Total Synthesis of Kaitocephalin, the First Naturally Occurring AMPA/KA Receptor Antagonist

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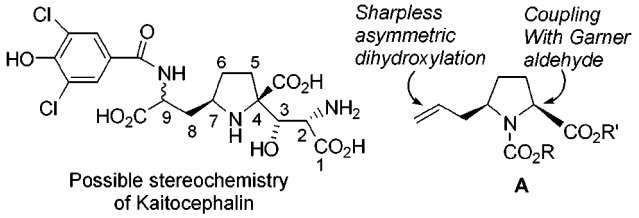
Excitatory neuronal transmission within the central nervous system (CNS) is mediated predominantly by L-glutamate, which plays a role of utmost importance in many physiological processes such as neural plasticity, memory, and learning.[1] However, excessive of L-glutamate release can result in neuronal cell death, a phenomenon that has been termed excitotoxcity.[2] It is now commonly accepted that excitotoxic cell death substantially contributes to the pathophysiology of both acute and chronic neurodegenerative disorders in the CNS. These disorders include epilepsy, focal and global ischaemia, stroke, pain, and neurodegenerative diseases.[3] These observations have stimulated considerable research efforts on the development of selective and potent antagonists for glutamate receptors, particularly compounds acting at the *N*-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA), and kainic acid (KA) receptor subtypes.[4] Some AMPA/KA receptor antagonists have shown promising usage for treatment of epilepsy and cerebrovascular ischemia.[5]

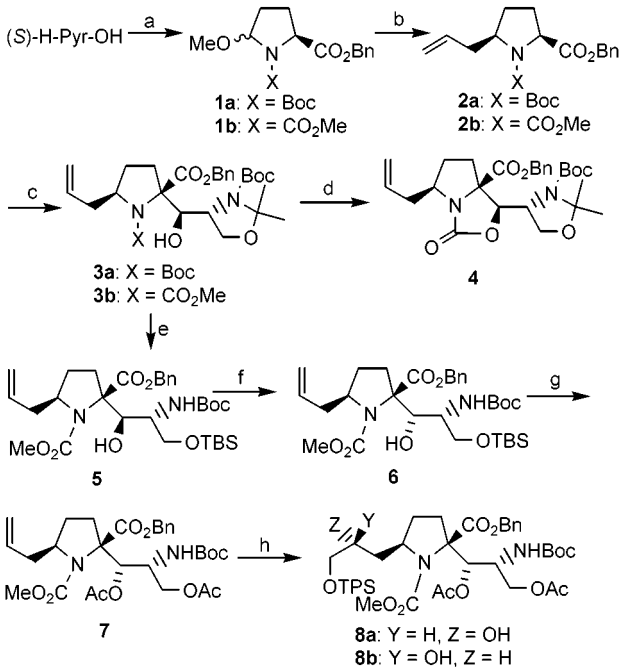
In 1997, kaitocephalin, the first natural AMPA/KA antagonist, was isolated from *Eupenicillium shearii*. In the models of chick primary telencephalic and rat hippocampal neurons, this compound showed protection from kainate toxicity at 500 μM with EC_{50} values being 0.68 and 2.4 μM, respectively, and from AMPA/cyclothiazide (500 μM/50•M) toxicity with EC_{50} values 0.6 and 0.4 μM, respectively. Unlike the known AMPA/KA antagonists with a quinoxalinedione skeleton, kaitocephalin does not have any cytotoxic effect.[6] Thus, SAR studies on this compound may open a new avenue to the development of therapeutic tools for protection of excitotoxicity. However, before comprehensive SAR studies become a reality, an efficient route to kaitocephalin is required. Toward this goal we report here the first total synthesis of kaitocephalin.

On the basis of the proposed stereochemistry of kaitocephalin,[7] we described a synthetic plan as shown in Scheme 1. The 2,5-disubstituted pyrrolidines **A** were envisioned to be ideal building blocks for synthesizing the target molecule because its 2-position could be lithiated and then coupled with (*R*)-Garner aldehyde to assemble the right-hand part of kaitocephalin, and its C−C double bond could be converted into the left-hand moiety through Sharpless asymmetric dihydroxylation.[8] The detailed studies were outlined in Scheme 2. Protection of the acid and amide groups of (*S*)-pyroglutamic acid under ordinary conditions followed by reduction with DIBAL-H provided **1a** and **1b**.[9] Treatment of **1** with allyltrimethylsilane and $TiCl_4$ in methylene chloride afforded *cis*-**2** as the major product, together with some separable *trans*-isomer.[10] The aldol condensation reaction was obviously a key step for this synthesis and therefore tested under many conditions. Initially, lithiation of **2a** with LDA at −78 °C followed by trapping the resultant anion with (*R*)-Garner aldehyde gave the condensation products quantitatively. However, it was found that four isomers were formed in this reaction in almost equal amounts.

Scheme 1. Structure of Kaitocephalin and Synthetic Analysis



Scheme 2[a]



[a] Reagents and conditions: (a) i) BnOH, $SOCl_2$, 0 °C to rt, 96%; ii) $(Boc)_2O$ or $ClCO_2Me$, Et_3N, DMAP, 86−95%; iii) DIBAL-H, THF, −78 °C, then MeOH, TsOH, rt, 95%; (b) allyltrimethylsilane, $TiCl_4$, −78 °C, 95% for **2a**, 77% for **2b**; (c) LiHMDS, then (*R*)-Garner aldehyde, −78 °C, 60% for **3a**, 86% for **3b**; (d) LiHMDS, −42 °C, 100%; (e) i) TsOH, MeOH, 85%; ii) TBSCl, Et_3N; 97%; (f) i) DMSO, $(COCl)_2$ then Et_3N, 95%; ii) $NaBH_4$, MeOH; 90%; (g) i) TBAF, HOAc, 98%, ii) Ac_2O, Et_3N, 95%; (h) i) $K_2OsO_2(OH)_4$ 1%, $(DHQD)_2PHAL$ 5%, $K_3Fe(CN)_6$ 3 equiv, K_2CO_3 3equiv, *t*-BuOH/H_2O (1/1), rt ii) TPSCl, DMAP, Et_3N, 92% for two steps.

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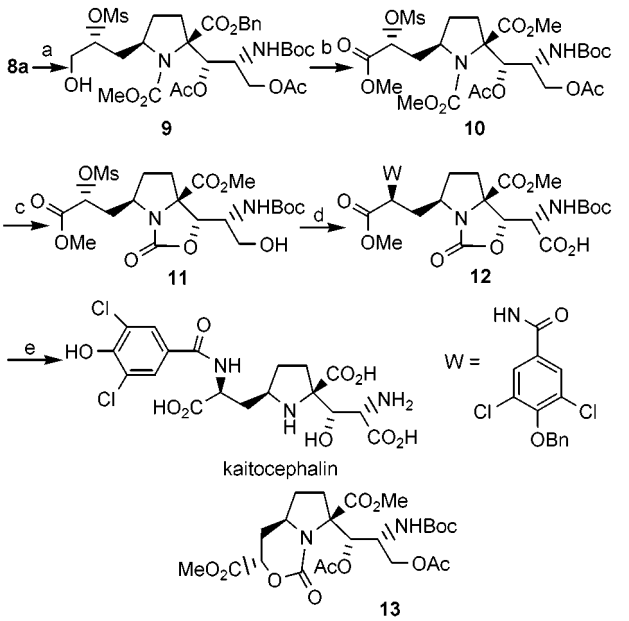
Switching the base to LiHMDS provided improved results, and a major isomer **3a** was isolated in 60% yield (with its stereochemistry assigned by single-crystal X-ray analysis). Fortunately, when **2b** was used as substrate with LiHMDS as base, the aldol reaction provided alcohol **3b** as a single product in 86% yield. Raising the temperature of aldol reaction from −78 °C to −42 °C or treating **3b** with LiHMDS at −42 °C produced the bicyclic oxazolidinone **4** in excellent yields. The structure of **4** was established by its single-crystal X-ray analysis, thereby confirming the stereochemistry of **3b**. Although we obtained **3b** in high diastereoselectivity, the configuration of its 3-OH was wrong for synthesizing kaitocephalin. Considering that our product was a *Cram*-selective isomer, we tried to add anhydrous $ZnBr_2$ or CuI to the aldol reaction to reach *anti-Cram* selectivity to get 3*S*-isomer.[11] However, this attempt failed to obtain any coupling products. At this moment we planned to continue the synthesis by reverting the configuration of the 3-OH of **3b**. Accordingly, the oxazolidine ring of **3b** was opened, and the primary hydroxy group was selectively protected with TBSCl to afford the alcohol **5**. Swern oxidation of **5** followed by reduction with $NaBH_4$ in THF/MeOH provided 3*S*-isomer **6** as a major product in 86% yield. The alcohol **5** was also isolated in <10% yield after reaction, which implied that the diastereoselectivity for the reduction step was 9/1. It was notable that, when **3b** was subjected to this oxidation/reduction method, no desired 3*S*-isomer was obtained at all after reduction. After the cleavage of the silyl ether in **6**, the diol was protected with acetic anhydride to afford **7**, which was submitted to Sharpless asymmetric dihydroxylation, and then protecting of the primary hydroxy group with TPSCl provided **8a** and **8b**. We found the ratio of **8a** to **8b** was about 2.2/1 when commercial AD-mix-β was used, which indicated that the chiral centers in **7** had some mismatched effect on the diastereoselectivity in the dihydroxylation. Moreover, by using enriched AD-mix-β, we raised the ratio of **8a** to **8b** to 6.8/1.

Mesylation of **8a** followed by removal of the silyl-protecting group provided mesylate **9** (Scheme 3). Hydrogenolysis of **9** followed by Jones oxidation and subsequent esterification with diazomethane gave diester **10**. To distinguish 1-OAc and 3-OAc and convert the *N*-methoxycarbonyl group to the oxazolidinone ring that was easier to be cleavaged, the diester **10** was treated with 3 equiv of magnesium in methanol to afford **11** in 78% yield.[12] This step was essential for this total synthesis because we found that the *N*-methoxycarbonyl-protecting group could not be removed under various conditions in the final stage. The solvent in this transformation was critical, because we observed that when **10** was treated with 3 equiv of magnesium in ethanol either no reaction occurred (at 40 °C) or another oxazolidinone **13** was formed (at 50 °C). Clearly, **13** was produced by an intramolecular S_N2 reaction. Its X-ray structure supported the configuration of 9-OH in **8a**. Next, reaction of the mesylate **11** with sodium azide followed by PtO_2-catalyzed hydrogenation produced the primary amine, which was treated with 3,5-dichloro-4-benzoxybenzoic chloride to afford an amide, which was submitted to Jones oxidation to give acid **12**. Finally, **12** was transformed into kaitocephalin by following deprotection steps: (1) hydrogenolysis to remove benzyl group, (2) treatment with 2 N HCl to remove Boc group, and (3) hydrolysis with 1 N NaOH to cleave the ester and oxazolidinone ring. Comparison of the spectroscopic data of the product with those of authentic kaitocephalin confirmed the identity of our synthetic kaitocephalin.

Scheme 3[a]



[a] Reagents and conditions: (a) i) MsCl, Et_3N, DMAP, CH_2Cl_2, 0 °C, ii) TBAF, HOAc, 90% for two steps; (b) i) PtO_2, H_2, 100%, ii) Jones oxidation then CH_2N_2, 85%; (c) 3 equiv Mg, MeOH, 35−40 °C, 78%; (d) i) NaN_3, DMF, 30 °C, ii) Pd/C, H_2, iii) 3,5-dichloro-4-benzoxybenzoic chloride, Et_3N, CH_2Cl_2, rt, iv) Jones oxidation, 53% for four steps; (e) i) Pd/C, H_2, 100%, ii) 2 N HCl, 100%, iii) 1 N NaOH, 92%.

This first total synthesis of kaitocephalin includes a number of key steps which are of broad interest, including the highly diastereoselective aldol reaction of **2b** with (*R*)-Garner aldehyde to provide **3b** and various functional group manipulations involving internal protection and group selectivity. In addition, This synthetic approach (25 linear steps, 8% overall yield) should permit the preparation of useful quantities of kaitocephalin and its analogues, greatly facilitating the ongoing pharmacological studies of AMPA/KA receptors.

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Supporting Information Available: Experimental procedures and characterizations for kaitocephalin and compounds **1**−**12** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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