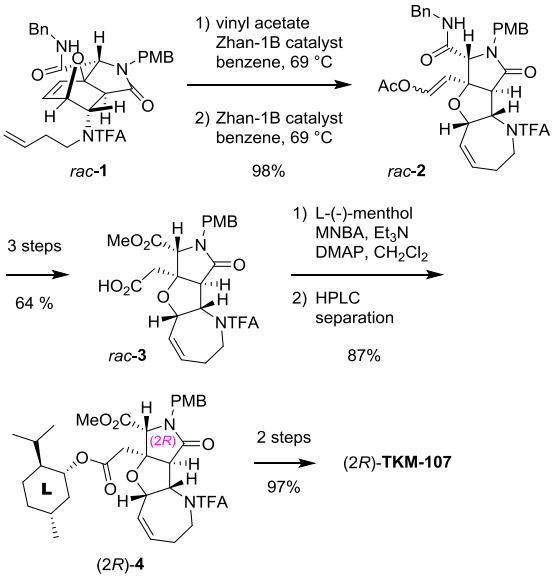
(*Division of Materials Science, International College of Arts and Sciences, Yokohama City University*) ○Shuntaro Tsukamoto, Kenji Morokuma, Yuichi Ishikawa, Masato Oikawa

Keywords: Glutamate Analogs; Asymmetric Synthesis; AMPA Receptor; *in vivo* Activity; Opposite Neuronal Activities

(2*R*)-IKM-159 is a selective AMPA receptor modulator,[1] developed in our laboratory as an artificial tricyclic glutamate analog inspired by two marine-derived natural products, dysiherbaine and kainic acid. From preliminary biological evaluations *in vivo*, (2*R*)-IKM-159 had been shown to be hypoactive, while (2*R*)-IKM-154, the analog bearing seven-membered oxepane ring, is hyperactive.[2] Herein, we report our efforts directed toward asymmetric synthesis of other analogs wherein the C-ring of (2*R*)-IKM-159 is substituted with azepine (TKM-107) or pyran (MC-27).



Starting from tandem four-component reaction previously reported, alkenylated oxanorbornene **1** was prepared, after conjugate addition of *N*-butenyl TFA amide. Modified domino metathesis mediated by Zhan-1B catalyst in the presence of vinyl acetate proceeded smoothly to provide heterotricycle **2**, via intermediary triene (structure not shown). After Boc protection and methanolysis followed by Pinnick oxidation, we obtained carboxylic acid **3**, which, in turn, was converted to chiral diastereomers by esterification with chiral alcohol. HPLC separation successfully furnished (2*R*)-**4**, whose structure was elucidated on the basis of NOESY analysis. *N*-PMB group of (2*R*)-**4** was then removed by CAN, and global deprotection using 6 M hydrochloric acid finally provided (2*R*)-TKM-107. We are now working on the synthesis of (2*R*)-MC-27 as well, by using the same procedure. The synthesis and *in vivo* activities will be presented.



1) M. B. Gill, S. Frausto, M. Ikoma, M. Sasaki, M. Oikawa, R. Sakai, G. T. Swanson, *Br. J. Pharmacol.* **2010**, *160*, 1417. 2) H. Itagaki, Y. Ishikawa, M. Oikawa, *The 97th CSJ Annual Meeting* **2017**, 1C8-11.