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# Total Synthesis of (−)-Kainic Acid via Intramolecular Michael Addition: A Second-Generation Route

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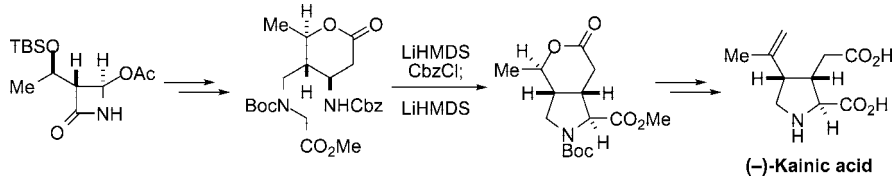
## ABSTRACT




**A total synthesis of (−)-kainic acid starting from the commercially available 2-azetidinone is described. The key *δ*-lactone intermediate was concisely prepared from the commercially available azetidinone through the Reformatsky-type reaction and an introduction of a glycine moiety. The construction of the functionalized pyrrolidine ring was executed by a one-pot sequential elimination-Michael addition protocol of a *β*-amino-*δ*-lactone intermediate with high diastereoselectivity.**

(−)-Kainic acid (**1**), the parent member of the kainoid family,[1] was isolated in 1953 from the Japanese marine alga *Digenea simplex*[2] and has also been found in the related algae.[3] Since kainoids display potent anthelminthic properties[4] and neurotransmitting activities[5] in the mammalian central nervous system, kainic acid in particular has been widely used as a tool in neuropharmacology[6] for stimulation of nerve cells and the mimicry of disease states such as epilepsy,[7] Alzheimer's disease, and Huntington's chorea.[8] Despite its importance in the neurosciences, this compound is costly due to the limited supply from natural resources and the lack of practical synthesis.[9]

In addition to its irreplaceable utility, the structural features of **1**, namely, a highly functionalized trisubstituted pyrrolidine ring with three contiguous chiral centers, have attracted considerable attention to **1** as a synthetic target. Accordingly, a number of total syntheses and synthetic approaches have so far been reported,[10,11] including two from this laboratory.[12,13]

After completion of our earlier total synthesis of **1** utilizing a regio- and stereoselective lithiation of pyrrolidine ring,[12] we established a more efficient route to **1**,[13] as outlined in Scheme 1. A diastereoselective Evans-type

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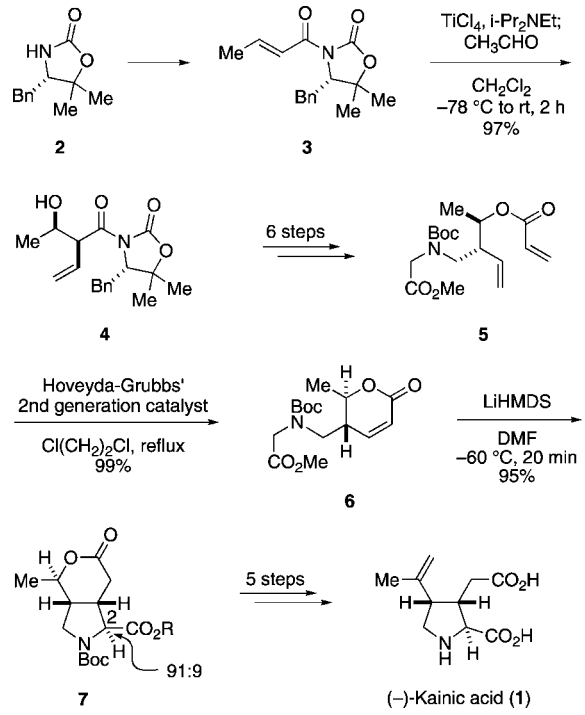
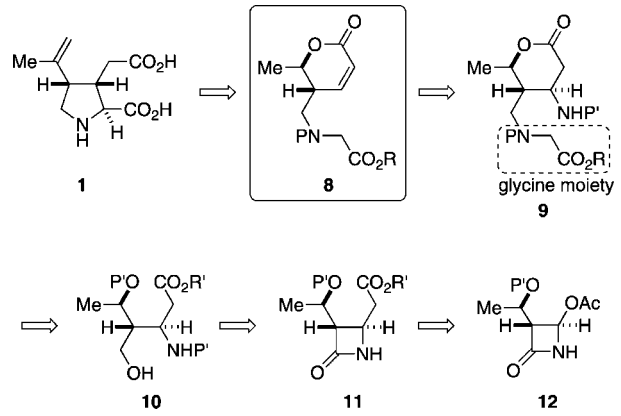
**Scheme 1.** Outline of Total Synthesis of (−)-Kainic Acid (**1**)




**Scheme 2.** Strategy for Second-Generation Synthesis




aldol reaction between crotonamide detivative **3** and acetaldehyde afforded an aldol product **4** as a single isomer, which was converted to an acrylate derivative **5** by a six-step sequence. The fully functionalized trisubstituted pyrrolidine ring **7** was constructed by the ring-closing metathesis followed by an intramolecular Michael addition of the resultant α,β-unsaturated lactone **6** with high diastereoselectivity. Finally, formation of the isopropenyl group and manipulation of the functional groups furnished kainic acid **1**. While the key intramolecular Michael addition proved to be highly effective for the formation of the fully elaborated pyrrolidine ring, synthetic accessibility of the precursor **6** was not efficient since it requires the chiral auxiliary-controlled construction of the framework and the intramolecular olefin metathesis under dilute reaction conditions. In this letter, we disclose our second-generation intramolecular Michael addition route with improved in situ preparation of the precursor **6**. This scalable route allowed us to synthesize (−)-kainic acid in a 12-step longest linear sequence in 14% overall yield from the commercially available, inexpensive azetidinone **13**.

The strategy of our second-generation synthesis is illustrated in Scheme 2. We planned to maintain the intramolecular Michael addition to the key intermediate **8** and the end game sequence established for the first-generation synthesis. Retrosynthetically, if we were to append an amino group to the intermediate **8**, the resultant **9** would be easily prepared from the azetidinone **11** by reductive opening of the β-lactam ring, followed by installation of a glycine moiety and lactone formation. Compound **11** could be obtained from the commercially available azetidinone derivative **12**,[14] which has been manufactured on an industrial scale as a starting material for β-lactam antibiotic drugs such as imipenem.

Our synthesis commenced with the introduction of a carbobutoxymethyl group on [3*R*(1′*R*, 4*R*)-4-acetoxy-3-[1-(*tert*-butyldimethylsilyloxy)ethyl]-2-azetidinone (**13**, Kaneka Corporation) using *t*-butyl bromozincacetate **14**[15] under improved literature conditions[15b] (Scheme 3). Activation of the β-lactam ring with a Cbz group followed by reduction with $NaBH_4$ afforded amino alcohol **17**. Introduction of the glycine moiety was then carried out by Mitsunobu reaction[16] of **17** with Nosyl (Ns)-activated glycine ester **18** to provide **19**.[17] Upon treatment with trifluoroacetic acid, **19** underwent cyclization to give lactone **20**. Finally, switching from the Ns group to the Boc group in one-pot furnished the desired **21** in 46% overall yield from **13**.

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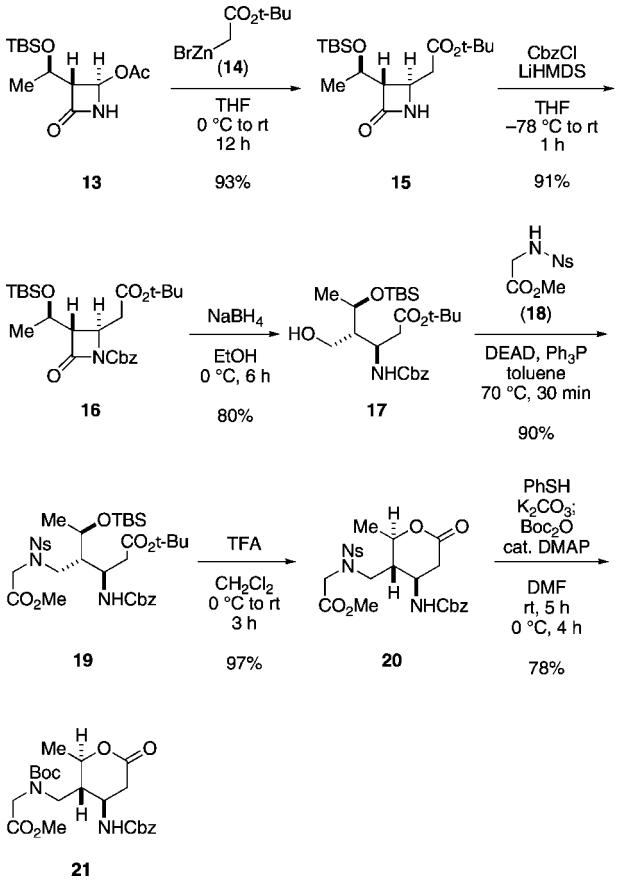
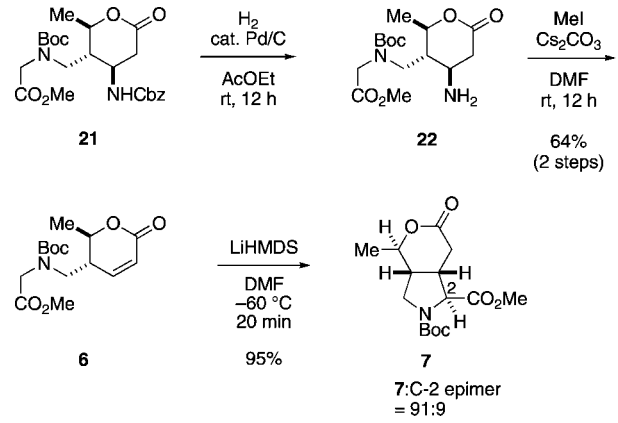
**Scheme 3.** Synthesis of the Key Intermediate **21**




With the desired $\beta$-amino-$\delta$-lactone **21** in hand, we next examined the elimination of the amino group and the key intramolecular Michael addition reaction to form the pyrrolidine ring. After removal of the Cbz group of **21** by hydrogenolysis, the resultant primary amine was treated with a 10-fold molar excess of iodomethane in the presence of cesium carbonate. The Hofmann elimination[18] proceeded as expected to give the desired $\alpha,\beta$-unsaturated lactone **6** in 64% in two steps (Scheme 4). The key stereoselective construction of the 2,3-*cis*-pyrrolidine ring was carried out as reported previously.[13] Thus, upon treatment of **6** with LiHMDS in DMF at −78 °C, intramolecular Michael addition took place smoothly to afford a diastereomeric mixture of the desired pyrrolidine derivative **7** and its C-2 epimer in a 91:9 ratio.

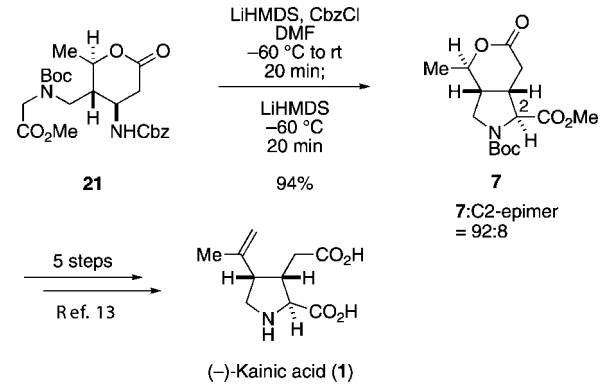
**Scheme 4.** Synthesis of the Pyrrolidine Ring by Hofmann Elimination and Intramolecular Michael Addition




As a significant improvement, the above elimination and Michael addition sequence was executed in a single operation involving treatment of Cbz-protected amine **21** first with LiHMDS (1.0 equiv) and CbzCl (1.1 equiv), and then with by additional LiHMDS (2.5 equiv) (Scheme 5). The sequential elimination-Michael addition cascade by way of di-Cbz imide intermediate proceeded quite nicely to give a mixture of the desired pyrrolidine derivative **7** and its C-2 epimer in high diastereoselectivity (ratio of **7** to its C-2 epimer was 92:8) in 94% yield. Finally, the five-step end game strategy, which we developed in the first- generation route,[13] was applied to **7** to provide (−)-kainic acid (**1**).

In summary, we have achieved a second-generation total synthesis of (−)-kainic acid (**1**) utilizing our intramolecular Michael addition strategy. The highlights of this improved synthesis include (1) a facile preparation of the key lactone intermediate **21** from the commercial available, inexpensive azetidinone derivative **13** and (2) a highly efficient one-pot cascade reaction including acylation, $\beta$-elimination, and intramolecular Michael addition to construct the fully functionalized pyrrolidine ring with high diastereoselectivity. With this improved and scalable route, (−)-kainic acid (**1**) was synthesized from **13** in 12 steps in 14% overall yield.

**Scheme 5.** One-pot Sequential Elimination-Michael Addition Protocol and End Game of Total Synthesis

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**Supporting Information Available:** Experimental details and $^{1}H$ and $^{13}C$ NMR spectra for all new compounds. This material is available free of charges via the Internet at http://pubs.acs.org.

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