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Total Synthesis of (−)-(α)-Kainic Acid via a Diastereoselective Intramolecular [3 + 2] Cycloaddition Reaction of an Aryl Cyclopropyl Ketone with an Alkyne

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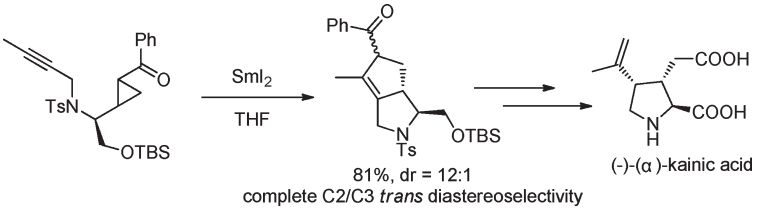
ABSTRACT



An enantioselective synthesis of (−)-(α)-kainic acid in 15 steps with an overall yield of 24% is reported. The pyrrolidine kainoid precursor with the required C2/C3 *trans* stereochemistry was prepared with complete diastereoselectivity via an unprecedented SmI_2-catalyzed intramolecular [3 + 2] cycloaddition reaction of an aryl cyclopropyl ketone and an alkyne. Double bond isomerization was then employed to set the remaining stereochemistry at the C4 position en route to (−)-(α)-kainic acid.

Kainoids are an important class of natural nonproteinogenic amino acids which have a common characteristic structure consisting of a pyrrolidine nucleus with two carboxylic groups. They also display potent anthelmintic properties[1] and neurotransmitting activities[2] in the mammalian central nervous system. In particular, (−)-α-kainic acid (**1**) (Figure 1), the parent member of the kainoid family,[3] isolated in 1953 from the Japanese marine alga *Digenea simplex*,[4] has been widely used as a tool in neuropharmacology[5] for simulating central nervous system (CNS) disorders, such as epilepsy,[6] Alzheimer's disease, and Huntington's chorea.[7] Due to its importance in neuroscience, a limited supply from natural resources,[8] and the synthetic challenge posed by a highly functionalized trisubstituted pyrrolidine ring with three contiguous chiral centers, the synthesis of (−)-α-kainic acid has received considerable attention, and several total syntheses and synthetic approaches[9] have been reported. Herein, we describe an efficient synthetic route to **1**, featuring an

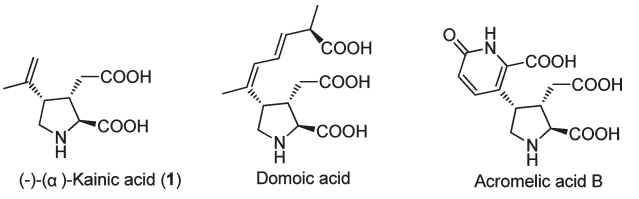


Figure 1

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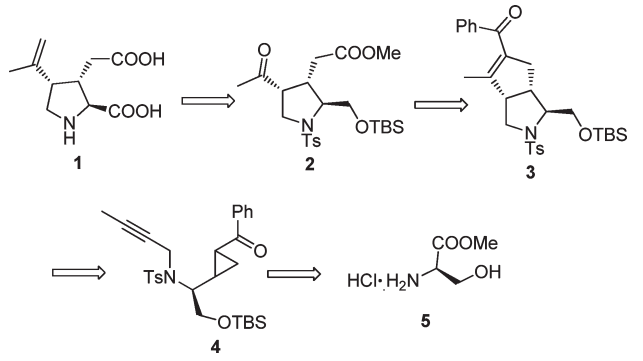
intramolecular [3 + 2] cycloaddition reaction of an aryl cyclopropyl ketone with an alkyne for the stereoselective construction of the functionalized pyrrolidine ring.

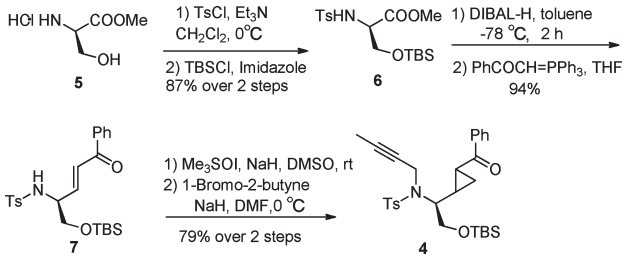
Scheme 1. Synthetic Strategy for (−)-α-Kainic Acid (**1**)



Our synthetic strategy is outlined in Scheme 1. We planned to introduce the isopropylidene fragment through an olefination of the ketone **2**. This disconnection would also enable easy access to domoic acid as well, through use of a different olefination reagent. Ketone intermediate **2** could be formed by oxidative cleavage of the bicyclic compound **3** which could be obtained by an intramolecular radical [3 + 2] cycloaddition of aryl cyclopropyl ketones **4**, installing the *cis* C3−C4 side chains of kainic acid, with the *trans* C2−C3 relationship induced by a bulky TBS ether. The cyclization substrate **4** could be derived from commercially available D-serine methyl ester hydrochloride **5**.

It was obvious that success of the plan would primarily hinge on whether the intramolecular radical [3 + 2] cycloaddition of aryl cyclopropyl ketones **4** could proceed satisfactorily with good diasteroselectivity. It was feared, however, and with some foundation, that most [3 + 2] cycloadditions of cyclopropanes reported to date have utilized "donor−acceptor" cyclopropanes,[10] or methylene cyclopropanes.[11] Moreover, cyclopropyl ketyl radicals have most commonly been exploited for their propensity to undergo reductive fragmentations[12] and have not been examined as intermediates in [3 + 2] cycloaddition reactions except for a few intermolecular examples catalyzed by Ni^0 complexes[13] and particularly scarce intramolecular examples catalyzed by $Ru(bpy)_3$ with visible light.[14]

Scheme 2. Synthesis of Precursor **4**



D-Serine methyl ester hydrochloride **5** was converted in 87% yield into *N*-tosyl methyl ester derivative **6**,[15] which was reduced with DIBAL-H to the corresponding aldehyde. A Wittig olefination[16] provided the enone **7** in 94% yield (two steps from **6**) (Scheme 2). Cyclopropanation of **7** with Me_3SOI followed by *N*-alkylation with 1-bromo-2-butyne delivered the key precursor **4** as a 1.2:1 mixture of diastereomers in 79% yield over two steps.

With the precursor **4** in hand, we then investigated the key annulation reaction (Table 1). We began our investigation by opening cyclopropanes with $[Ni(cod)_2]$ and a variety of Lewis acids (entries 1−4).[13] Unfortunately, we

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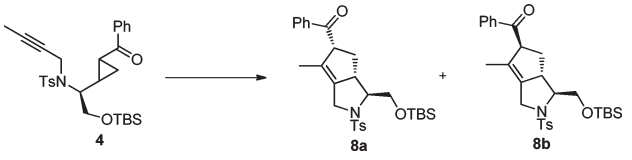
observed no evidence of ring opening for **4**. We then screened visible light photocatalyzed [3 + 2] cycloadditions by formation of anion radicals (entry 5).[14] However, visible light photocatalysis failed to promote the desired cycloaddition. We speculated that weak visible light photocatalysis might not activate the cyclopropyl ketone toward a one-electron reduction or could not stabilize the ketyl radical intermediate. In an attempt to increase the reduction potential of the reagent, we turned to using SmI_2[17] as a one-electron reducing agent. To our delight, substrate **4** indeed underwent cycloaddition with SmI_2 and HMPA to afford products **8a** and **8b** in 50% yield with a ratio of 4:1 (entry 6). More importantly, complete C2/C3 *trans* stereochemistry was observed in this annulation reaction. A higher yield (81%) and excellent diastereoselectivity (**8a:8b** = 12:1) were obtained when the reaction proceeded in the absence of HMPA (entry 7). Remarkably, the stereoselectivity of this cyclization was substrate-controlled and formed the desired isomer at the C-3 center. The two diastereomers of compound **4** showed almost the same reactivity for this annulation reaction. Attempts to perform the reaction at lower temperature resulted in a decrease in yield (entry 8). The mechanism we envision for the [3 + 2] cycloaddition reaction involves initial formation of the ketyl radical **A**, followed by rapid cleavage of the cyclopropyl ring (Scheme 3). Sequential radical cyclizations might then give rise to cyclized ketyl radical **D**, with the *trans* C2−C3 relationship induced by the bulky TBS ether. Loss of an electron would produce **8a** and **8b** as the products of the formal intramolecular [3 + 2] cycloaddition of **4**. The relative configuration of **8a** and **8b** was confirmed by NOE experiment.

Table 1. Screening the Intramolecular [3 + 2] Cycloaddition Reaction of Aryl Cyclopropyl Ketone **4**

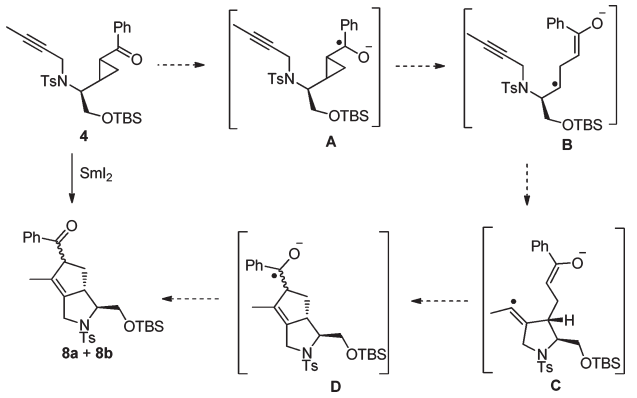


entry	conditions	yield (%)[c]	**8a:8b**[d]
1[a]	$[Ni(cod)_2]$, Me_2AlOTf, THF, 50 °C	–	–
2[a]	$[Ni(cod)_2]$, Me_2AlCl, THF, 50 °C	–	–
3[a]	$[Ni(cod)_2]$, Me_3Al, THF, 50 °C	–	–
4[a]	$[Ni(cod)_2]$, Ti(O-*t*-Bu)$_4$, *t*BuOK, PhMe, 90 °C	–	–
5[b]	$Ru(bpy)_3Cl_2$, $La(OTf)_3$, TMEDA, MeCN, rt	–	–
6	SmI_2 (2.5 equiv), HMPA (2.5 equiv), THF, rt	50	4:1
7	SmI_2 (2.5 equiv), THF, rt	81	12:1
8	SmI_2 (2.5 equiv), THF, 0 °C	13	14:1

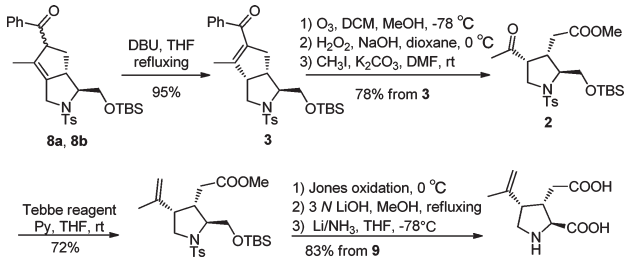
[a] The reaction was performed with 0.1 equiv of $[Ni(cod)_2]$ and 1 equiv of Lewis acid. [b] Subjected to irradiation with a 23 W compact fluorescent bulb. [c] Isolated yields of **8a** and **8b**. [d] Determined by ^1H NMR prior to workup.

With the key intermediates **8a** and **8b** in hand, removal of the aryl ketone was next addressed. Treatment of **8a** and **8b**

Scheme 3. Proposed Mechanism for the [3 + 2] Cycloaddition Reaction of Aryl Cyclopropyl Ketone **4**



Scheme 4. Synthesis of (−)-Kainic Acid **1**



with DBU isomerized the double bond to afford the expected bicyclic enone **3** in 95% yield (Scheme 4). Ozone oxidation of the bicyclic enone **3**, followed by oxidative cleavage of the resulting diketone group with basic hydrogen peroxide in a biphasic medium (2 M aqueous NaOH−H_2O_2 in dioxane, 10 min, 0 °C), and subsequent protection of the resulting carboxylic group provided the key intermediate **2** in 78% yield over three steps. Treatment of methylketone **2** with Tebbe's reagent[18] gave the olefin **9** in 72% yield. No epimerization occurred in the buildup of the propenyl group. One-pot deprotection and Jones oxidation of the TBS ether provided the corresponding carboxylic acid.[19] Ester hydrolysis followed by tosyl deprotection using Birch conditions afforded (−)-kainic acid **1** ($[\alpha]^{20}_D$ −14.5 (*c* 0.11, H_2O), natural (−)-(α)-kainic acid ($[\alpha]^{23}_D$ −14.6 (*c* 0.9, H_2O)) in 83% yield over three steps.

In summary, we have successfully synthesized (−)-(α)-kainic acid in enantiopure form in 15 linear steps from inexpensive D-serine methyl ester hydrochloride, using

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an intramolecular [3 + 2] cycloaddition reaction of an aryl cyclopropyl ketone with an alkyne. To the best of our knowledge, this is the first example of a SmI_2 catalyzed [3 + 2] cycloaddition reaction of an aryl cyclopropyl ketone with an alkyne with excellent diastereoselectivity.

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

The authors declare no competing financial interest.