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Synthesis of the proposed structure and revision of stereochemistry of kaitocephalin

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Abstract—A stereoselective total synthesis of the proposed structure of kaitocephalin (**1**) was accomplished starting from L-proline and D- and L-serines. However, its ^{1}H NMR spectral data and retention time on HPLC were not identical with those of authentic natural kaitocephalin. The revised stereochemistry of natural kaitocephalin, (2*R*)-isomer (**16**), was inferred from further experiments employing diastereomers and model compounds.

Kaitocephalin (**1**) was isolated from *Eupenicillium shearii* PF1191 in 1997 as a novel NMDA (*N*-methyl-D-aspartic acid) and AMPA/KA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid/kainic acid) receptors antagonist.[1] This compound protected chick primary telencephalic neurons from kainate toxicity at 500 μM with EC_{50} value 0.68 μM,[1] which is almost the same level as that of the well known AMPA/KA antagonist CNQX (EC_{50} value 0.53 μM). More recently, the absolute stereochemistry of kaitocephalin (**1**) was reported to be 2*S*,3*S*,4*R*,7*R*,9*S*.[2] We were interested in this unique structure as well as its potent biological activities, and have been investigating a stereoselective synthesis of kaitocephalin to confirm the absolute configuration of **1** (Fig. 1).

Herein, we report a total synthesis of proposed structure **1** using a novel stereoselective coupling reaction of a nitrone and a halide as a key step. However, ^{1}H NMR spectral data of our synthetic **1** and its retention time on HPLC were not identical with those of authentic natural kaitocephalin.[3]

A synthesis of **1** is shown in Scheme 1. Aldol reaction between Seebach's lactone **2**[4] and Garner's aldehyde **3**[5] provided **4a** and **4b** (58% combined yield, **4a**/**4b** = 4:1). These stereochemistries were determined by NOESY experiments of **5a** and **5b**, which were derived from **4a** and **4b**, respectively. Major product **4a** was converted into desired **4b** by Dess–Martin oxidation followed by reduction with $NaBH_4$ (43% from **4a**). After transacetalization of *t*-butyloxazoline and hydrolysis of dimethyloxazoline with 10% H_2SO_4, the liberated carboxyl and hydroxyl groups were protected successively to give **6** in 62% yield over three steps. Hydrolysis of *t*-butyloxazoline with 80% AcOH (62%) followed by protection of the secondary alcohol and oxidation of the secondary amine with $MeReO_3$–urea·H_2O_2[6] provided the desired nitrone **7** (67%, three steps).

When **7**, **8**, Zn powder and CuI in THF/H_2O (3.3:1) were sonicated at ambient temperature, hydroxylamine **9** was obtained in high yield (85%) as a single isomer. Although these reaction conditions were originally

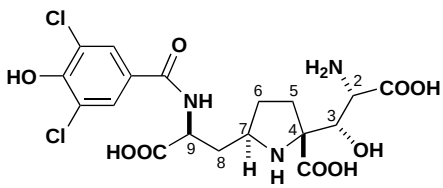

Figure 1. Proposed structure of kaitocephalin (**1**).

Keywords: kaitocephalin; total synthesis; NMDA antagonist; AMPA/KA antagonist.

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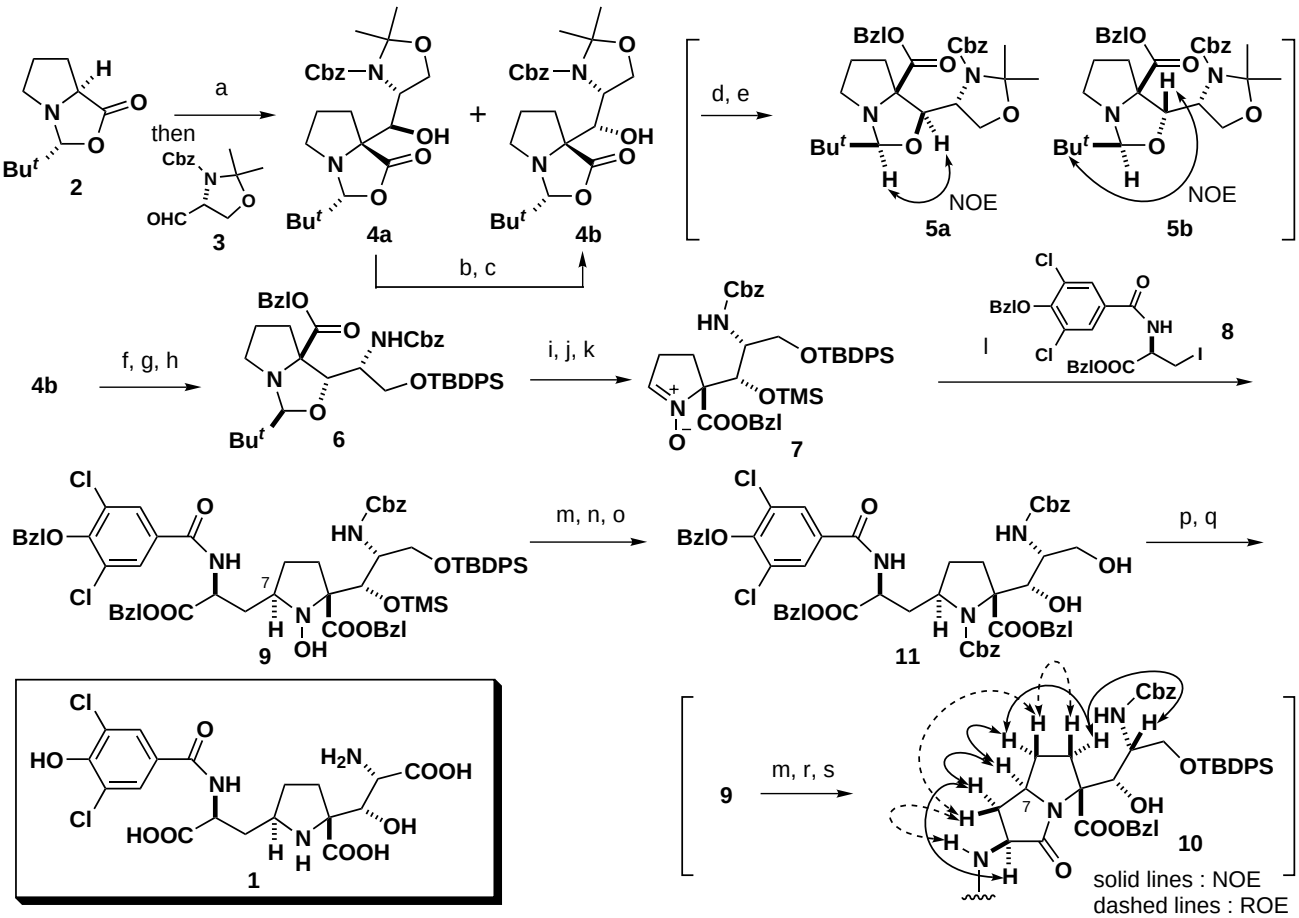


Scheme 1. Synthesis of the proposed structure of kaitocephalin (**1**). (a) LDA, THF, −78°C, 58% (**4a**/**4b** = 4:1); (b) Dess–Martin periodinane, CH_2Cl_2, Py, 0°C, 89%; (c) $NaBH_4$, MeOH/THF (2:1), 0°C, 48%; (d) 10% H_2SO_4, 1,4-dioxane, rt; (e) BzlOH, Ph_3P, DEAD, THF; (f) 10% H_2SO_4, 1,4-dioxane, rt ~ 80°C; (g) BzlBr, $NaHCO_3$, THF/DMF (2:1), rt; (h) TBDPSCl, Et_3N, DMAP, CH_2Cl_2, rt, 62%; (i) 80% AcOH, 60°C, 62%; (j) TMSCl, imidazole, DMF, 0°C, 80%; (k) $MeReO_3$, Urea·H_2O_2, MeOH, rt, 85%; (l) Zn (8 equiv.), CuI (3.6 equiv.), THF/H_2O (3.3:1), ultrasound, rt, 85%; (m) Zn, sat. NH_4Cl, EtOH, 90°C, 71%; (n) CbzCl, K_2CO_3, toluene/H_2O; (o) TBAF, AcOH, THF, rt, 50%; (p) 4-methoxy–TEMPO, KBr, sat. $NaHCO_3$, NaClO, CH_2Cl_2, 0°C, 67%; (q) H_2, 20% $Pd(OH)_2$-C, EtOH/$CHCl_3$ (10:1), rt 30%; (r) TMSCl, MeOH; (s) AcOH (cat.), toluene, reflux.

developed by Luche et al. for a coupling reaction of an alkyl halide and a conjugated enone,[7] our result is the first example of the introduction of an alkyl group to a nitrone in aqueous media. The stereochemistry at C-7 was determined by assigning NOESY and ROESY spectra of lactamized compound **10**. After hydroxylamine **9** was reduced with zinc and ammonium chloride (71% yield), protection of the resulting amine followed by removal of the silyl ethers afforded diol **11** in 50% yield for two steps. Selective oxidation of the primary alcohol of **11** (4-methoxy–TEMPO, excess NaClO)[8] provided carboxylic acid in 67% yield. Hydrogenolysis of the five benzylic protective groups with H_2/20% $Pd(OH)_2$-C was successful when $CHCl_3$ was used as a co-solvent to prevent undesired dechlorination, and **1** was obtained in 30% yield after preparative HPLC purification. However, the ^1H NMR spectral data of synthetic compound **1**[9] and retention time on HPLC were not identical with those of authentic natural kaitocephalin.

To ascertain the correct stereochemistry of natural kaitocephalin, we then synthesized 3-*epi*-**1**, 9-*epi*-**1** and simpler analogs (**12a**–**c**, Fig. 2).[10] Although neither 3-*epi*-**1** nor 9-*epi*-**1** were identical with the natural compound,[11] comparison of ^1H NMR data of our synthetic compounds with natural kaitocephalin suggested a solution of the stereochemistry.

As shown in Fig. 2, stereoisomers of **1** and **12** were classified into groups A–D according to the stereochemistry at C-2, 3 and 4, and chemical shifts of H-2 and 3 and coupling constants between these protons were compared. Compound **12d** has not been synthesized yet due to unexpected inapplicability of the same approach. However, we noticed that (1) the chemical shifts and coupling constants of the compounds in the same group were quite similar irrespective of the presence or absence of the left side chain at C-7 (**12a** versus **1** and 9-*epi*-**1**, **12b** versus 3-*epi*-**1**); (2) the compounds in groups A and B showed different patterns from that of the natural compound (as highlighted by underlines);

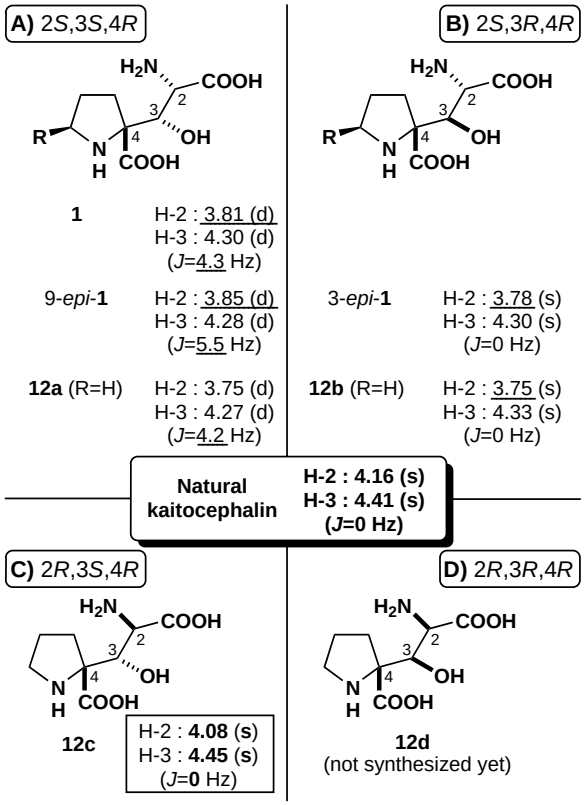
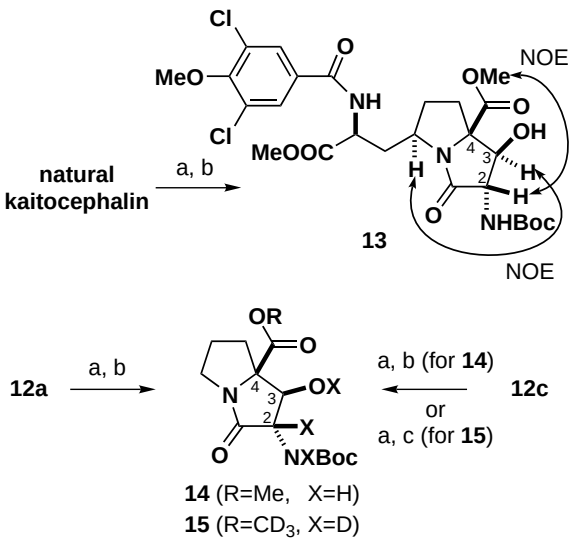


Figure 2. Comparison of ^{1}H NMR spectral data of the stereoisomers of kaitocephalin, model compounds **12**, and natural kaitocephalin.

(3) compound **12c** showed quite similar patterns to those of the natural compound.

Thus, we assumed the correct stereochemistry of kaitocephalin to be 2*R*,3*S*,4*R*,7*R*,9*S* and verified the previous assignment. As described in Ref. 2, kaitocephalin was transformed into protected lactam **13** to observe



Scheme 2. (a) $(Boc)_2O$, Na_2CO_3, 1,4-dioxane/H_2O; (b) $TMSCHN_2$, MeOH; (c) $TMSCHN_2$, CD_3OD.

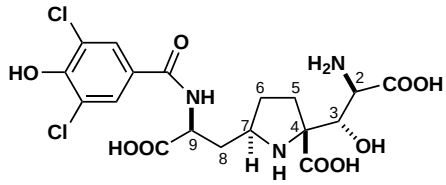


Figure 3. Revised structure of kaitocephalin (**16**).

significant NOE correlation (Scheme 2). We suspected that an epimerization has taken place during this two-step conversion, and reproduced the reactions by using **12a** and **12c**. Surprisingly, both compounds gave the same product (**14**) and a deuteration experiment (**12c**→ **15**) revealed that the epimerization had taken place at C-2 in the second methylation step.

From all of these results, we reached the conclusion that the stereochemistry of kaitocephalin has been misassigned due to the unexpected and unfortunate epimerization at C-2 during derivatization and the correct stereochemistry of kaitocephalin must be 2*R*,3*S*,4*R*,7*R*,9*S* (Fig. 3). This revised stereochemistry was confirmed by a total synthesis, as described in the following paper.[12]

Acknowledgements

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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. Very recently, the first synthesis of **1** was reported: Ma, D.; Yang, J. *J. Am. Chem. Soc*. **2001**, *123*, 9706–9707. We cannot understand why their synthetic **1** was identical to the natural compound.
4. (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.
5. (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.
6. (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.

7. (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.
8. Anelli, P. L.; Biffi, C.; Montanari, F.; Quici, S. *J. Org. Chem*. **1987**, *52*, 2559–2562.
9. The data for synthetic compound **1**: ^{1}H NMR (500 MHz, D_2O) δ 1.57 (m, 1H), 2.05 (m, 1H), 2.09–2.15 (m, 2H), 2.31 (dd, 1H, $J=6.7$, 12.2 Hz), 2.36 (m, 1H), 3.61 (m, 1H), 3.81 (d, 1H, $J=4.3$ Hz), 4.30 (d, 1H, $J=4.3$ Hz), 4.33 (dd, 1H, $J=5.5$, 9.2 Hz), 7.62 (s, 2H). [Lit.[1] ^{1}H NMR (500 MHz, D_2O) δ 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).]
10. These compounds were synthesized in the same manner employed for the synthesis of **1** by using enantiomers of **3** or **8**. Detailed experimental procedures and analytical data will be given in a full account.
11. The data of synthetic compounds 9-*epi*-**1** and 3-*epi*-**1**: 9-*epi*-**1**: ^{1}H NMR (500 MHz, D_2O) δ 1.69 (m, 1H), 2.20–2.27 (m, 4H), 2.37 (dd, 1H, $J=5.5$, 11.6 Hz), 3.65 (m, 1H), 3.85 (d, 1H, $J=5.5$ Hz), 4.28 (d, 1H, $J=5.5$ Hz), 4.38 (dd, 1H, $J=6.1$, 7.9 Hz), 7.71 (s, 2H); 3-*epi*-**1**: ^{1}H NMR (300 MHz, D_2O) δ 1.59 (m, 1H), 2.08–2.24 (m, 4H), 2.44 (m, 1H), 3.66 (m, 1H), 3.78 (brs, 1H), 4.30 (brs, 1H), 4.45 (m, 1H), 7.82 (s, 2H).
12. Watanabe, H.; Okue, M.; Kobayashi, H.; Kitahara, T. *Tetrahedron Lett*. **2002**, *43*, 861–864.