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Total Synthesis of (−)-Kaitocephalin

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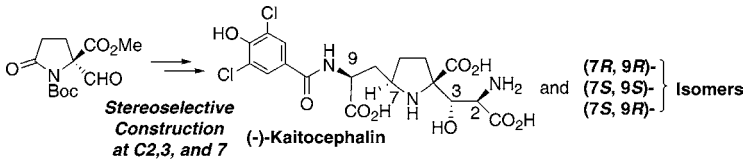
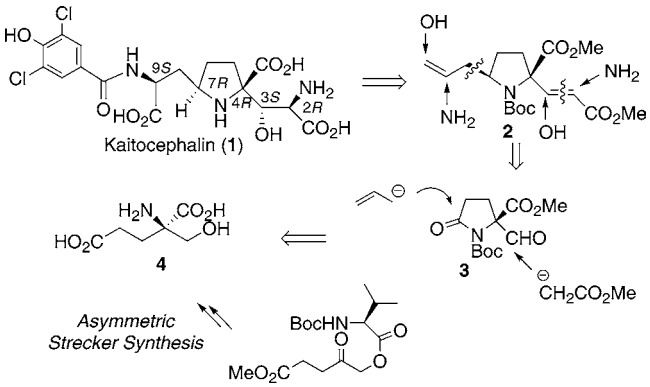
ABSTRACT



Total synthesis of the potent AMPA/KA receptor antagonist (−)-kaitocephalin (1) and its three diastereomers has been accomplished. The synthesis features strictly substrate-controlled operations to α-formylglutamate 3 starting with α-hydroxymethylglutamate 4. The requisite 2*R*,3*S*,7*R*-stereocenters were efficiently constructed by manipulation of stereoselective reactions: dihydroxylation of 7 followed by azide substitution of the corresponding thionocarbonate 10 and Cu-mediated allylation of an acyliminium ion 21. All of the protecting groups in 26 were removed simultaneously by $AlCl_3/Me_2S$ to give 1.

Kaitocephalin (**1**), isolated from a filamentous fungus *Eupenicillium shearii* PF1191 by Seto and Shin-ya et al.,[1] has attracted much attention due to its potent antagonist activities to AMPA ((*S*)-α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid)/KA (kainic acid) receptors,[2] a major subtype of ionotropic glutamate receptors. These receptors mediate the majority of excitatory signal transmission at synapses in the mammalian central nervous system and have been implicated in the construction of memory and learning, as well as in the profound neuron damage by ischemic injury to cause acute neuronal diseases. Since antagonists of AMPA/KA receptors exhibit potent activities for protection of neuronal death, even when administered after an ischemic attack,[3] kaitocephalin has considerable potential as a promising lead compound for development of therapeutic agents toward ischemia−reperfusion injury, such as stroke and epilepsy. However, its neurobiological actions, in detail as well as SAR studies, have not been sufficiently carried out owing to the extremely small amount of samples available from the fungus. The structure of kaitocephalin (**1**) is characterized by its α-substituted proline core assembled by *N*-acylalanine and serine moieties connected with a carbon−carbon bond. The structure was originally assigned to have 2*S*,3*S*,4*R*,7*R*,9*S* configuration by the NMR studies of **1** and its bicyclic lactam derivative.[1b] Recently, Ma[4] and Kitahara[5] groups have independently reported the total synthesis of **1**. Kitahara's work has proven the structure revision at C2 to have an *R* configuration (Scheme 1). In the following, we describe a new approach to the total synthesis of **1** together with three diastereomers of **1** regarding its C7 and C9 stereocenters.

Scheme 1. Synthetic Plan



(1) (a) Shin-ya, K.; Kim, J.-S.; Furihata, K.; Hayakawa, Y.; Seto, H. *Tetrahedron Lett*. **1997**, *38*, 7079−7082. (b) Kobayashi, H.; Shin-ya, K.; Furihata, K.; Hayakawa, Y.; Seto, H. *Tetrahedron Lett*. **2001**, *42*, 4021−4023.

(2) (a) Hollmann, M.; Heinemann, S. *Annu. Rev. Neurosci*. **1994**, *17*, 31−108. (b) Madden, D. R. *Nat. Rev. Neurosci*. **2002**, *3*, 91−101.

(3) (a) Sheardown, M. J.; Nielsen, E. P.; Hansen, A. J.; Jacobsen, P.; Honore, T. *Science* **1990**, *247*, 571−574. (b) Bleakman, D.; Lodge, D. *Neuropharmacology* **1998**, *37*, 1187−1204 and references therein.

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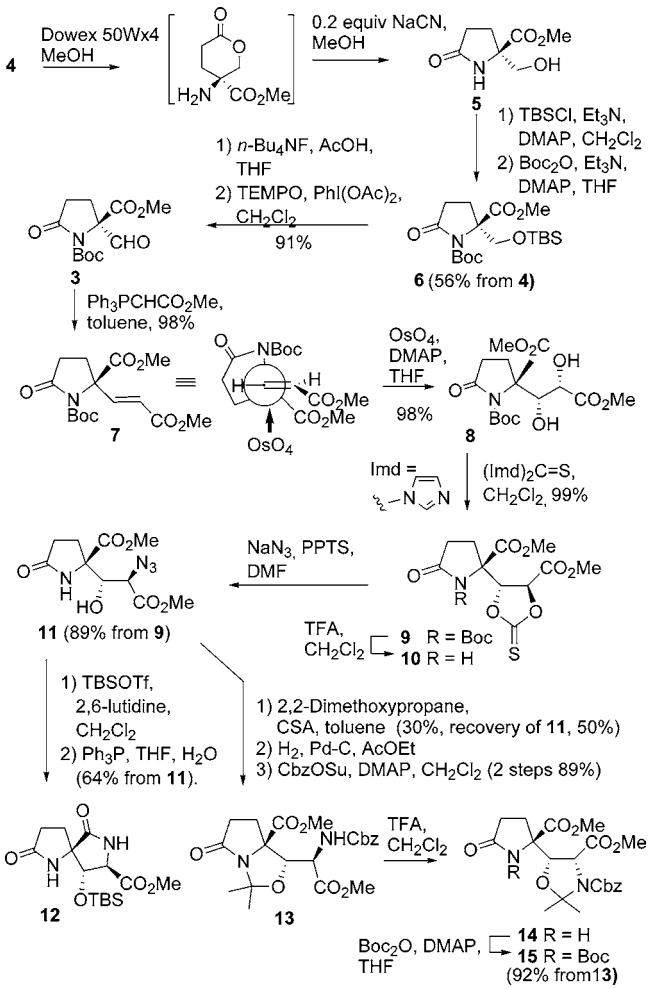
We envisioned that α-formylpyroglutamate **3** can be a key precursor to **1** via **2**, anticipating that its formyl and lactam carbonyl groups would allow introduction of an α,*β*-unsaturated ester for the C1−C3 unit and an allyl group for the C8−C10 *N*-acylalanine moiety, respectively (Scheme 1). The (2*R*,3*S*)-2-amino-3-hydroxy moiety would be constructed by an initial dihydroxylation and subsequent amination at C2. A survey of allylic metal species in an allylation reaction of an acyliminium ion[6] would afford an allylated product with 7*R* configuration (e.g., **2**).

We began the synthesis with (2*R*)-α-hydroxymethylglutamate **4**,[7] available in a large quantity from an α-amino acyloxyketone using an asymmetric version of the Strecker synthesis.[8] Upon dehydration of **4**, leading to pyroglutamate **5**, we employed Dowex 50Wx4 resin (H^+ form) as an acid catalyst in methanol to avoid a hazardous purification of the water-soluble product. Filtration gave a *δ*-lactone intermediate, which, upon treatment with a catalytic amount of NaCN, gave pyroglutamate **5** in excellent yield. Since protection of **5** with Boc_2O gave an undesired *O*-Boc derivative, its conversion to **3** was carried out in four steps involving protecting group manipulations. To install the requisite 2*R*,3*S*-stereocenters to **3**, we chose a stereochemically prospective approach[9] from (*E*)-α,*β*-unsaturated ester **7**. Dihydroxylation of **7** would occur preferentially from the opposite side of the *N*-Boc group to give (2*S*,3*S*)-diol **8** followed by S_N2 azidation at C2 to produce (2*R*,3*S*)-azide **11**. As expected, dihydroxylation under anhydrous conditions proceeded in a highly stereoselective manner to give the diol **8**.[10] Upon substitution with an azide, our choice was the use of a cyclic thionocarbonate **9** according to Ko's method.[11] However, the reaction did not proceed at all to recover **9**, due probably to the steric hindrance of the Boc and/or methoxycarbonyl group. Thus, the Boc group was removed to give sterically less congested lactam **10**. As expected, **10** underwent smooth azidation to give **11** in 89% yield. Reduction of the azide group gave spirolactam **12**, which was found to be resistant to its ring opening. To prevent the undesired lactam formation, N^4,O^3-acetonide was introduced to form a bicyclic intermediate **13**. In this molecule, spirolactam formation was not observed at all under the reducing conditions. Protection of the resulting amine with a Cbz group gave **13**. Conversion to acyliminium ion precursor **15** for the next allylation reaction at C7 requires

Scheme 2. Synthesis of *N*-Boc Lactam **15**



reconstitution of the N^4,O^3-acetonide to the desired acetonide. To our delight, upon exposure of **13** to TFA, the *N*,*O*-migration occurred to give **14** that was protected with a Boc group to afford **15**.

It has been reported that Lewis acid-promoted allylation of **16a** with allyltrimethylsilane occurs stereoselectively from the same face as the methoxycarbonyl group to give *cis*-**17a**.[12] The allylation using a model substrate **16b** gave a 7*R*-isomer **17b**, exclusively. Contrary to these observations, allylation of **18** with allyltrimethylsilane furnished (7*S*)-**19** as the sole diastereomer.[13] After numerous attempts, we found that the use of an allylcopper reagent prepared from the CuBr−SMe_2 complex and allylmagnesium bromide gave (7*R*)-**20** as a major product (**19**:**20** = 1:2).[14,15]

Since the minor isomer **19** could not be removed at this stage, the mixture was used for the conversion to kaito-

(4) Ma, D.; Yang, J. *J. Am. Chem. Soc*. **2001**, *123*, 9706−9707. The synthesis of the 2*S*-isomer of **1** was reported.

(5) (a) Okue, M.; Kobayashi, H.; Shin-ya, K.; Furihata, K.; Hayakawa, Y.; Seto, H.; Watanabe, H.; Kitahara, T. *Tetrahedron Lett*. **2002**, *43*, 857−860. (b) Watanabe, H.; Okue, M.; Kobayashi, H.; Kitahara, T. *Tetrahedron Lett*. **2002**, *43*, 861−864.

(6) Pichon, M.; Figadere, B. *Tetrahedron: Asymmetry* **1996**, *7*, 927−964.

(7) Kawasaki, M.; Namba, K.; Tsujishima, H.; Shinada, T.; Ohfune, Y. *Tetrahedron Lett*. **2003**, *44*, 1235−1238.

(8) (a) Moon, S.-H.; Ohfune, Y. *J. Am. Chem. Soc*. **1994**, *116*, 7405−7406. (b) Namba, K.; Shinada, T.; Teramoto, T.; Ohfune, Y. *J. Am. Chem. Soc*. **2000**, *122*, 10708−10709. (c) Ohfune, Y.; Shinada, T. *Bull. Chem. Soc. Jpn*. **2003**, *76*, 1115−1129 and references therein.

(9) Addition of an enolate derived from a glycine ester to **3** resulted in a deformylation to give methyl pyroglutamate.

(10) The structure to have 2*S*,3*S* configuration was determined by converting it to a bicyclic derivative (Supporting Information).

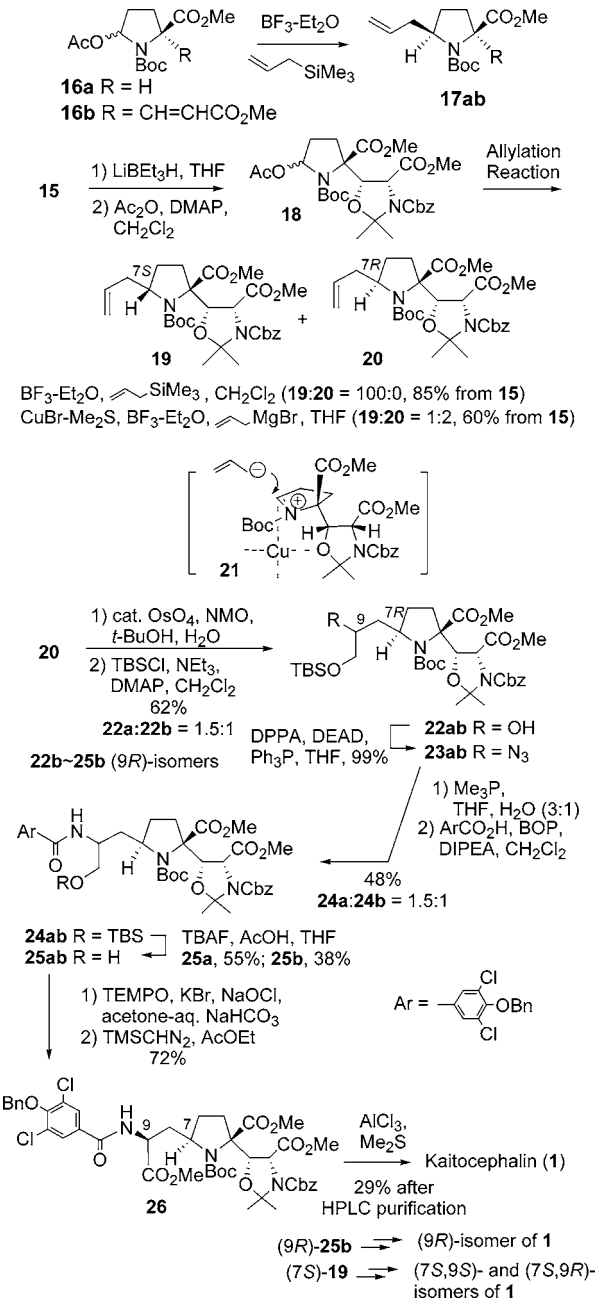
(11) Ko, S. Y. *J. Org. Chem*. **1995**, *60*, 6250−6251.

(12) (a) Shono, T.; Fujita, T.; Matsumura, Y. *Chem. Lett*. **1991**, 81−84. (b) Oba, M.; Koguchi, S.; Nishiyama, K.; Kaneno, D.; Tomoda, S. *Angew. Chem., Int. Ed*. **2004**, *43*, 2412−2415.

(13) This was found after conversion of **19** to 7*S*-isomers of **1**, whose ^1H NMR spectrum and HPLC profile were not identical to that of natural **1** (Supporting Information).

(14) Addition of an alkylcopper reagent to an acyliminium ion: (a) Collado, I.; Ezquerra, J.; Pedregal, C. *J. Org. Chem*. **1995**, *60*, 5011−5015. (b) Hanessian, S.; Claridge, S.; Johnstone, S. *J. Org. Chem*. **2002**, *67*, 4261−4274.

Scheme 3. Total Synthesis of Kaitocephalin



cephalin and its diastereoisomers. Dihydroxylation of the mixture followed by protection of the resulting primary alcohol gave an inseparable mixture of TBS ethers **22ab** containing their 7*S*-isomers.[16] Substitution of the secondary hydroxy group with an azide group provided a mixture of **23ab**. Reduction of the azide group with PMe_3[17] followed by benzoylation gave a mixture of **24ab**. The 7*S*-isomers derived from **19** were chromatographically separated at this stage. Removal of the TBS group gave a separable mixture of alcohols (9*S*)-**25a** and (9*R*)-**25b**. Oxidation of **25a** gave protected kaitocephalin **26** possessing three methyl esters, *N*-Cbz, *N*-Boc, *N*,*O*-acetonide, and benzyl ether groups. We found that cooperative use of a hard Lewis acid ($AlCl_3$) and a soft nucleophile (Me_2S) reported by Node et al.[18] effected complete removal of all protecting groups to give **1** without epimerization at C2 and C9 and spirolactam formation at the C4 ester group.[19] Removal of the resulting aluminum complex with Dowex 50Wx4 resin (H^+ form) followed by fractionation with RP-HPLC gave **1**, which was identical in all aspects (^{1}H NMR, HRMS, HPLC profile, and optical rotations) with natural **1**.[1] (9*R*)-**25b** and 7*S*-isomers derived from **19** were converted into the corresponding 9*R*-, 7*S*,9*S*-, and 7*S*,9*R*-isomers of kaitocephalin, respectively, in the same manner as those from **25a**. In conclusion, we have achieved total synthesis of kaitocephalin and its three diastereomers regarding the C7 and C9 positions. The synthesis was highlighted by a stereocontrolled construction of the asymmetric centers of C2, -3, -4, and -7 and the use of $AlCl_3$/Me_2S for final deprotection. Studies of neuropharmacological activity using the synthetic **1** and its diastereomers are currently being undertaken.

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Supporting Information Available: Experimental and characterization details, structure determination of **8**, and ^{1}H NMR spectra of natural and synthetic **1**, and its 9*R*-, 7*S*,9*S*-, and 7*S*,9*R*-diastereomers (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) The stereoselectivity would be explained by a proposed model **21** in which the electron-rich ether oxygen is participating to form a chelate complex with copper (Scheme 3). Formation of a copper complex in the allylation of **16a** with an organocopper reagent was discussed. Skrinjar, M.; Wistrand, L.-G. *Tetrahedron* **1991**, *47*, 573−582.

(16) The structures of the *R*-isomers **22ab**−**24ab** are depicted in Scheme 3.

(17) Me_3P was a superior reductant compared to Ph_3P in view of its faster reaction rate, better yields, and easy removal of the resulting phosphine oxide.

(18) Node, M.; Nishide, K.; Sai, M.; Fuji, K.; Fujita, E. *J. Org. Chem.* **1981**, *46*, 1991−1993.

(19) A C7 isomer of **26** was used for the removal of the protecting groups as a model. The C4 methyl ester was found to be resistant to alkaline hydrolysis (1 N NaOH or 1 N LiOH). Upon exposure to 30% HBr, a spirolactam was formed between the C2 amino and C4 ester groups.