Pergamon

Tetrahedron Letters 43 (2002) 861–864

TETRAHEDRON LETTERS

# The first synthesis of kaitocephalin based on the structure revision

Hidenori Watanabe,* Masayuki Okue, Hiroyuki Kobayashi and Takeshi Kitahara*

*Department of Applied Biological Chemistry, Graduate School of Agricultural and Life Sciences, The University of Tokyo, 1-1-1 Yayoi, Bunkyo-ku, Tokyo 113-8657, Japan*

Received 1 November 2001; revised 21 November 2001; accepted 22 November 2001

**Abstract**—A total synthesis of kaitocephalin (**2**), a glutamate receptor antagonist, was accomplished employing a novel stereoselective C–C bond forming reaction of a nitrone (**8**) and a halide (**11**) with zinc in aqueous solvent under sonication as a key step. The absolute configuration of kaitocephalin was confirmed to be 2*R*,3*S*,4*R*,7*R*,9*S*. 

Kaitocephalin was isolated from *Eupenicillium shearii* PF1191 by Shin-ya and Seto et al. in 1997.[1] This compound exhibits potent inhibitory activity against neuronal cell death by the action of antagonist for NMDA (*N*-methyl-D-aspartic acid) and AMPA/KA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid/kainic acid) receptors. The initially proposed stereochemistry (**1**) of kaitocephalin is depicted below.[2] The first total synthesis of **1** was announced very recently by Ma et al. and the spectroscopic data of their synthetic **1** were reported to be identical with those of natural kaitocephalin.[3] However, after we had also finished a synthesis of **1**, we found that $^1$H NMR spectral data of our synthetic **1** and its retention time on HPLC were not identical with those of the natural compound. Additionally, epimerization at C-2 of natural kaitocephalin during a derivatization was suggested by model experiments, and a revised structure (**2**) was proposed in the preceding paper.[4]

Herein, we report a total synthesis of kaitocephalin (**2**, revised structure) employing a newly developed reaction of a nitrone and an alkylhalide as a key step (Fig. 1).

Our strategy shown in Scheme 1 is to construct compound **A** by a C–C bond forming reaction of nitrone **B** and halide **C**. Nitrone **B** can be derived from an aldol reaction between the known compounds (**3** and **4**) followed by standard functional group manipulation.

The preparation of nitrone **8** and iodide **11**, precursors of the key reaction, is shown in Scheme 2. The sequence began from lactone **3** which was prepared from L-proline using Seebach's method.[5] Treatment of aldehyde **4** (prepared from L-serine by Garner's method[6]) with the lithium enolate of lactone **3** (THF, −78°C) provided *syn*-alcohol **5a** and *anti*-alcohol **5b** (51% combined yield, **5a**/**5b** = 2:3). The stereochemistries of **5a** and **5b** were determined by NOESY experiments of derivatives

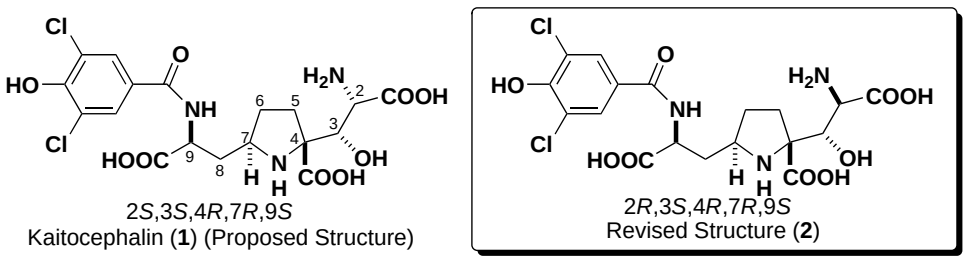
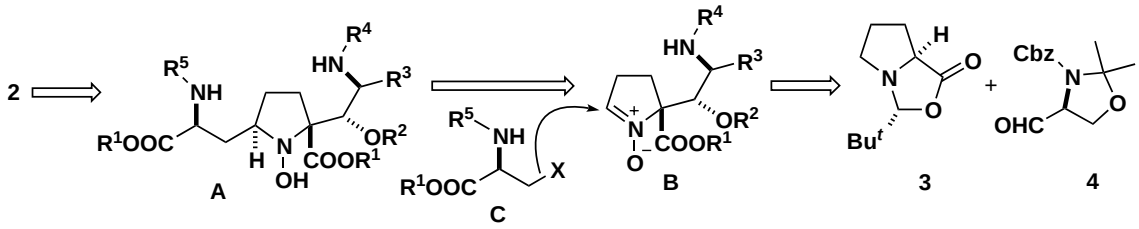


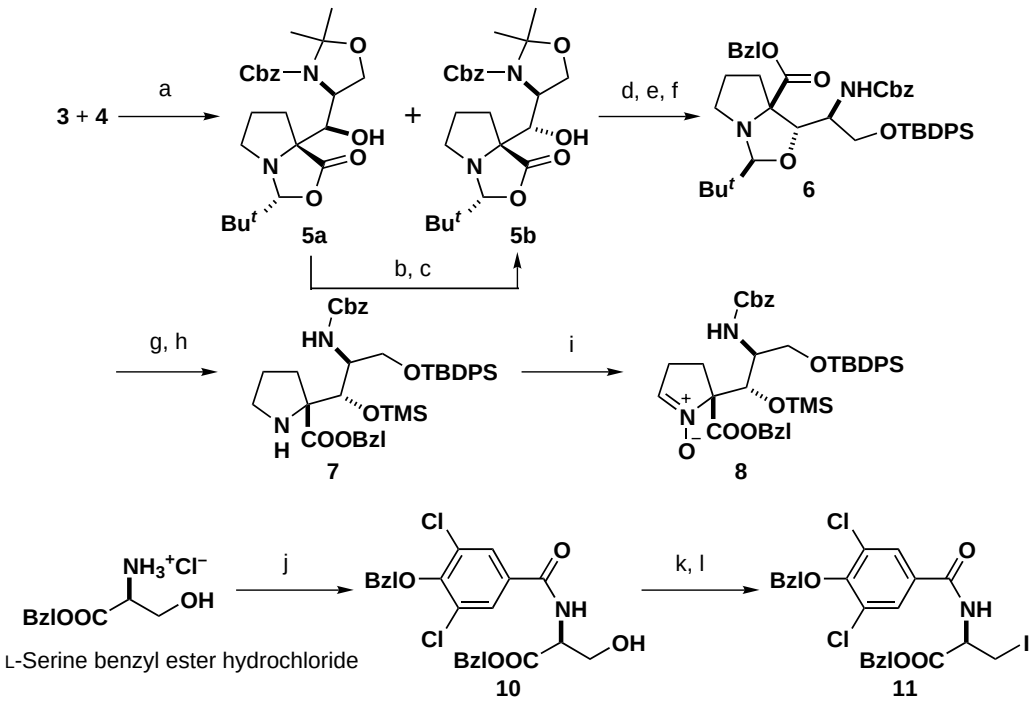

**Figure 1.**

*Keywords*: kaitocephalin; total synthesis; NMDA antagonist; AMPA/KA antagonist.
* Corresponding authors. Fax: 81-3-5841-8019; e-mail: atkita@mail.ecc.u-tokyo.ac.jp

0040-4039/02/$ - see front matter 
PII: S0040-4039(01)02255-9



**Scheme 1.** Synthetic plan.

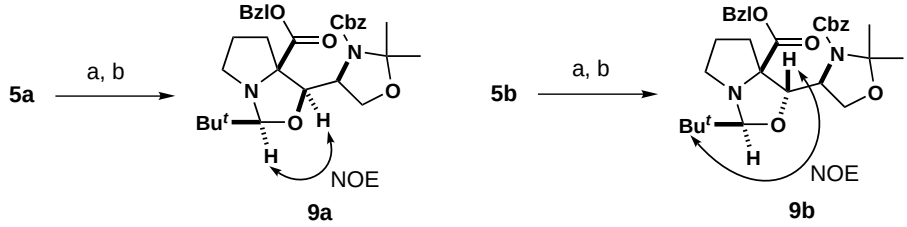


**Scheme 2.** Synthesis of **8** (=**B**) and **11** (=**C**). (a) LDA, THF, −78°C, 51% (**5a**/**5b**=2:3); (b) Dess–Martin periodinane, $CH_2Cl_2$, Py, 0°C; (c) $NaBH_4$, EtOH/THF (5:1), 0°C, 31%; (d) 10% $H_2SO_4$, 1,4-dioxane, rt–80°C; (e) BzlBr, DBU, $CH_3CN$, rt; (f) TBDPSCl, $Et_3N$, DMAP, $CH_2Cl_2$, rt, 84%; (g) 80% AcOH, 60°C, 52%; (h) TMSCl, imidazol, DMF, 0°C, 96%; (i) $MeReO_3$, Urea·$H_2O_2$, MeOH, rt, 84%; (j) 4-benzyloxy-3,5-dichlorobenzoic acid, BOP reagent, $Et_3N$, $CH_2Cl_2$, 0°C–rt, 92%; (k) MsCl, $Et_3N$, $CH_2Cl_2$, 0°C, 74%; (l) NaI, acetone, rt, 84%.

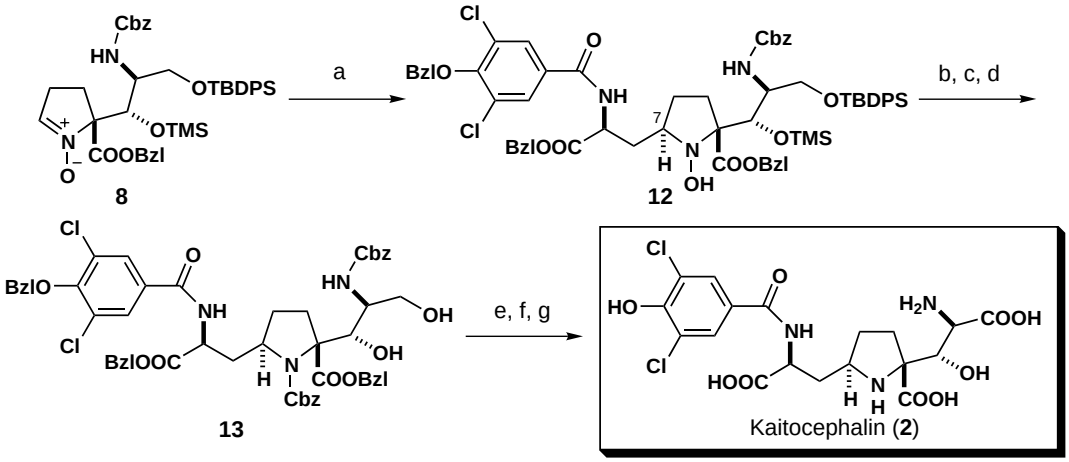
**9a** and **9b** (Scheme 3). The minor product **5a** was converted into desired diastereomer **5b** by Dess–Martin oxidation followed by reduction with $NaBH_4$ (31% from **5a**). Treatment of **5b** with 10% $H_2SO_4$ caused an intramolecular transacetalization of *t*-butyloxazoline and hydrolysis of dimethyloxazoline. Benzylation of the carboxyl group followed by protection of the primary alcohol with TBDPSCl gave **6** in 84% yield over three steps. Hydrolysis of *t*-butyloxazoline with 80% AcOH (52% yield) and subsequent protection of the secondary alcohol as the TMS ether provided **7** (96% yield). Oxidation of the secondary amine of **7** with $MeReO_3$–urea·$H_2O_2$[7] afforded nitrone **8** (=**B**, 84% yield).

Meanwhile, another precursor [**11** (=**C**)] for the key coupling reaction was prepared from L-serine benzyl ester hydrochloride. Amidation with 4-benzyloxy-3,5-dichlorobenzoic acid by BOP reagent in the presence of triethylamine provided **10**. The hydroxyl group of **10** was then converted into iodide **11** via the mesylate in 62% yield. The iodide could be synthesized via the tosylate as well, but the use of mesylate allowed an easy purification of **11** by simple recrystallization.

The key C–C bond forming step of nitrone **8** and halide **11** with zinc under ultrasound irradiation is outlined in Scheme 4. Treatment of nitrone **8** and iodide **11** with zinc activated by CuI under irradiation of ultrasound (THF/$H_2O$=3.3:1, ambient temperature)[8] gave hydroxylamine **12** in 75% yield as a single isomer. The stereochemistry at C-7 of **12** was inferred from analogy with 2-*epi*-**12** whose stereochemistry had already been determined.[4] After reduction of hydroxylamine with zinc and ammonium chloride (98% yield), protection of the secondary amine with CbzCl followed by removal of TBDPS and TMS groups by TMSCl–MeOH system afforded diol **13** in 45% yield over two steps. Stepwise oxidation of the primary alcohol of **13** proceeded selec-




**Scheme 3.** NOEs of **9a** and **9b**. (a) 10% $H_2SO_4$, 1,4-dioxane, rt; (b) BzlBr, DBU, $CH_3CN$, rt.




**Scheme 4.** Completion of the synthesis of **2**. (a) **11**, Zn (8 equiv.), CuI (3.6 equiv.), $THF/H_2O$ (3.3:1), ultrasound, rt, 75%; (b) Zn, satd $NH_4Cl$, EtOH, 90°C, 98%; (c) CbzCl, $K_2CO_3$, toluene/$H_2O$; (d) TMSCl, MeOH, rt, 45%; (e) 4-methoxy-TEMPO, KBr, satd $NaHCO_3$, NaClO, $CH_2Cl_2$, 0°C; (f) $NaClO_2$, 2-methyl-2-butene, $NaH_2PO_4$, Bu$^t$OH/$H_2O$ (10:3), rt, 86%; (g) $H_2$, 20% $Pd(OH)_2$–C, EtOH/$CHCl_3$ (10:1), rt 27%, after preparative HPLC.

tively with 4-methoxy-TEMPO and co-oxidizing reagent system[9] followed by sodium hypochlorite to give carboxylic acid (86%, two steps). Finally, hydrogenolysis of the benzylic protective groups with $H_2$/20% $Pd(OH)_2$–C afforded the target molecule, kaitocephalin (**2**). In this step, chloroform was indispensable as it minimized dechlorination of the aromatic ring. $^1$H NMR spectral data, retention time on HPLC and specific rotation of synthetic **2** were identical with those of authentic natural kaitocephalin.[10]

In conclusion, the first total synthesis of the revised structure of kaitocephalin (**2**) was accomplished starting from L-proline and L-serine. For combining the three amino acid units stereoselectively, Seebach's aldol reaction and the newly developed reaction of nitrone and halide were employed. The overall yield was 1.2% over 14 steps from **3**. By this work, the absolute configuration of kaitocephalin has been proven to be 2*R*,3*S*,4*R*,7*R*,9*S*.

## Acknowledgements

We thank Professor H. Seto and Dr. K. Shin-ya of the University of Tokyo for a kind gift of the $^1$H NMR spectrum of natural kaitocephalin, HPLC analysis of our synthetic **2** and discussions. This work was supported by a Grant-in-Aid for Scientific Research (Priority Area (A) 'Exploitation of Multi-Element Cyclic Molecules' and General Research (B); No. 12460050) from the Japanese Ministry of Education, Culture, Sports, Science and Technology. We also thank Sankyo Foundation of Life Science and Suntory Institute for Bioorganic Research for financial support.

## References

1. Shin-ya, K.; Kim, J.-S.; Furihata, K.; Hayakawa, Y.; Seto, H. *Tetrahedron Lett*. **1997**, *38*, 7079–7082.
2. Kobayashi, H.; Shin-ya, K.; Furihata, K.; Hayakawa, Y.; Seto, H. *Tetrahedron Lett*. **2001**, *42*, 4021–4023.
3. Ma, D.; Yang, J. *J. Am. Chem. Soc*. **2001**, *123*, 9706–9707.
4. Okue, M.; Kobayashi, H.; Shin-ya, K.; Furihata, K.; Hayakawa, Y.; Seto, H.; Watanabe, H.; Kitahara, T. *Tetrahedron Lett*. **2002**, *43*, 857–860.
5. (a) Seebach, D.; Boes, M.; Naef, R.; Schweizer, W. B. *J. Am. Chem. Soc*. **1983**, *105*, 5390–5398; (b) Beck, A. K.; Blank, S.; Job, K.; Seebach, D.; Sommerfeld, T. *Org. Synth*. **1993**, *72*, 62–73.
6. (a) Garner, P.; Park, J.-M. *J. Org. Chem*. **1987**, *52*, 2361–2364; (b) Garner, P.; Park, J.-M. *Org. Synth*. **1991**, *70*, 18–28; (c) Marshall, J. A.; Beaudoin, S. *J. Org. Chem*. **1996**, *61*, 581–586.

7. (a) Murray, R. W.; Iyanar, K.; Chen, J.; Wearing, J. T. *J. Org. Chem.* **1996**, *61*, 8099–8102; (b) Goti, A.; Nannelli, L. *Tetrahedron Lett.* **1996**, *37*, 6025–6028.
8. The same conditions for a conjugate addition to an enone, see: (a) Petrier, C.; Einhorn, J.; Luche, J. L. *Tetrahedron Lett.* **1985**, *26*, 1449–1452; (b) Petrier, C.; Dupuy, C.; Luche, J. L. *Tetrahedron Lett.* **1986**, *27*, 3149–3152; (c) Luche, J. L.; Allavena, C. *Tetrahedron Lett.* **1988**, *29*, 5369–5372; (d) Dupuy, C.; Petrier, C.; Sarandeses, L. A. Luche, J. L. *Synth. Commun.* **1991**, *21*, 643–651.
9. Anelli, P. L.; Biffi, C.; Montanari, F.; Quici, S. *J. Org. Chem.* **1987**, *52*, 2559–2562.
10. Data for synthetic compound **2**: $^1$H NMR (500 MHz, $D_2O$) $\delta$ 1.57 (m, 1H), 1.97 (m, 1H), 2.02 (m, 1H), 2.07 (m, 1H), 2.24 (ddd, 1H, $J=2.1$, 5.2, 13.7 Hz), 2.38 (ddd, 1H, $J=5.5$, 6.4, 14.4 Hz), 3.65 (m, 1H), 4.11 (brs, 1H), 4.31 (dd, 1H, $J=5.2$, 8.2 Hz), 4.36 (brs, 1H), 7.59 (s, 2H); $[\alpha]_D^{25}$ −26.6° (*c* 0.19, $H_2O$). [lit.[1] $^1$H NMR (500 MHz, $D_2O$) $\delta$ 1.61 (m), 2.01 (m), 2.06 (m), 2.12 (m), 2.28 (ddd, $J=2.0$, 6.0, 14.0 Hz), 2.41 (ddd, $J=6.0$, 7.0, 14.5 Hz), 3.70 (m), 4.16 (brs), 4.35 (dd, $J=6.0$, 8.0 Hz), 4.41 (brs), 7.62 (s, 2H); $[\alpha]_D^{21}$ −31° (*c* 0.7, $H_2O$)].