

# Asymmetric Total Synthesis of (–)- $\alpha$ -Kainic Acid Using an Enantioselective, Metal-Promoted Ene Cyclization

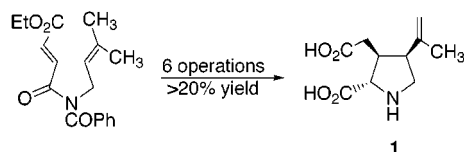
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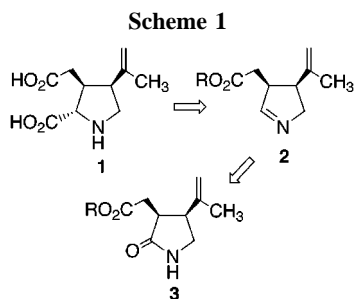
Received December 18, 2000

## ABSTRACT



A short and efficient asymmetric total synthesis of the title compound **1**, which is an important neurotransmitter, has been achieved. The synthesis features a metal-promoted, enantioselective ene reaction that provides entry into the kainic acid ring system from very simple precursors. Moreover, the zirconium-mediated Strecker reaction, which represents an outgrowth of earlier amide-to-imine methodology developed in our laboratory, demonstrates remarkable chemoselectivity and stereoselectivity.

The role of excitatory amino acids such as L-glutamic acid and (–)- $\alpha$ -kainic acid (kainic acid; **1** in Scheme 1) in



mediating synaptic responses has made these naturally occurring compounds important reagents for investigations into Alzheimer's disease, epilepsy, and other neurological disorders.<sup>1</sup> Compound **1** has also been used as an antiworm-

ing agent to eliminate parasites from humans and animals.<sup>2</sup> Recent news reports described a worldwide shortage of kainic acid<sup>3,4</sup> that for over a year has handicapped the neuroscience community and prompted a search for alternative sources of **1**. A total of 53 laboratory syntheses of **1** have been reported,<sup>5,6</sup> although none is practical on a preparative scale. Here we describe a short, practical, and efficient enantioselective synthesis of **1** that uses an asymmetric, magnesium–bis-oxazoline catalyzed ene cyclization to introduce the key structural and stereochemical elements of **1**.

Scheme 1 depicts our retrosynthetic strategy. We planned to introduce the  $\alpha$ -amino acid moiety of **1** by a Strecker reaction on imine **2**, which might be prepared by the partial reduction of pyrrolidone **3** using Cp<sub>2</sub>ZrHCl, a method developed in our laboratory for amide-to-imine reductions.<sup>7</sup> We envisioned making lactam **3** by an intramolecular ene

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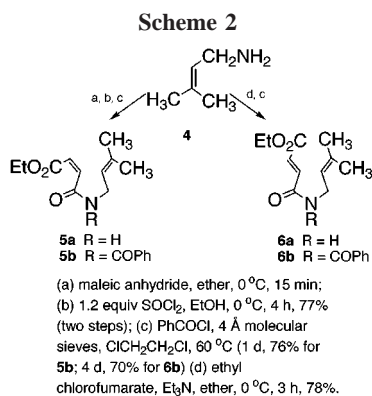
(4) Tremblay, J.-F. *Chem. Eng. News* **2000**, March 6th, 131.

(5) For a very recent synthesis, see: Chevliakov, M. V.; Montgomery, J. *J. Am. Chem. Soc.* **1999**, *121*, 11139–11143.

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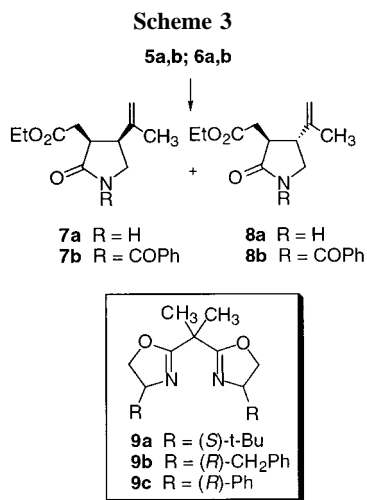
reaction. Such a strategy was first used by Oppolzer et al. to transform chiral dienes to trisubstituted pyrrolidines for the synthesis of kainic and allokainic acids.<sup>8</sup> However, the possibility of developing metal-promoted, enantioselective variants of the intramolecular ene reaction using achiral diene precursors led us to pursue this new approach.

Dienes **5a,b** and **6a,b** were prepared as shown in Scheme 2 from *N*-prenylamine **4**.<sup>9</sup> Reaction of **4** with maleic



anhydride followed by esterification afforded **5a**. Similarly, condensation of **4** with ethyl fumaryl chloride<sup>10</sup> afforded **6a**. Both **5a** and **6a** were converted to the corresponding *N*-benzoyl derivatives **5b** and **6b** in good yields.

The thermal and metal-catalyzed intramolecular ene reactions of dienes **5a,b** and **6a,b** can form either *cis*-substituted or *trans*-substituted pyrrolidones **7a,b** and **8a,b**, respectively (Scheme 3).



Cyclizations were studied under a variety of conditions (Table 1). In the absence of catalyst, cyclization of **5a**

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required prolonged heating at 190 °C, forming **7a** and **8a** (3.3:1 ratio) in good yields. The desired *cis*-isomer **7a** was obtained as a pure racemate by crystallization from ethyl acetate:hexanes, mp 104–107 °C. Isomer **6a** failed to cyclize at 190 °C (entry 2) but at higher temperatures (entry 3) afforded predominantly the *trans*-isomer **8a**. Control experiments at 210 °C indicated that diene **5a** slowly isomerized to **6a** and that pure **7a** epimerized only slowly (<10% after 4 d). Thus, the stereochemistry of the cyclized product was strongly influenced by the stereochemistry of the enophile in the diene precursor.

Attempted cyclization of **5a** with various metal salts [ZnCl<sub>2</sub>, Zn(OTf)<sub>2</sub>, Cu(OTf)<sub>2</sub>] led instead to the formation of *N*-prenylmaleimide. However, in the presence of ZnCl<sub>2</sub> or Mg(ClO<sub>4</sub>)<sub>2</sub>, diene **6a** generated predominantly the desired *cis*-isomer **7a** (entries 4 and 5).

The *N*-benzoylated dienes **5b** and **6b** underwent faster and higher-yielding uncatalyzed cyclizations (entries 6 and 7) than did the parent dienes **5a** and **6a**, with **6b** strongly favoring the desired *cis*-product **7b**. Stoichiometric amounts of Mg(ClO<sub>4</sub>)<sub>2</sub> further accelerated cyclizations of **5b** and **6b** (entries 8 and 9), but with less favorable stereoselectivities.

Asymmetric intramolecular ene cyclizations have been developed using covalently linked chiral auxiliaries.<sup>11</sup> However, metal-promoted asymmetric versions of such reactions using chiral ligands are rare. Intramolecular ene/conjugated alkene cyclizations have been achieved using chiral titanium alkoxides<sup>12</sup> or bis-oxazoline–magnesium perchlorate.<sup>13</sup> In each case, stoichiometric quantities of both metal and ligand were required, and moderate to good enantioselectivity was observed. The cyclization of **6b** was conducted with a variety of metal–ligand combinations, and the best results were achieved using the bis-oxazoline–magnesium system reported by Desimoni et al. (entries 10–12).<sup>13</sup> Three different commercially available bis-oxazolines **9a–c** were screened. Optimal results were obtained using 2 equiv of both metal and ligand, indicating that sequestration of the metal–ligand complex by the product was significant. Ligands **9a–c** were readily recoverable by chromatography of the product mixture and could be reused.

All three bis-oxazolines promoted Mg(II)-catalysis, and in each case, cyclization strongly favored the desired *cis*-diastereomer. The rate enhancement was most pronounced with diphenyl-bis-oxazoline **9c** and weakest with **9a**,<sup>14</sup> as was the enantioselectivity (presented as the ratio of dextro- and levorotatory enantiomers in the final column in Table

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**Table 1.** Uncatalyzed and Catalyzed Ene Reactions of Dienes **5** and **6**

entry	substrate	catalyst	ligand	conditions	products	ratio (% yield)	(+)- <b>7a</b> :(-)- <b>7a</b>
1	<b>5a</b>			190 °C, toluene, 4 d	<b>7a:8a</b>	3.3:1 (84)	
2	<b>6a</b>			190 °C, toluene, 4 d	SM <sup>c</sup>		
3	<b>6a</b>			200–10 °C, toluene, 4 d	<b>7a:8a</b>	1:5 (78)	
4	<b>6a</b>	ZnCl <sub>2</sub> <sup>a</sup>		110 °C, 1 d	<b>7a:8a</b>	5:1 (60)	
5	<b>6a</b>	Mg(ClO <sub>4</sub> ) <sub>2</sub> <sup>a</sup>		110 °C, toluene, 42 h	<b>7a:8a</b>	10:1 (50)	
6	<b>5b</b>			110 °C, toluene, 5 h	<b>7b:8b</b>	2:1 (99)	
7	<b>6b</b>			110 °C, toluene, 22 h	<b>7b:8b</b>	10:1 (98)	
8	<b>5b</b>	Mg(ClO <sub>4</sub> ) <sub>2</sub> <sup>a</sup>		rt, CH <sub>2</sub> Cl <sub>2</sub> , 2 d	<b>7b:8b</b>	1:2 (94)	
9	<b>6b</b>	Mg(ClO <sub>4</sub> ) <sub>2</sub> <sup>a</sup>		rt, CH <sub>2</sub> Cl <sub>2</sub> 2 d	<b>7b:8b</b>	2.2:1 (81)	
10	<b>6b</b>	Mg(ClO <sub>4</sub> ) <sub>2</sub> <sup>b</sup>	<b>9a</b> <sup>b</sup>	rt, CH <sub>2</sub> Cl <sub>2</sub> 18 h	<b>7b:8b</b>	20:1 (66)	1.0
11	<b>6b</b>	Mg(ClO <sub>4</sub> ) <sub>2</sub> <sup>b</sup>	<b>9b</b> <sup>b</sup>	rt, CH <sub>2</sub> Cl <sub>2</sub> 12 h	<b>7b:8b</b>	20:1 (64)	0.59
12	<b>6b</b>	Mg(ClO <sub>4</sub> ) <sub>2</sub> <sup>b</sup>	<b>9c</b> <sup>b</sup>	rt, CH <sub>2</sub> Cl <sub>2</sub> 3 h	<b>7b:8b</b>	>20:1 (72)	4.8

<sup>a</sup> 1 equiv. <sup>b</sup> 2 equiv. <sup>c</sup> SM = starting material.

1). Interestingly, **9b** and **9c** gave opposite enantioselectivities, which were ascertained as follows. Mild acid hydrolysis of the **7b:8b** mixture (4 N HCl, EtOH, rt, 2 h, 89%), followed by chromatography, afforded a dextrorotatory sample of **7a** (entry 12;  $[\alpha]_D +3.7^\circ$  in CHCl<sub>3</sub>), which was analyzed by NMR using the chiral shift reagent<sup>15</sup> Eu(tfc)<sub>3</sub>.

Lactam (+)-**7a** was transformed into (–)- $\alpha$ -kainic acid as depicted in Scheme 4. Reaction with Schwartz's reagent

Schwartz's reagent, no hydrozirconation of the isopropenyl group in **7a** was detected.

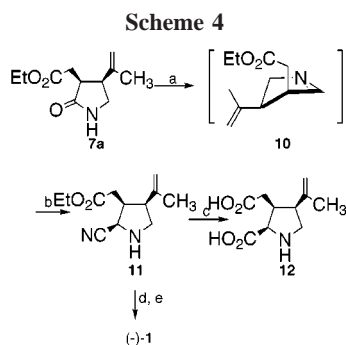
The unexpected *syn*-addition of cyanide leading to **11** was established by hydrolysis of both the nitrile and ester groups in **11** using aqueous acid to afford  $\beta$ -kainic acid **12**, whose NMR spectrum matched published values.<sup>16</sup> Base-promoted epimerization of diesters of **12** to the corresponding diesters of **1** has been reported under a variety of conditions.<sup>17</sup> Therefore, nitrile **11** was reacted with 4 N HCl–methanol and then directly basified with KOH to afford **1** in 97% yield. This procedure presumably involves alcoholysis of the nitrile in **11** to a diester, which undergoes epimerization and saponification to **1**.

Synthetic  $\alpha$ -kainic acid prepared in this fashion was converted to the (+)-ephedrine salt and recrystallized following a literature procedure<sup>8a</sup> to afford optically pure (–)- $\alpha$ -kainic acid, whose spectroscopic and physical data [mp 245–248 °C,  $[\alpha]_D -15^\circ$  (*c* 0.52, H<sub>2</sub>O)] matched published values. Overall, enantiomerically pure (–)-**1** can be prepared in six laboratory operations on a 1–2 g scale from readily available starting materials in an overall yield exceeding 20%.

**Acknowledgment.** This research was supported in part by the U.S. National Institutes of Health (GM 04842 to Professor George P. Hess of the Department of Molecular Biology and Genetics at Cornell). We are grateful to Professor Hess for bringing this problem to our attention and for his helpful advice and support as a colleague and collaborator. Support of the Cornell NMR Facility has been provided by NSF (CHE 7904825; PGM 8018643) and NIH (RR02002).

**Supporting Information Available:** <sup>1</sup>H and <sup>13</sup>C NMR data for all synthetic intermediates leading to (–)-**1**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(Cp<sub>2</sub>ZrHCl, 1.5 equiv in THF) generated imine **10**, which was subjected without purification to cyanotrimethylsilane (TMSCN) in CH<sub>2</sub>Cl<sub>2</sub> to afford the all-cis nitrile **11** in 70% overall yield from **7a**. Although alkenes readily react with

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