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Short Total Synthesis of (−)-Kainic Acid

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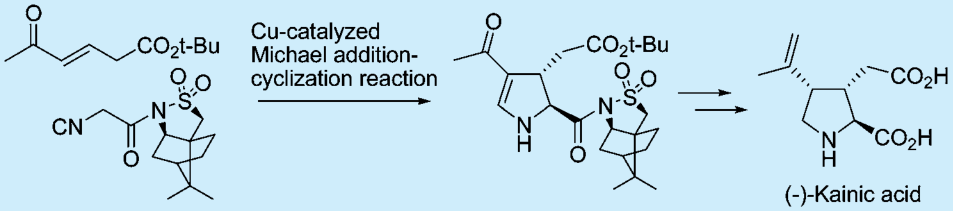
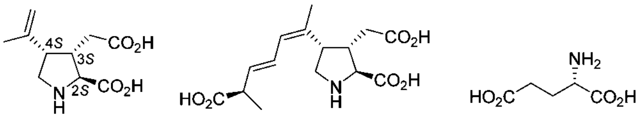
Supporting Information



ABSTRACT: A short total synthesis of (−)-kainic acid has been developed involving a novel diastereofacial differentiating Cu-catalyzed Michael addition−cyclization reaction, which provided access to a chiral pyrroline in a highly stereoselective manner. The chiral pyrroline was converted to (−)-kainic acid via the stereoselective 1,4-reduction of the pyrroline double bond in three steps.

Kainic acid (**1**), the parent member of the kainoid family, was first isolated in 1953 from the marine alga *Digenea simplex* by Takemoto et al. (Figure 1).[1] Kainoids such as **1** and **2** have been reported to behave as agonists toward kainate receptors which are ionotropic glutamate receptors and exert potent excitatory neurotoxicity in the mammalian central nervous system.[2,3] Compounds belonging in this class are useful tools for investigation of the role of kainate receptors in excitatory neurotransmission, as well as inducing neurodegeneration with the aim of exploring the pathogenesis of excitotoxicity in neurodegenerative disorders of the central nervous system.[2−4]



Kainic acid (**1**) Domoic acid (**2**) Glutamic acid (**3**)

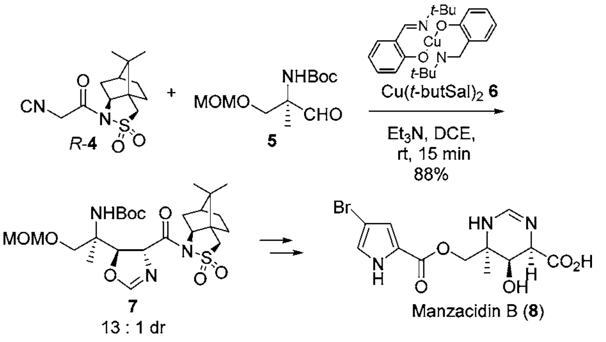
Figure 1. Structure of two kainoids and glutamic acid.

Structurally, the kainoid core consists of a pyrrolidine ring with three contiguous stereogenic centers at C2, C3, and C4 as a core skeleton. The characteristic structural features and biological activities of kainoids have elicited significant interest from researchers in many areas of chemistry, including organic chemistry, natural product chemistry, chemical biology, and pharmaceutical chemistry.[5]

Kainoids have inspired many synthetic investigations toward the stereoselective synthesis of their pyrrolidine core, which plays a crucial role in the binding affinity of these compounds and their derivatives to the kainate receptors.[2a,5] Various original synthetic methods have consequently been developed for construction of the pyrrolidine ring in this context and applied to the total synthesis of kainoids. Among them, the total synthesis of kainic acid (**1**) has been studied extensively, and more than 35 total syntheses of **1** have been reported in the literature.[5,6] Several short, efficient, and practical syntheses of **1** have been achieved.[6i,7]

We have recently reported an efficient total synthesis of manzacidin B[8] via the stereoselective aldol addition reaction of an optically active isonitrile **4** bearing Oppolzer's camphorsultam chiral auxiliary[9] and the aldehyde **5** bearing a quarternary amino carbon center (Scheme 1). In this synthesis, we used a new and mild Cu catalyst **6** to promote the key reaction, which allowed for the stereoselective synthesis of **7** in high yield. A scalable total synthesis of manzacidin B (**8**) on a 600 mg scale was achieved by taking advantage of this Cu-catalyzed aldol reaction.

Scheme 1. Total Synthesis of Manzacidin B (8) via Cu-Catalyzed Aldol Reaction



In terms of our synthetic strategy, it was envisioned that an efficient total synthesis of **1** could be achieved by the Cu-catalyzed tandem Michael addition−cyclization reaction of

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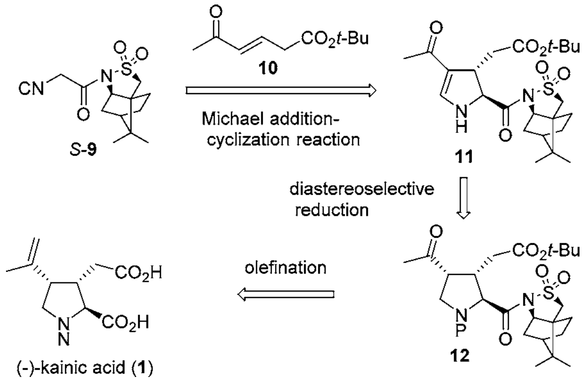
chiral isonitrile **9** with *α*,*β*-unsaturated ketone **10**. This key reaction would provide access to the chiral 2,3-disubstituted pyrroline **11**, bearing similar functionalities to those of **1**, which could be transformed into **1** in just a few short steps (Scheme 2).[10]

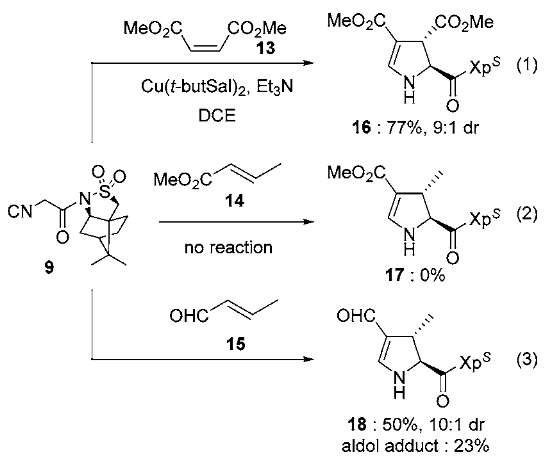
Scheme 2. Synthetic Strategy for the Short Synthesis of Kainic Acid (1)



The use of a Michael addition−cyclization reaction for the synthesis of substituted pyrrolines was first reported by Ito et al.[10,11] Grigg et al. later employed a Ag(I) catalyst to promote this transformation.[12] Although several catalytic asymmetric versions of this process have been developed and reported in the literature,[13] these have not been developed to the extent that would allow us to overcome the challenges associated with our current synthetic goal. For example, the applicability of these methods to chiral isonitriles has not yet been examined. Reports pertaining to the use of Michael reaction acceptors such as *β*-alkyl substituted *α*,*β*-unsaturated enone **10** for the synthesis of pyrrolidine are rare, likely because of their poor reactivities. Enone **10** has two possible electrophilic sites, and very little work has been conducted with regard to examining the regioselectivity (i.e., aldol reaction vs the Michael addition reaction) of this reaction toward substrates of this nature.[10−13]

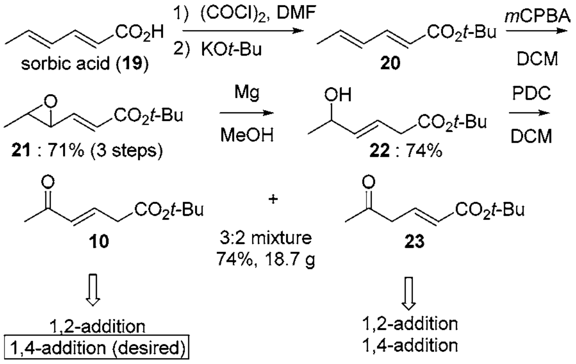
To assess the reactivity of **9** toward Michael acceptors, we conducted a series of model reactions using dimethyl maleate (**13**) (Scheme 3), methyl crotonate (**14**), and crotonaldehyde (**15**). Dimethyl maleate (**13**) reacted smoothly with **9** in the presence of Cu catalyst **6** and triethylamine to give **16** in 77% yield (eq 1). The relative and absolute stereochemistries were confirmed by X-ray analysis of **16** (see Supporting Information (SI)). In contrast, the application of the same reaction conditions to methyl crotonate (**14**) resulted in no reaction (eq 2). Crotonaldehyde (**15**) gave **18** in 50% yield together with the aldol product in 23% yield (eq 3). These results indicated that the Cu catalyzed reaction system exhibits a unique mode of reactivity, in that (i) nucleophilic addition to *β*-substituted *α*,*β*-unsaturated esters occurred at a much slower rate than it did to *β*-substituted *α*,*β*-unsaturated aldehydes and (ii) the Michael addition−cyclization reaction was preferred to the aldol addition reaction.

Scheme 3. Michael Addition Cyclization Reaction with 9



We next investigated the key reaction described in our synthetic strategy and prepared the Michael reaction acceptor **10** on a large scale (18 g) from sorbic acid (**19**) in five steps (Scheme 4). Sorbic acid (**19**) was converted to epoxide **21** via *tert*-butyl ester **20** in three steps. The reductive ring-opening reaction of **21** gave deconjugated ester **22** in 74% yield which was oxidized with PDC to give an inseparable 3:2 mixture of conjugated ketone **10** and ester **23**.

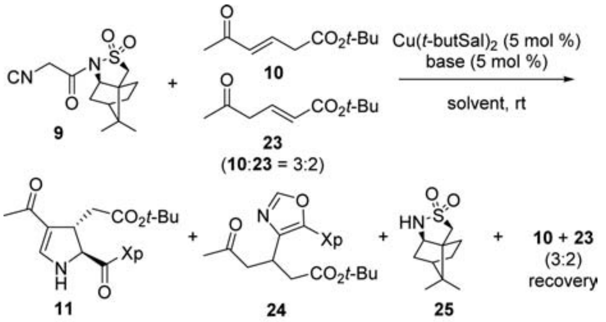
Scheme 4. Synthesis of the Michael Addition Reaction Acceptor 10



The use of this mixture in the next key reaction potentially gave rise to three possible products, including two aldol products from **10** and **23**, and a pyrroline product from ester **23**. It was envisaged, however, that the desired reaction to provide **11** would be a major reaction pathway of the three possibilities listed above because of the characteristic reactivity displayed in the model study in Scheme 3. Furthermore, it was envisaged that the addition reaction of the chiral isonitrile **9** to ketone **10** would be slower than the addition reaction of **9** to the less sterically hindered aldehyde **15**.

The mixture of **10** and **23** was subjected to the key reaction with **9** in the presence of triethylamine and the Cu catalyst **6** (Scheme 5; see also Table SI-1). Disappointingly, the reaction only afforded a trace amount of **11** (entry 1). Use of the stronger bases 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) led to a slight improvement in the yield (entries 2 and 3). After extensive experimentation, it was established that the reaction performed most effectively when it was conducted in the presence of the Cu catalyst **6** without any base.[14] When 1 equiv of the mixture **10** and **23** was employed under these conditions, compound **11** was obtained in 24% yield (entry 4). The product yield was improved to 54% using 2 equiv of the regioisomeric mixture (entry 5). Although the reaction conditions that are currently used as a standard protocol gave **11** in 54% yield, the synthetic process could be scaled-up to the 4 g scale without any

Scheme 5. Synthesis of Chiral Pyrroline 11[a]



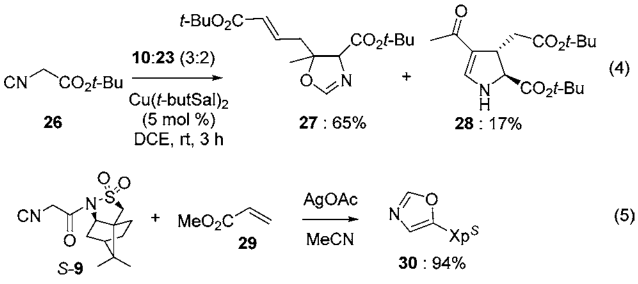
entry	base	solvent (0.1 M)	acceptor (equiv)	time (min)	11 (%)	24 (%)	25 (%)
1	Et_3N	DCE	1	16 h	trace	trace	45
2	DBU	DCE	1	120	11	10	55
3	TBD	DCE	1	120	20	14	46
4	none	DCE	1	60	24	20	14
5[a]	none	THF (0.5 M)	2	40	54	24	9

[a] 4.25 g scale.

discernible loss in selectivity. During the course of this study, we found that the ratio of **10** and **23** was always maintained at 3:2. This consistency in the ratio was attributed to the occurrence of a rapid olefin isomerization process between **10** and **23**, which allowed for the *α*,*β*-unsaturated ketone **10** to be effectively recovered and recycled.

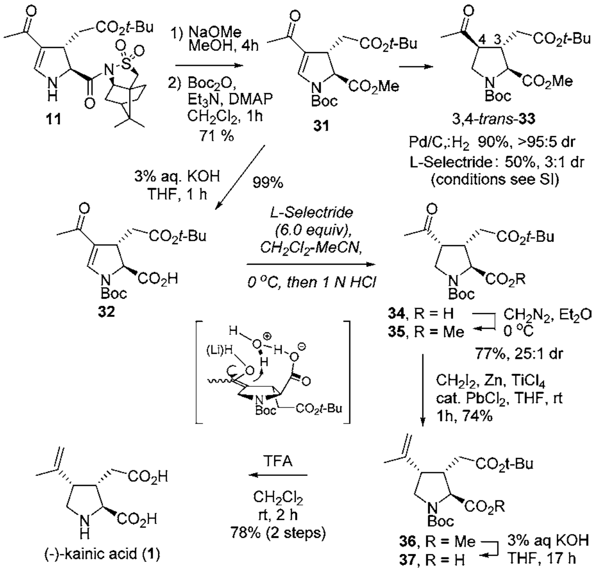
To develop a deeper understanding of the reaction mechanism, we employed isocyanoacetate **26** as a substrate for the reaction. In contrast to the reaction of **9** with a mixture of **10** and **23**, the reaction of **26** with the same mixture gave aldol adduct **27** as the major product (Scheme 6, eq 4). Grigg et al. reported the facile Ag-catalyzed Michael addition−cyclization reaction of methyl isocyanoacetate with methyl acrylate (**29**) to provide the corresponding pyrroline derivative.[12] With this in mind, the same Ag catalyst was used for the reaction of **9** and **29**, where it facilitated the self-cyclization of **9** to give oxazole **30** (eq 5). These results indicated that the combination of the sultam auxiliary with the Cu catalyst **6** was critical to the success of the key reaction.

Scheme 6. Comparable Experiments



We then investigated the stereoselective reduction of the C═C double bond of the pyrrolidine **11** to allow for the introduction of 3,4-*cis* stereogenic centers. The sultam auxiliary of **11** was initially removed because the sultam had an adverse impact on the downstream transformations. Treatment of **11** with sodium methoxide followed by the protection with Boc_2O gave **31**. Although a variety of different reaction conditions were evaluated for the reduction of **31**, the thermodynamically more stable 3,4-*trans*-product **33** was always isolated as the major product (Table SI-2).[15] To overcome this issue, we adopted a challenging approach of using the carboxylic acid moiety as a directing group for the proton donor.[16] Of the various reduction conditions tested (Table SI-3),[17] the stereoselective process was achieved by treatment with L-Selectride (6 equiv) in THF followed by acidification with 1 N HCl.[18] This process was also found to be amenable to scale up and was conducted on a gram scale. After the esterification reaction, *cis*-**35** was obtained in 77% yield in a highly stereoselective manner (1:25). The application of the same reaction conditions to methyl ester **31** gave *trans*-**33** as the major product (3:1). These results indicated that the carboxylic acid moiety played an important role in the reaction as a directing group. We also found that the nature of the protonation reagent and the presence of water had a significant impact on the selectivity of the reaction (i.e., 1 N HCl (**33**:**35** = 1:25), AcOH (**33**:**35** = 4:1), H_2O (**33**:**35** = 1:2.4); see also Table SI-4). Based on these results, we have proposed a reaction mechanism for the trasformation, which is depicted in Scheme 7. The chelation of a water molecule to the carboxylate would contribute to the protonation on the upper face to give *cis*-**34**.

Scheme 7. Total Synthesis of Kainic Acid (1) via Stereoselective Reduction of Pyrrolines



Ketone **35** has been reported to readily epimerize to more stable *trans*-**33** under the basic reaction conditions.[19] Fukuyama et al. recently reported a mild olefination reaction using the Nozaki reagent; it occurred without any epimerization.[20] Our application of the same conditions to **35** afforded **36** in 74% yield. Subsequent deprotection of **36** completed the total synthesis of (−)-kainic acid (**1**). Our analytical data for the synthetic kainic acid (**1**) were found to be identical in all respects with those reported in the literature for the authentic material.[7a]

In summary, we have developed an efficient nine step procedure for the total synthesis of (−)-kainic acid. The total synthesis was conducted on a 300 mg scale in 16.8% overall yield from the chiral isonitrile **9**. The application of this synthetic strategy to the synthesis of a range of other kainoid analogues is currently being investigated in our laboratory, as well as the use of these compounds in chemical biology[21] as glutamate receptor ligands.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Detailed experimental procedures, spectroscopic data, copies of ^{1}H and ^{13}C NMR spectra, and X-ray structure of **16**. This material is available free of charge via the Internet http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(14) See SI.

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