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Total Synthesis

A Short Scalable Route to (−)-α-Kainic Acid Using Pt-Catalyzed Direct Allylic Amination

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Abstract: An increased supply of scarce or inaccessible natural products is essential for the development of more sophisticated pharmaceutical agents and biological tools, and thus the development of atom-economical, step-economical and scalable processes to access these natural products is in high demand. Herein we report the development of a short, scalable total synthesis of (−)-α-kainic acid, a useful compound in neuropharmacology that is, however, limited in supply from natural resources. The synthesis features sequential platinum-catalyzed direct allylic aminations and thermal ene-cyclization, enabling the gram-scale synthesis of (−)-α-kainic acid in six steps and 34% overall yield.

The dramatic evolution of organic chemistry in the twentieth century enabled the syntheses of many complex molecules, including highly functionalized natural products.[1] An increased supply of scarce or inaccessible natural products is essential for the production of more sophisticated pharmaceutical agents and biological tools. Practical syntheses of such complex molecules, however, remain quite difficult, even with modern organic chemistry techniques, and thus the development of highly practical, atom-economical, and step-economical processes is in high demand.[2]

(−)-α-Kainic acid (**1**), a member of the kainoid family containing a glutamic acid scaffold[3] (Figure 1), exhibits a potent neural-excitability effect and is widely used in neuropharmacological studies of the mechanisms of neuronal apoptosis,[4] amyotrophic lateral sclerosis,[5] Alzheimer's disease,[6] and Huntington's disease.[7] The huge demand for (−)-α-kainic acid (**1**) in the neuroscience field and its limited supply from natural sources has resulted in a worldwide shortage and a high price of **1**.[8] Although **1** is a potential target for total synthesis, the construction of three contiguous stereogenic centers in the pyrrolidine ring, especially the thermodynamically less favorable C3–C4 *cis* configuration, is highly challenging.[9] Since the pioneering achievement of the enantioselective synthesis of **1** by Oppolzer and Thirring,[10] several efficient total syntheses of **1** have been reported.[11] Recently, Fukuyama and co-workers accomplished a multigram-scale practical synthesis of **1** using an intramolecular olefin ring-closing metathesis, but the process required 13 linear steps.[11ai] Lin and co-workers reported the shortest synthesis of **1** (7 steps) with approximately 40% overall yield, but the process provided **1** only on a scale of less than 50 mg.[11an] Thus, there remains much room to develop a highly practical, atom-economical, and step-economical process of **1**.

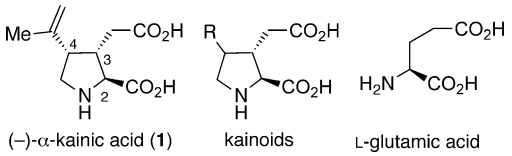
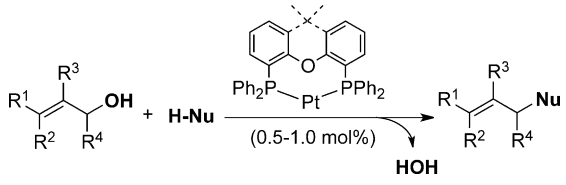


Figure 1. Structures of (−)-α-kainic acid, kainoids, and L-glutamic acid.

Herein we disclose a short and scalable synthesis of (−)-α-kainic acid (**1**), featuring sequential platinum-catalyzed direct allylic aminations and ene-cyclization. A gram-scale synthesis of **1** also proceeded with the same efficiency to afford chemically and optically pure crystalline **1** in 6 steps and 34-37% overall yield. Moreover, a one-pot process of Pt-catalyzed allylic amination and ene-cyclization further improved the pot-economy of the whole process to only 5 pots.

To satisfy the global demand for (−)-α-kainic acid (**1**) in an environmentally friendly manner, we planned to develop an atom- and step-economical scalable production of **1**. We recently reported the successful development of a direct catalytic substitution of allylic alcohols with aryl amines, alkyl amines, ammonia, or carbon nucleophiles, promoted by the combination of [Pt(cod)Cl_2] and a large bite-angle ligand, DPEphos or Xantphos (Scheme 1).[12] This process proceeded in a highly



Scheme 1. Pt-catalyzed direct catalytic substitution of allylic alcohols.

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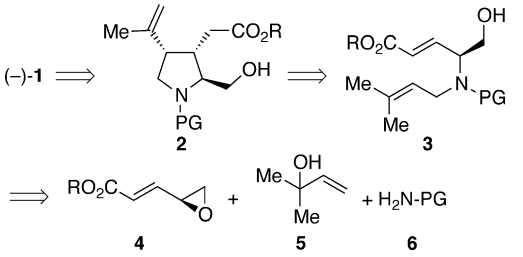
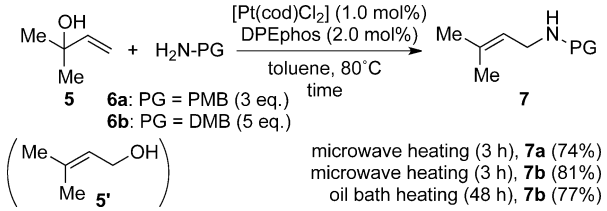
monoallylation-selective manner to afford the desired monoallylation products in high yield, because a sterically congested π-allyl–Pt intermediate created by the large bite angle ligand allows for a preferential selective reaction with the substrate over the monoallylated products, thereby preventing problematic over-reactions.[13] This process does not require the pre-activation of allylic alcohols, and produces the desired allylated products together with water as the sole coproduct. In terms of atom-economical and environmental aspects, this is a more straightforward and desirable method than conventional transition-metal catalyses, which require pre-activated allylic alcohols such as allylic acetates and carbonates. We therefore envisioned the use of this Pt catalysis for the construction of diallylamine **3** having different allyl moieties from allylic alcohol **5** and alkenyl epoxide **4** (Scheme 2). Subsequent enecyclization would provide fully functionalized pyrrolidine **2** in a diastereoselective manner.



Scheme 2. Retrosynthetic analysis for (−)-α-kainic acid (**1**).

The synthesis of (−)-α-kainic acid **1** commenced with the direct amination of α,α-disubstituted allylic alcohol **5** rather than γ,γ-dimethyl allylic alcohol **5′**, because platinum catalysis is more strongly affected by steric congestion around the C=C double bond in the allylic alcohol than that around the hydroxy group[12] (Scheme 3). Initially, 4-methoxybenzyl (PMB)



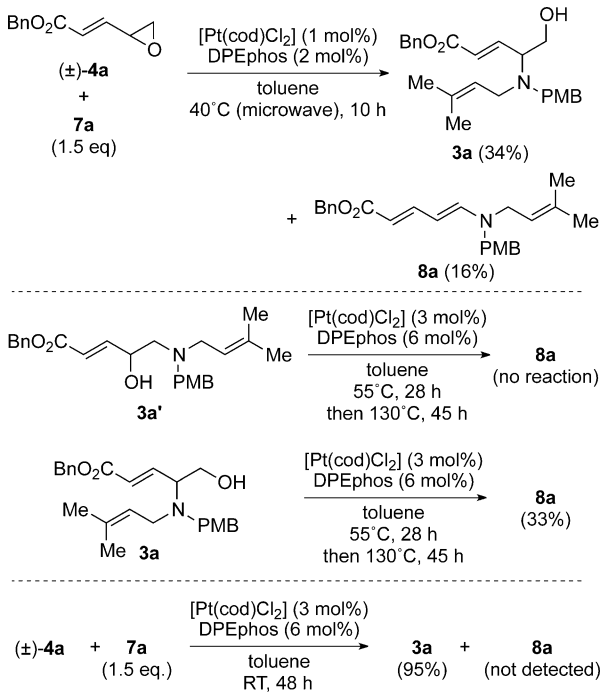
Scheme 3. Synthesis of monoallylamine **7** using Pt-catalyzed direct amination of allylic alcohol **5**.

amine (**6a**) was examined as a nitrogen nucleophile, but we finally selected 2,4-dimethoxybenzyl (DMB) amine (**6b**), because of the ease of removing the DMB group under acidic conditions in the last stage of the synthesis. Although combining the alkylamine and the alkyl-substituted allylic alcohol was difficult due to the low reactivity and potential risk of β-hydride elimination, respectively, the Pt-catalyzed direct substitution of **5** with **6a** and **6b** proceeded smoothly under microwave heating conditions (3 h) to give the desired monoallylamines **7a** and **7b** in 74% and 81% yield, respectively, without undesired over diallylation or β-hydride elimination. Excess DMB amine **6b** was recovered quantitatively by column chromatography. The product **7b** was also obtained in 77% yield under conventional heating conditions (48 h), and we selected this condition for the large-scale production of **7b** (see below).

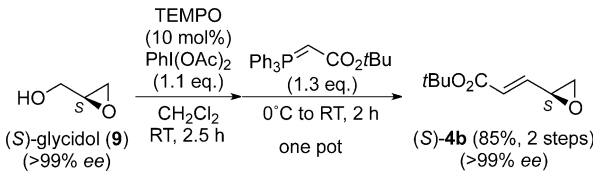
The second allylation reaction to give diallyl product **3** was key to the synthesis of **1**. First, we examined ethyl 4,5-dihydroxy-2-butenoate and its acetonide derivative as an electrophile, but, despite intensive investigation of the reaction conditions, only a trace amount of the desired coupling product was obtained due to the presence of an electron-withdrawing ester group, which greatly reduced the electron density of the C=C double bond and diminished the reactivity towards π-allyl complex formation.[13] Next, we examined the more reactive alkenyl epoxide **4** as the electrophile. Because the electrophilicity of alkenyl epoxide **4** was higher than that of the allylic alcohol, an epoxide-opening reaction proceeded without any reagent or catalyst, but amine **7** attacked only the less-hindered terminal position (δ-position) to give regioisomer **3′**. We also examined various Brønsted and Lewis acids as well as base additives, but these conditions gave only an inseparable mixture of regioisomers (**3a**/**3a′** = 1:2–4). Under transition-metal catalyzed allylic amination conditions, the amine nucleophile was expected to attack the desired allylic position (γ-position) to give diallylamine **3** in a highly regioselective manner because the reaction proceeds through a π-allyl–metal complex, but Pd catalyst[14] also gave a mixture of regioisomers (**3a**/**3a′** = 1.2:1).[13] Under the optimized conditions for the Pt catalysis, the desired coupling reaction of (±)-**4a**[13] with **7a** proceeded to give the desired diallylamine **3a**, suggesting the superiority of the Pt catalysis, although the yield of **3a** was only 34% and unexpected dienylamine byproduct **8a** was obtained in 16% yield (Scheme 4). Although **8a** was first thought to be formed via regioisomer **3a′**, treatment of isolated **3a′** under the same Pt catalysis conditions did not give **8a**. Finally we found that **8a** was produced from **3a** under Pt catalysis conditions, probably through retro-reaction (π-allyl–Pt formation) or aziridinium cation formation and the following β-hydride elimination.[13] This side reaction was effectively suppressed by decreasing the reaction temperature to room temperature, and after optimizing the reaction conditions the desired product **3a** was obtained in 95% yield without the formation of **8a**.

For the synthesis of (−)-α-kainic acid **1**, (*S*)-**4** was designed as the coupling partner of amine **7** because platinum-catalyzed allylation via a π-allyl complex was expected to proceed with double inversion of the chiral center. From commercially available optically pure (*S*)-glycidol **9**, the epoxide (*S*)-**4b** was synthesized in 85% yield without loss of enantiopurity (>99% *ee*) by a one-pot sequential catalytic 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) oxidation and Wittig reaction (Scheme 5).[13]

When chiral epoxide (*S*)-**4b** was used as the substrate for the second allylation, the reaction afforded **3b** in 94% yield, but partial epimerization occurred (92% *ee*) (Table 1, entry 1). To accelerate nucleophilic attack of allylamine **7b** to π-allyl–Pt intermediate in preference to undesired epimerization, we

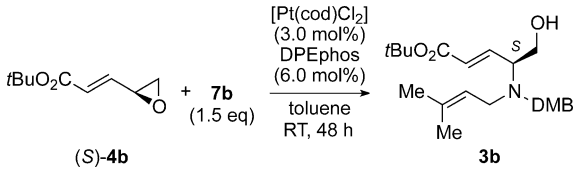


Scheme 4. Synthesis of diallylamine **3a** using Pt-catalyzed amination of (±)-**4a**.



Scheme 5. One-pot synthesis of optically pure alkenyl epoxide (*S*)-**4b**.

Table 1. Concentration effects on Pt-catalyzed allylic amination of (*S*)-**4b**.

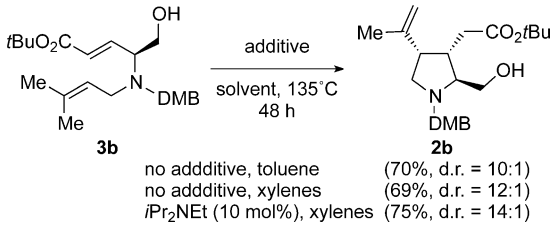


Entry	Concentration [M]	Yield [%][a]	*ee* [%][b]
1	0.25	94	93
2	0.40	93	95
3	0.50	95	98

[a] Yield of isolated product; [b] *ee* was determined by chiral HPLC (Chiralpak OD3, hexane/*i*PrOH/DEA = 98:2:0.1, 1 mL min^{-1}, λ = 254 nm).

screened various conditions and finally found that higher concentration conditions (0.5 M) efficiently suppressed the epimerization, and the desired product was obtained in 95% yield and 98% *ee* (Table 1, entry 3). The absolute configuration of **3b** was determined to be *S*, after its conversion into the final product (−)-α-kainic acid **1** (see below), indicating that the reaction proceeded with the expected double-inversion mechanism.

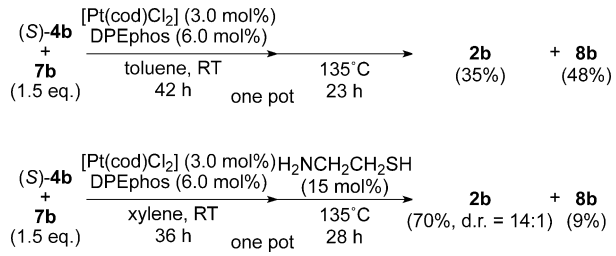
With the desired chiral diallylamine **3b** in hand, we then performed an ene-cyclization to construct the pyrrolidine ring with three contiguous stereogenic centers. Based on the previous synthesis of a structurally related compound,[10] a toluene solution of **3b** was heated at 135 °C in a sealed tube, and the desired cyclized compound **2b** was obtained in 70% yield with 10:1 diastereoselectivity (minor diastereoisomer **2b'** was the allokainic acid-type C-4 epimer; Scheme 6). For large-scale



Scheme 6. Synthesis of pyrrolidine **2b** using thermal ene-cyclization.

production, we changed the solvent to xylene, allowing this thermal reaction to proceed with ordinal open reactors. The addition of a catalytic amount of *i*Pr$_2$NEt effectively prevented the partial decomposition of the substrate, and under the optimized conditions **2b** was obtained in 75% yield with higher diastereoselectivity (14:1).

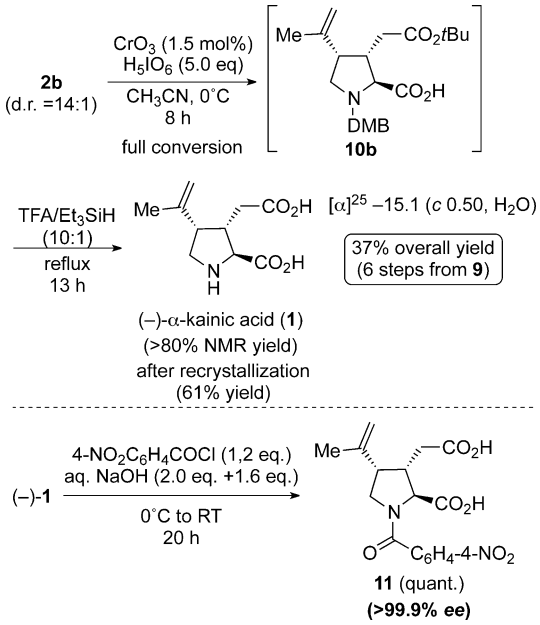
To make our synthesis more sophisticated, we considered "pot economy," which allows the elimination of several purification steps, to minimize the generation of waste chemicals and save time.[15] We therefore tackled a one-pot sequential Pt-catalyzed epoxide opening and ene-cyclization process. After the first Pt-catalyzed reaction of of alkenyl epoxide **4b** with allylamine **7b** at room temperature, the reaction mixture was heated to 135 °C. This one-pot procedure gave the desired pyrrolidine **2b**, but the yield of isolated **2b** was only 35% and dienylamine **8b** was obtained as the major product (48%; Scheme 7). Based on the aforementioned mechanism of the



Scheme 7. One-pot sequential Pt-catalyzed allylic amination and ene-cyclization process.

formation of **8** through Pt-catalyzed reaction at high temperature, we anticipated that the addition of a platinum scavenger before the ene-cyclization step might prevent such an undesired side reaction. Indeed, the addition of 2-aminoethanethiol or silica-supported dimercaptotriazine effectively suppressed the formation of **9b** and greatly improved the yield of **2b** to 70% (2 steps from **4b**) with 14:1 diastereoselectivity.[13,16]

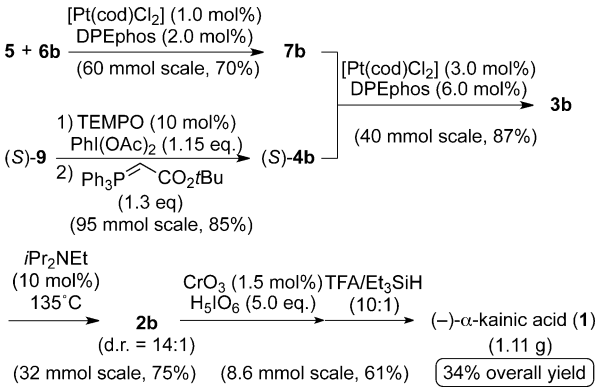
Completion of the total synthesis of (−)-α-kainic acid **1** required the oxidation of primary alcohol to carboxylic acid and the removal of the DMB and *t*Bu groups of **2b**. We screened several common oxidation conditions for the oxidation of primary alcohol **2b** to carboxylic acid **10b**, such as TEMPO, 2-azaadamantane *N*-oxyl (AZADO), tetrapropylammonium perruthenate (TPAP), pyridinium dichromate (PDC), and Jones oxidation. Among them, only classical Jones oxidation gave satisfactory results (full conversion of **2b**; Scheme 8). Even



Scheme 8. Completion of total synthesis of (−)-α-kainic acid **1** from **2b** and determination of its optical purity.

when the amount of CrO_3 was reduced to 1.5 mol% with 5.0 equivalents of terminal oxidant H_5IO_6, the reaction proceeded with the same efficiency. After oxidation, crude material was passed through a short silica-gel column to remove chromium metal, and then subjected to the final deprotection process. In our initial studies using *N*-PMB-protected analog **2a** or **10a** instead of DMB-protected **2b** or **10b**, the PMB group showed substantial resistance to acids and oxidants as follows: 1) Reactions under strongly acidic conditions lead to decomposition or formation of undesired isokainic acid- and δ-lactone-type byproducts, and 2) reactions with oxidants such as cerium(IV) ammonium nitrate (CAN) afforded only low yields (20–30%) of the corresponding free amine. To our delight, both DMB and *t*Bu groups were easily removed under mildly acidic conditions using trifluoroacetic acid (TFA) with Et_3SiH to give (−)-α-kainic acid **1** in >80% yield (NMR yield). Further purification by recrystallization of the crude material from ethanol afforded optically pure **1** (61%, 2 steps), whose optical rotation ($[\alpha]_D^{25} = -15.1$ (*c* 0.50, H_2O)) was consistent with that of the natural (−)-**1** ($[\alpha]_D^{24} = -14.8$ (*c* 1.0, H_2O)).[3] The overall yield of this process was 37% (6 steps from **9**). The synthetic **1** was further determined to be optically pure (>99% *ee*) by chiral HPLC analysis after conversion to *N*-4-nitrobenzyoyl-kainic acid **11**.

Finally, to demonstrate the practicality of this process, we conducted a gram-scale synthesis of (−)-α-kainic acid **1**. All reactions (8.6 to 95 mmol scale) proceeded with nearly identical efficiency, and 1.11 g of pure **1** was obtained in 34% overall yield in an only 6-step chemical transformation (Scheme 9).



Scheme 9. Gram-scale synthesis of (−)-α-kainic acid.

In conclusion, we have achieved the shortest total synthesis of (−)-α-kainic acid reported to date from commercially available allylic alcohol **5** and (*S*)-glycidol **9** (6 steps, 34–37% overall yield). The key intermediate, diallylamine **3b**, was synthesized using platinum-catalyzed allylic amination reactions with high monoallylation selectivity and regioselectivity. This process can be performed with ordinary equipment and readily available reagents and does not require any special operation or cryogenic conditions, suggesting the potential of our synthetic protocol to supply the global demand for (−)-α-kainic acid in an efficient and environmentally friendly manner. Further investigation for large-scale production using a flow system is ongoing in our laboratory.

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Keywords: allylic amination · amino acids · homogeneous catalysis · platinum · total synthesis

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[16] Chemically and optically pure **2b** can be obtained by recrystallization of a diastereomixture of **2b** (d.r. = 14:1).

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Total Synthesis

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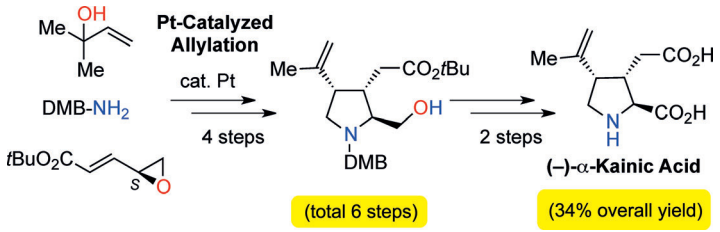
A Short Scalable Route to (−)-α-Kainic Acid Using Pt-Catalyzed Direct Allylic Amination



Kainoid enabled: A short and scalable synthesis of (−)-α-kainic acid, featuring sequential platinum-catalyzed direct allylic aminations and ene-cyclization is reported. Gram-scale synthesis of (−)-α-kainic acid proceeds with high efficiency to afford the chemically and optically pure crystalline product in six steps and 34% overall yield.