Studies towards a Short and Scalable Total Synthesis of (-)-α-Kainic Acid Using Pt-Catalyzed Allylic Amination

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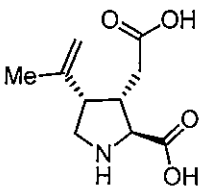
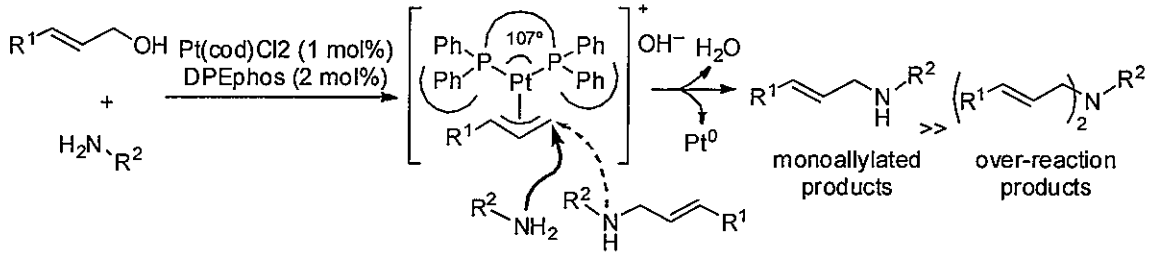
【Object】

(–)-α-Kainic acid (**1**), the parent member of kainoid family, was first isolated from the marine alga *Digenea simplex* in 1953. It has been widely used as a tool in neuropharmacology for mimicry of various stages of neuronal disorders due to its potent neuroexcitatory activity which is attributed to its conformational similarity to the neurotransmitter glutamic acid. However, it suffers a worldwide supply shortage from natural sources and a high price. Furthermore, the construction of a highly functionalized trisubstituted pyrrolidine ring with three contiguous stereogenic centers posed a considerable synthetic challenge. Therefore, KA has attracted considerable attention from synthetic chemists. Although many different groups have reported syntheses of KA, the development of short-step and practical synthetic methods is still very desirable.



(–)-α-Kainic acid (**1**)



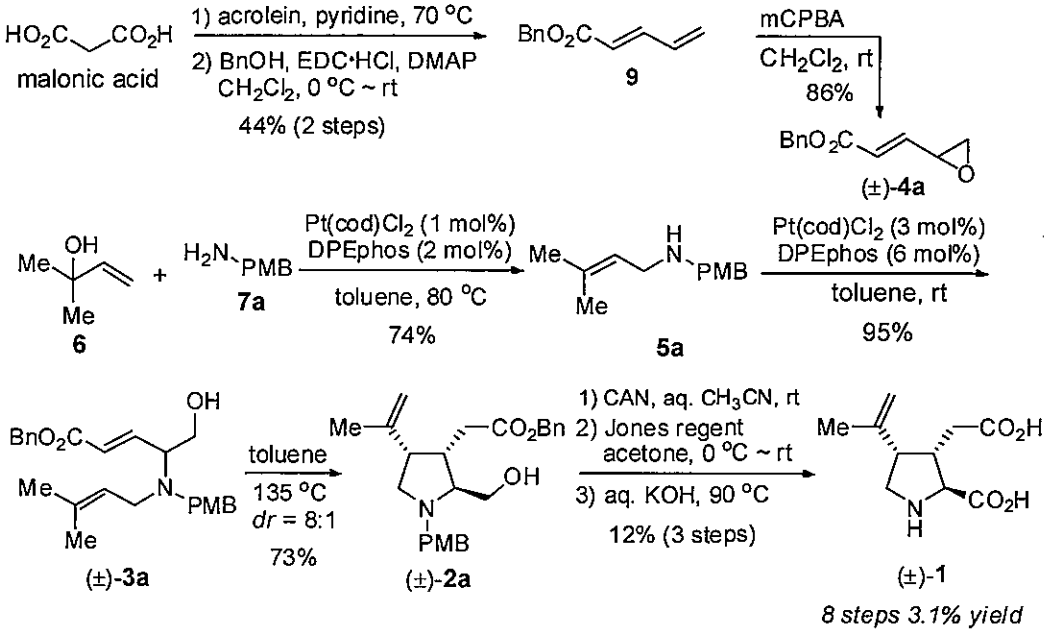
Scheme 1. Pt-catalyzed direct amination of allylic alcohols reported by our group

In our laboratory, we have developed a new catalyst system comprising the platinum catalyst $Pt(cod)Cl_2$ and a ligand DPEphos with a large bite angle for the catalytic direct amination of inactive allylic alcohols (**Scheme 1**). It allows for the selective preparation of various monoallylamines. Therefore, by using the direct allylic amination reaction with the platinum catalyst, I decided to develop a short and practical total synthesis of (–)-α-kainic acid.

【Method】

Firt generation synthesis

First, to synthesize the fragment **5a**, and to introduce a protecting group PMB simultaneously, allyl alcohol **6** was subjected to direct amination reaction with 4-methoxybenzylamine (**7a**) using the platinum catalyst (**Scheme 2**). Next, the epoxide (±)-**4a** was synthesized via three steps from malonic acid by Doebner modification reaction, esterification and epoxidation. Then, the epoxide (±)-**4a** was subjected to the second Pt-catalyzed allylic amination reaction with **5a** using the same platinum catalyst to obtain the key intermediate (±)-**3a**. Subsequently, (±)-**3a** was converted into a pyrrolidine precursor (±)-**2a** by Oppolzer type intramolecular ene reaction.



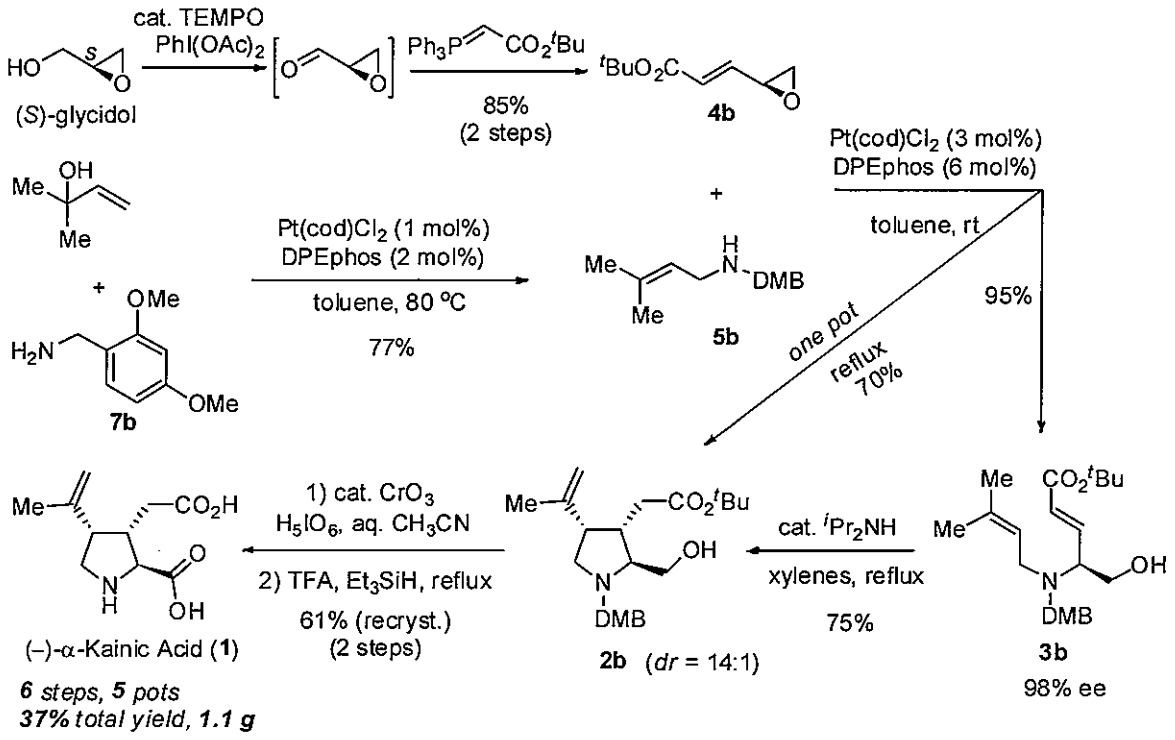
Scheme 2. First generation total synthesis of (±)-α-kainic acid

Finally, racemic synthesis of (±)-α-kainic acid was completed after deprotection with ceric ammonium nitrate (CAN), Jones oxidation and hydrolysis.

Second generation synthesis

First, allylamine **5b** was synthesized by Pt-catalyzed direct amination of allyl alcohol **6** with 2,4-dimethoxybenzylamine (**7b**) (**Scheme 3**). Next, the optically active epoxide **4b** was synthesized by a one pot sequential catalytic 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) oxidation and Wittig

reaction from commercially available optically pure (*S*)-glycidol. Then, the epoxide **4b** was subjected to the second Pt-catalyzed allylic amination reaction with **5b** to obtain the key intermediate **3b**. Subsequently, similarly to the first generation sthesis **3b** was converted into a pyrrolidine precursor **2b** by intramolecular ene reaction. A one-pot sequential Pt-catalyzed epoxide opening and ene-cyclization process was also conducted. After the first Pt-catalysis of alkenyl epoxide **4b** with allylamine **5b** at room temperature, the 2-aminoethanthiol or silica-supported dimercaptotriazine (DMT), which was used as a platinum scavenger, was added to the reaction mixture and heated at 135°C, delivering the desired pyrrolidine **2b**,

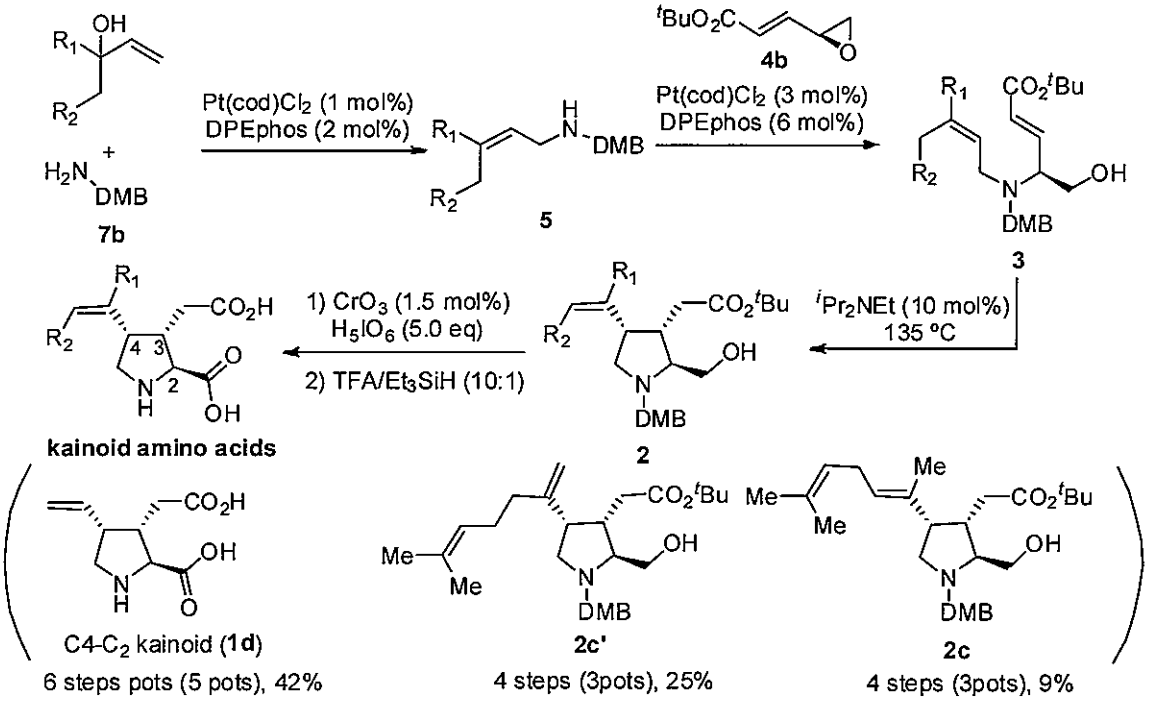


Scheme 3. Second generation total synthesis of (–)-α-kainic acid (**1**)

Finally, oxidation with 1.5 mol% amount of CrO_3 and 5.0 equivalents of terminal oxidant H_5IO_6, followed by subsequent deprotection of DMB and ^{t}Bu by trifluoroacetic acid (TFA) and Et_3SiH furnished the total synthesis of (–)-α-kainic acid (**1**).

Synthesis of kainoid anologue and kainoid precursors

Linaool and 3-buten-2-ol, which are inexpensive and readily available as the starting allylic alcohols, were subjected to the similar procedure for kainic acid. The kainoid precursors **2c**, **2c'** and a new kainoid **1d** were successfully synthesized (**Scheme 4**), almost under the identical conditions to that of kainic acid without much further optimization.



Scheme 4. Synthesis of kainoid anologue and kainoid precursors

【Results】

The shortest total synthesis of (–)-α-kainic acid (**1**) was developed with 6 steps (5 pots) and 37% overall yield, using platinum-catalyzed allylic amination reactions in two sequential steps. The practical synthesis in gram scale was also achieved with the same efficiency in 6-step chemical transformation. Moreover, a novel kainoid amino acid (**1d**) and two kainoid precursors (**2c**, **2c'**) were also synthesized using the process, proving that it is also applicable to general synthesis of a variety of other natural or unnatural kainiod amino acids.

【References】

(1) Ohshima, T.; Mashima, K. et al. *Org. Lett.* **2007**, *9*, 3371.
(2) Ohshima, T.; Mashima, K. et al. *J. Am. Chem. Soc.* **2009**, *131*, 14317.
(3) Ohshima, T.; Mashima, K. et al. *Angew. Chem. Int. Ed.* **2012**, *51*, 150.