Studies on Asymmetric Synthesis of Excitatory Agent IKM–154

(*Yokohama City University*) ○Hiyori Itagaki, Yuichi Ishikawa, Masato Oikawa
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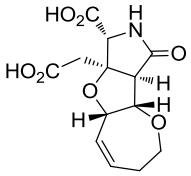
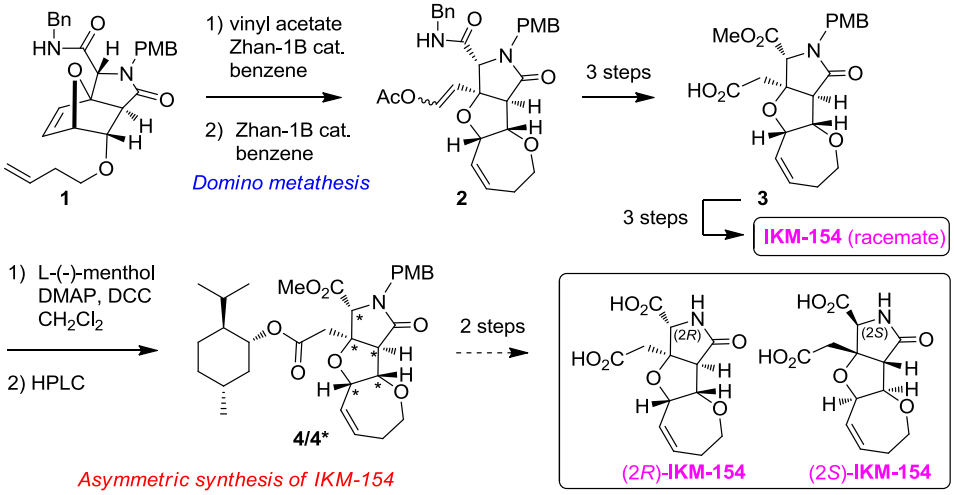
IKM–154 was developed in our laboratory as an artificial tricyclic glutamate analog inspired by two marine-derived natural products.[1] From the preliminary biological evaluations in vivo, IKM–154 had been suggested to be excitatory, in marked contrast to the fact that the closely related analog, IKM–159, is a selective AMPA receptor modulator and is inhibitory in vivo. Here, we studied to establish the synthetic route of IKM–154 in large quantities used for detailed studies on the pharmacology and the structural biology.



IKM-154 (racemate)

Starting from tandem four-component coupling reaction, alkenylated oxanorbornene **1** was obtained in tens of gram quantities, after conjugate addition of 3-buten-1-oxide. Modified domino metathesis mediated by Zhan–1B catalyst in the presence of vinyl acetate proceeded quite smoothly to give rise to heterotricycle **2**, via intermediary triene (structure not shown). According to our reported procedure, 200 mg of racemic IKM–154 was successfully synthesized after 6 steps, which exhibited hyperactivity upon mice intracerebroventricular injection.



Asymmetric synthesis of IKM-154

We next studied asymmetric synthesis of IKM–154 to determine the enantiomer responsible to the neuroactivity. We have studied three chiral reagents for optical resolution of the intermediates in the racemate synthesis, and found that menthyl ester formation allowed us to efficiently separate the diastereomers **4/4*** by using HPLC.

We are now trying to remove all the protecting groups toward both enantiomers of IKM–154. The syntheses and in vivo activities will be reported.

1) M. Oikawa, Y. Kasori, L. Katayama, E. Murakami, Y. Oikawa, Y. Ishikawa, *Synthesis*, **2013**, *45*, 3106-3117.