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Total Synthesis of (–)-(α)-Kainic Acid via a Diastereoselective Methylenecyclopropane Ring Expansion

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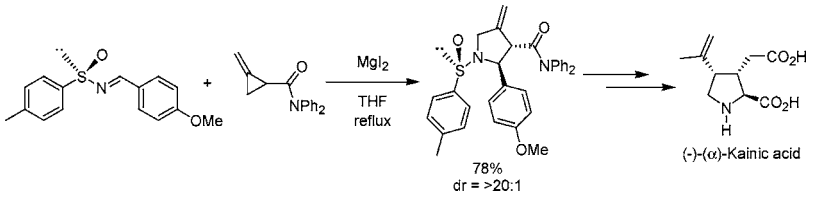
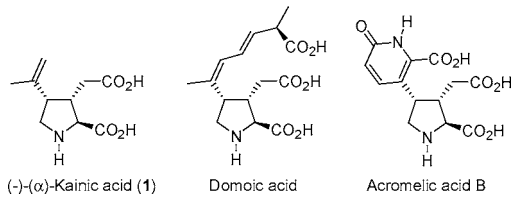
ABSTRACT



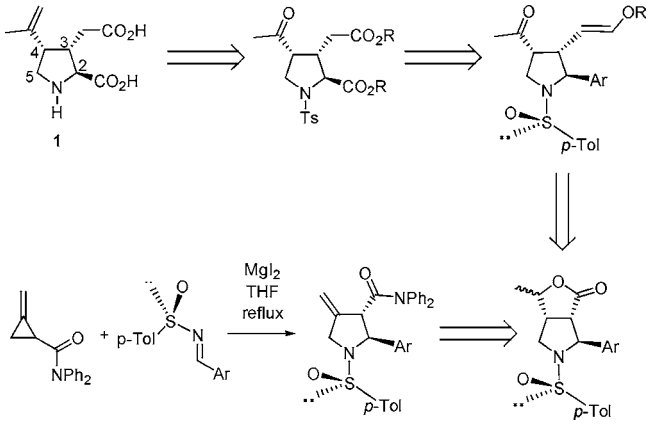
A concise and enantioselective synthesis of (–)-(α)-kainic acid in 13 steps with an overall yield of 15% is reported. The pyrrolidine kainoid precursor with the required C2/C3 trans stereochemistry was prepared with excellent diastereoselectivity (>20:1) via a MgI_2-mediated ring expansion of a tertiary methylenecyclopropyl amide. A selective hydroboration was then employed to set the remaining stereochemistry at the C4 position en route to (–)-(α)-kainic acid.

The kainoid amino acids are a potent class of neuroexcitant compounds whose biological activity stems from their ability to function as a conformationally restricted analogue of glutamic acid. For this reason, these amino acids have been used extensively by the neurological community in the study of Huntington's chorea and Alzheimer's disease.[1] Typically, these amino acids are composed of a *trans*-C2,C3/*cis*-C3,C4 pyrrolidine core which differs solely in the nature of the substituent at the 4-position.



Recently, we reported a highly diastereoselective route to *trans*-C2,C3-pyrrolidines using a magnesium iodide-mediated ring expansion of methylenecyclopropanes in the presence of a chiral sulfinimines.[2] Enantiopure pyrrolidines could then be obtained upon deprotection of the chiral auxiliary. We now report the use of this methodology toward the total synthesis of the (−)-(α)-kainic acid[3] **1** using the retrosynthetic methodology outlined in Scheme 1. Scheme 2 shows the synthesis of (−)-kainic acid.

Scheme 1. Retrosynthetic Analysis



MgI_2-mediated ring expansion of *N*,*N*-diphenylmethylenecyclopropyl amide **2** in the presence of chiral sulfinimine **3** gave the expected pyrrolidine **4** ($[\alpha]_D$ −55.2° (*c* 1.11,

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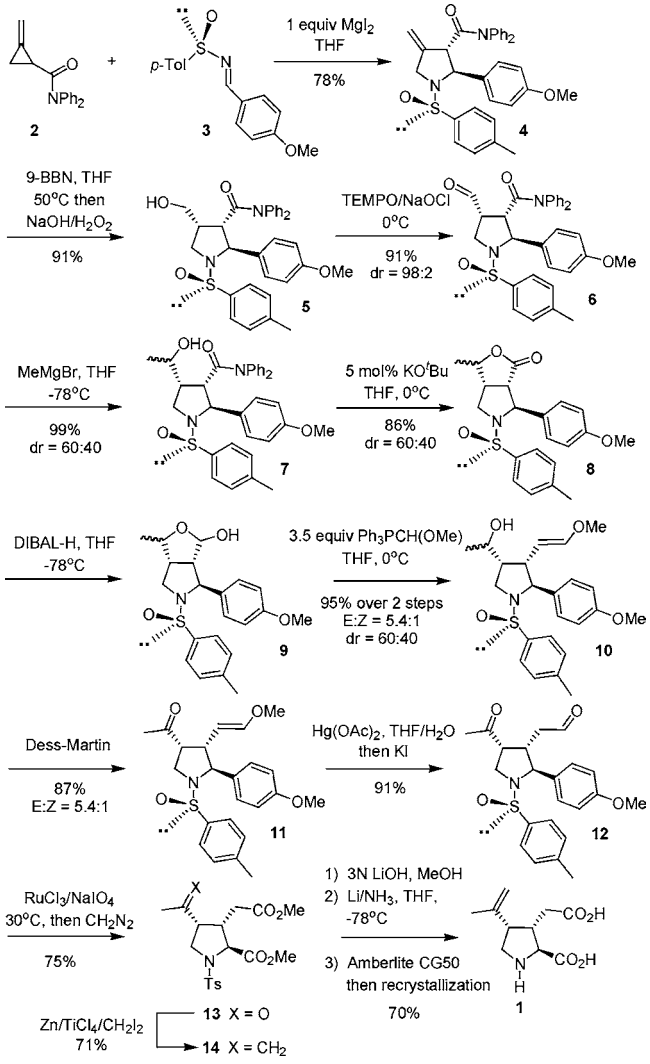
Scheme 2. Synthesis of (−)-Kainic Acid



$CHCl_3$)) in 78% yield.[2] Hydroboration from the least hindered face of the pyrrolidine ring using 9-BBN, followed by standard oxidative workup, afforded the primary alcohol **5** ($[\alpha]^{24}_D$ +33.4° (*c* 0.8, $CHCl_3$)) as a single diastereomer. Oxidation of the primary alcohol using a buffered TEMPO/NaOCl oxidation[4] furnished the expected aldehyde **6** ($[\alpha]^{24}_D$ +10.4° (*c* 0.8, $CHCl_3$)) in 91% total yield as a 98:2 ratio of C4-epimers. Next, installation of the methyl group to give the secondary alcohol **7** was achieved in near quantitative yield as a 3:2 ratio of diastereomers by slow addition of the aldehyde to MeMgBr at −78 °C. We found that the rate and order of addition was crucial in minimizing the amount of competing side products for this step.

Subsequent removal of the tertiary amide proved difficult under classical hydrolytic conditions, due in part to the lability of the chiral sulfoxyl group. This problem was circumvented by treating alcohol **7** with catalytic KO^{t}Bu in THF at 0 °C to afford lactone **8** in 86% yield as a 3:2 mixture of diastereomers. Reduction of **8** using DIBAL-H, followed by Wittig olefination of the lactol **9**, gave the vinyl methyl ether **10** in 95% yield over two steps as an inseparable mixture of diastereomers (dr = 3:2 and *E*:*Z* = 5.4:1). Dess−Martin oxidation of **10** afforded the vinyl methyl ether ketone **11** in 87% yield as an inseparable mixture of *E*/*Z* isomers, with no evidence of epimerization by ^{1}H NMR. Deprotection of **11** using $Hg(OAc)_2$ followed by KI workup then gave the desired aldehyde **12** in 91% yield ($[\alpha]^{24}_D$ −19.8° (*c* 0.4, $CHCl_3$)).

The next key step in the synthesis was a global oxidation of the aldehyde, sulfoxyl, and *para*-methoxy phenyl groups using $RuCl_3/NaIO_4$.[5] Gratifyingly, oxidation of **12** using these conditions, followed by diazomethane workup, afforded the dimethyl ester **13** in 75% ($[\alpha]^{24}_D$ −15.5° (*c* 0.8, $CHCl_3$)). We then set out to install the *exo*-methylene group. On the basis of previous studies by other groups,[6] we expected standard Wittig olefination approaches to give a substantial amount of the epimerized product. Use of the nonbasic Zn/$TiCl_4/CH_2I_2$[7,8] reagent furnished the desired olefin **14** cleanly in 71% yield with no evidence of the epimerized allo-isomer. All spectroscopic properties of the resulting olefin **14** were in accord with those previously reported ($[\alpha]^{25}_D$ −45.1° (*c* 1.3, $CHCl_3$), lit. ($[\alpha]^{15}_D$ −48.1° (*c* 1.0, $CHCl_3$)).[6a,9]

Conversion of **14** to **1** was then carried out as previously reported by Yoo and co-workers.[6a,9] Ester hydrolysis followed by tosyl deprotection using Birch conditions afforded crude **1** from **14**. Purification of **1** was then carried out using an ion-exchange resin (Amberlite CG50) followed by recrystallization to afford optically pure (−)-(α)-kainic acid ($[\alpha]^{23}_D$

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$-14.3°$ (*c* 0.8, H_2O), natural (−)-(α)-kainic acid $[\alpha]^{23}_D$ $-14.6°$ (*c* 0.9, H_2O))[10] in 70% yield over two steps.

In conclusion, we have successfully synthesized (−)-(α)-kainic acid in enantiopure form in 13 linear steps. Initial ring expansion of the methylenecyclopropyl amide in the presence of a chiral sulfinimine set the first two stereocenters in one convienent step. A highly selective hydroboration using the bulky tertiary amide to control facial selectivity then set the remaining stereocenter en route to the final product.

(10) An authentic sample of natural (−)-(α)-kainic acid was obtained from Ocean Produce International, NS, Canada.

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Supporting Information Available: Experimental procedures for the preparation of new compounds and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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