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A Practical Synthesis of (−)-Kainic Acid

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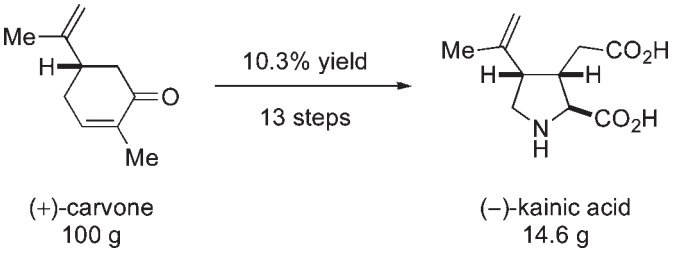
ABSTRACT



A highly practical stereoselective total synthesis of (−)-kainic acid is described. This synthesis features the stereoselective alkylation of an iodolactone intermediate that was efficiently prepared from (+)-carvone and introduction of carboxylic acid by hydrolysis of a nitrile accompanied by epimerizaion. This synthetic route enabled us to obtain 14.6 g of (−)-kainic acid.

(−)-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 since been found in related algae.[3] Kainoids display potent anthelmintic properties[4] and neurotransmitting activities[5] in the mammalian central nervous system, and kainic acid, in particular, has been widely used as a tool in neuropharmacology[6] to stimulate nerve cells and mimic disease states, such as epilepsy,[7] Alzheimer's disease, and Huntington's chorea.[8] Despite its importance in neuroscience, this compound remains quite expensive due to limited availability.[9]

Kainic acid (**1**) has attracted considerable attention as a synthetic target, not only for its utility but also for the challenge posed by its structure, featuring a highly functionalized trisubstituted pyrrolidine ring with three contiguous chiral centers. To date, several total syntheses and synthetic approaches have been reported,[10,11] including three from this laboratory.[12] However, there appear to be few synthetic routes that are amenable to a large-scale preparation, i.e., with an efficiency comparable to that of the conventional isolation from algae. Herein, we report a highly practical synthesis of (−)-kainic acid (**1**).

Our synthetic plan was based on utilizing the 2-propenyl group of the naturally abundant terpenes (Scheme 1). (+)-Carvone (**2**), a representative of such terpenes, is known to undergo oxidative degradation to give a versatile synthetic intermediate **3**.[13] For the purpose of an efficient synthesis of (−)-kainic acid (**1**), it occurred to us that **3** seems to have suitable functionalities for the stereoselective introduction of a C2 unit at the α-position of the carboxylic acid, installation of the nitrogen atom, and formation of the pyrrolidine ring.

Our synthesis commenced with epoxidation of (+)-carvone (**2**) using alkaline hydrogen peroxide to produce epoxide **4** in 89% yield (Scheme 2). Epoxide **4** was treated

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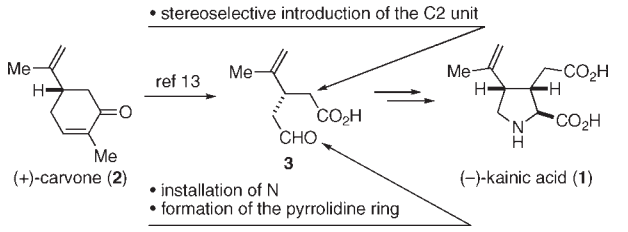
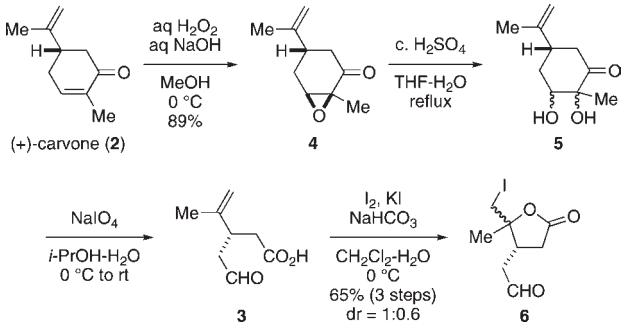
Scheme 1. Synthetic Plan for (−)-Kainic Acid

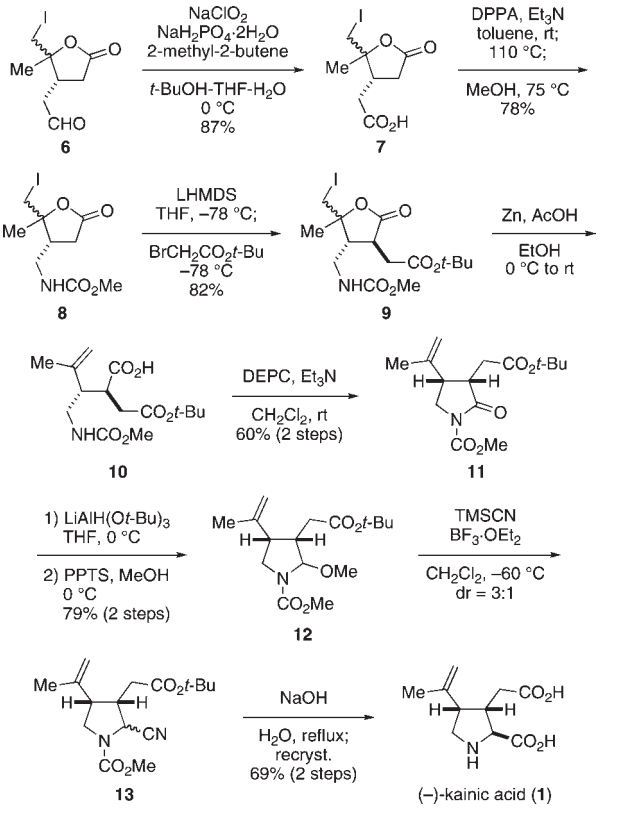


with aqueous H_2SO_4 in THF to give a diastereomeric mixture of diols **5**, which was subjected without further purification to oxidative cleavage with $NaIO_4$ to give carboxylic acid **3**.[13] After removal of nonacidic impurities by back extraction, iodolactonization of **3** was performed to rigidify the conformation for the stereoselective introduction of the C2 unit. Compound **3** was thus treated with iodine and potassium iodide under aqueous basic conditions. After completion of the reaction, simple extraction gave the desired iodolactone **6** in 65% yield from epoxide **4** as a 1:0.6 mixture of diastereomers.

Scheme 2. Synthesis of Iodolactone **6**



Scheme 3. Total Synthesis of (−)-Kainic Acid (**1**)



Having developed an efficient route to iodolactone **6**, we next focused on the introduction of the nitrogen atom and the ensuing stereoselective alkylation (Scheme 3). Oxidation of the aldehyde in **6** with $NaClO_2$[14] afforded carboxylic acid **7** in 87% yield. Curtius rearrangement of carboxylic acid **7** using DPPA and Et_3N, followed by

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treatment with MeOH, gave methyl carbamate **8** in 78% yield.[15] Deprotonation of **8** with 2.5 equiv of LHMDS followed by addition of *tert*-butyl bromoacetate at −78 °C furnished ester **9** in 82% yield. As expected, alkylation occurred from the opposite face of the substituent at the β-position of the carbonyl group.[16] The stereochemistry at the γ-position of the lactone did not affect the selectivity of the alkylation. A reductive ring-opening reaction of the iodolactone moiety in **9** was effected by treatment with Zn in the presence of acetic acid to produce carboxylic acid **10**, which, upon treatment with DEPC[17] and triethylamine at ambient temperature, underwent cyclization to afford the desired *cis*-substituted lactam **11** in 60% overall yield from **9**.[18]

Finally, we introduced a C1 unit at the α-position of the nitrogen atom. Lactam **11** was selectively reduced with $LiAlH(O\textit{t}\text{-}Bu)_3$ at 0 °C, and the resulting hemiaminal was treated with PPTS in methanol to give **12** in 79% yield as a single isomer. Treatment of **12** with TMSCN and $BF_3 \cdot OEt_2$ gave, via an acyliminium ion, aminonitrile **13** as a 3:1 mixture of diastereomers.[19] Fortunately, epimerization of the undesired isomer occurred during the course of the alkaline hydrolysis,[20,21] producing (−)-kainic acid (**1**). Thus, submission of the crude diastereomeric mixture of nitrile **13** to hydrolysis under refluxing NaOH conditions afforded, after recrystallization, pure (−)-kainic acid (**1**) in 69% yield (2 steps).

In conclusion, we have accomplished a highly practical total synthesis of (−)-kainic acid (**1**), featuring the efficient preparation of the iodolactone, Curtius rearrangement to introduce the nitrogen atom, stereoselective alkylation of the lactone to install the C2 unit, and basic hydrolysis of the nitrile accompanied by epimerization. This synthetic route enabled us to obtain 14.6 g of (−)-kainic acid (**1**) from 100 g of (+)-carvone (**2**) in 13 steps and 10.3% overall yield. In view of the ease of the entire operation and the use of the readily available and inexpensive reagents, we are convinced that our synthetic route alone would satisfy the global demand for (−)-kainic acid.

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Supporting Information Available. Experimental details and ^1H 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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(18) Other cyclization conditions produced the desired lactam **11** in poor yield or the epimer at the α-position of the lactam.

(19) The stereochemistry of **13** was determined by an X-ray crystallographic study of the major isomer, which had the same configuration as (−)-kainic acid (**1**).

(20) Base-promoted epimerization of the corresponding diester has been reported under a variety conditions (ref 11c, p, r, v). Ganem also reported that hydrolysis of a nitrile derivative of β-kainic acid under acidic conditions proceeded without epimerization (ref 11v).

(21) Hydrolysis of each isomer produced kainic acid with the same > 20:1 ratio of the products.