ORGANIC LETTERS

2012
Vol. 14, No. 6
1644–1647

Total Synthesis of (−)-Kaitocephalin Based on a Rh-Catalyzed C−H Amination

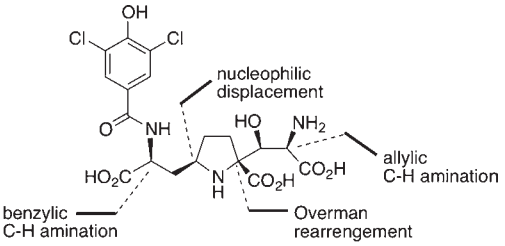
Keisuke Takahashi, Daisuke Yamaguchi, Jun Ishihara, and Susumi Hatakeyama*

Graduate School of Biomedical Sciences, Nagasaki University, Nagasaki, 852-8521, Japan

susumi@nagasaki-u.ac.jp

Received February 21, 2012

ABSTRACT



A total synthesis of (−)-kaitocephalin, an ionotropic glutamate receptor antagonist, is accomplished in highly stereocontrolled manner via Overman rearrangement, rhodium-catalyzed benzylic C−H amination, pyrrolidine formation involving nucleophilic opening of a cyclic sulfamate, and rhodium-catalyzed allylic C−H amination as key steps.

In 1997, Shin-ya and co-workers isolated kaitocephalin (**1**) from *Eupenicillium shearii* PF1191.[1] This structurally novel amino acid has attracted much attention due to its potent antagonistic activity against ionotropic glutamate receptors.[1,2] Excessive stimulation of these receptors by glutamic acid or other agonists causes a variety of neurodegenerative disorders including epilepsy, stroke, Parkinson's disease, and Alzheimer's disease.[3] Since antagonists of glutamate receptors are effective for the protection of neuronal injury or death, kaitocephalin (**1**) has potential as a promising lead compound for developing therapeutic agents against various neuronal diseases. However, detailed neurobiological studies and SAR studies have been hampered at present by the fact that the fungus has not produced a sufficient amount of kaitocephalin (**1**). Such extremely low availability from natural sources as well as the intriguing biological properties and structural challenges has made kaitocephalin (**1**) and its analogues attractive targets for synthesis. Thus, there have been a number of the synthetic studies[4,5] including total syntheses achieved by four groups.[6−9] In connection with our project directed toward the synthesis of natural products which selectively interact with ionotropic glutamate receptors,[4c,10] we became interested in the synthesis of

(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) Limon, A.; Reyes-Ruiz, J. M.; Vaswani, R. G.; Chamberlin, A. R.; Miledi, R. *ACS Chem. Neurosci*. **2010**, *1*, 175–181. Kaitocephalin inhibits NMDA and AMPA receptors but has only slight effects on KA receptors.

(3) Bigge, C. E. *Curr. Opin. Chem. Biol*. **1999**, *3*, 441–447. (b) Mayer, M. L. *Current Opin. Neurobiol*. **2005**, *15*, 282–288. (c) Dingledine, R.; Borges, K.; Bowie, D.; Traynelis, S. F. *Pharmcol. Rev*. **1999**, *51*, 7–61. (d) Madden, D. R. *Nat. Rev. Neurosci*. **2002**, *3*, 91–101.

(4) Synthetic approaches to **1**: (a) Loh, T.-P.; Chok, Y.-K.; Yin, Z. *Tetrahedron Lett*. **2001**, *42*, 7893–7897. (b) Kudryavtsev, K. V.; Nukolova, N. V.; Kokoreva, O. V.; Smolin, E. S. *Russ. J. Org. Chem*. **2006**, *42*, 412–422. (c) Takahashi, K.; Haraguchi, N.; Ishihara, J.; Hatakeyama, S. *Synlett* **2008**, 671–674.

(5) Total synthesis of 2-epimer of **1**: Ma, D.; Yang., J. *J. Am. Chem. Soc*. **2001**, *123*, 9706–9707.

(6) (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. (c) Doi, F.; Watanabe, H. *49th Symposium on the Chemistry of Natural Products*, 2007 (Sapporo), pp 533−538.

(7) (a) Kawasaki, M.; Shinada, T.; Hamada, M.; Ohfune, Y. *Org. Lett*. **2005**, *7*, 4165–4167. (b) Hamada, M.; Shinada, T.; Ohfune, Y. *Org. Lett*. **2009**, *11*, 4664–4667.

(8) Vasawani, R. G.; Chamberlin, R. *J. Org. Chem*. **2008**, *73*, 1661–1681.

(9) Yu, S.; Zhu, S.; Pan, X.; Yang, J.; Ma, D. *Tetrahedron* **2011**, *67*, 1673–1680.

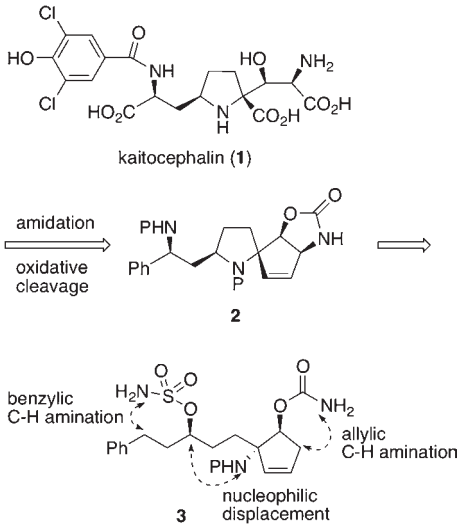
(10) (a) Masaki, H.; Maeyama, J.; Kamada, K.; Esumi, T.; Iwabuchi, Y.; Hatakeyama, S. *J. Am. Chem. Soc*. **2000**, *122*, 5216–5217. (b) Takahashi, K.; Matsumura, T.; Ishihara, J.; Hatakeyama, S. *Chem. Commun*. **2007**, 4158–4160. (c) Takahashi, K.; Matsumura, T.; Corbin, G. R. M.; Ishihara, J.; Hatakeyama, S. *J. Org. Chem*. **2006**, *71*, 4227–4231.

10.1021/ol300431n
Published on Web 03/05/2012

kaitocephalin (**1**). Herein, we report a novel stereocontrolled synthesis of (−)-kaitocephalin (**1**) which features two rhodium-catalyzed C−H amination reactions for the installation of both right-hand and left-hand sides of amino acid functionalities.

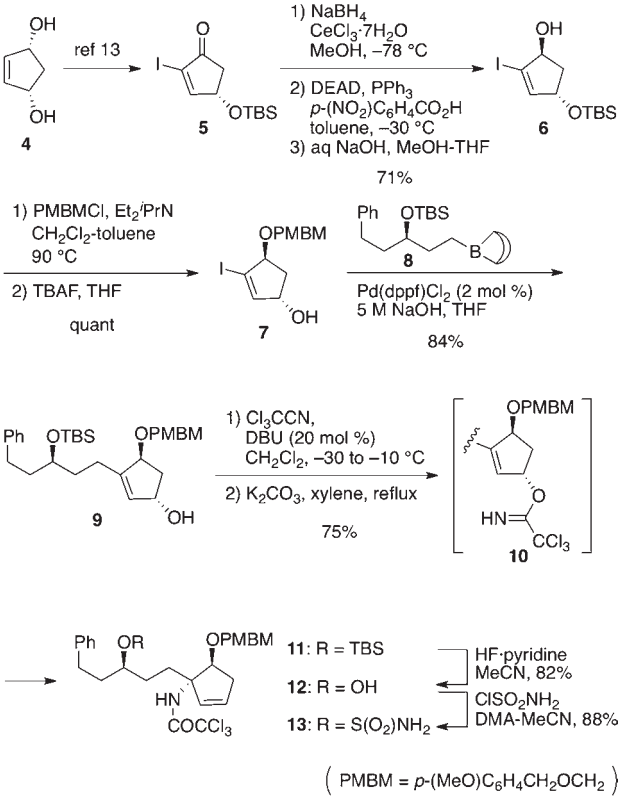
Scheme 1 illustrates our retrosynthetic analysis of kaitocephalin (**1**). We envisaged **2** as a precursor of **1** by focusing on three carboxylic acids which could be available by oxidative cleavage of a phenyl group and a cyclopentene ring simultaneously. We then postulated that this intermediate could be accessed from **3** via rhodium-catalyzed benzylic and allylic C−H amination reactions followed by an intramolecular nucleophilic attack of a nitrogen atom on a sulfamate group, based on Du Bois' protocol.[11,12]

Scheme 1. Retrosynthetic Analysis of Kaitocephalin (**1**)



Our synthesis of **1** thus began with the enantio- and stereoselective preparation of sulfamate **13** (Scheme 2). Iodoenone **5**,[13] readily available from (1*R*,3*S*)-cyclopent-4-ene-1,3-diol (**4**),[14] was first converted to **7** via **6** by a five-step sequence involving Luche reduction,[15] Mitsunobu reaction,[16] saponification, protection as a *p*-methoxybenzyloxymethyl (PMBM) ether,[17] and desilylation in 71% overall yield. Alkenyl iodide **7** was then subjected to Suzuki-Miyaura coupling[18] with borane **8**, in situ prepared from (*R*)-3-(*tert*-butyldimethylsilyloxy)-5-phenylpent-1-ene[19] and 9-BBN, to give allyl alcohol **9** in 84% yield. At this stage, after conversion of **9** to trichloroacetimidate **10**, we examined its Overman rearrangement[20] under various

Scheme 2. Preparation of Sulfamate **13**



conditions in order to introduce a nitrogen atom to the quaternary center stereoselectively. As a result, we gratifyingly found that when a solution of **10** in xylene was heated with K_2CO_3 at 170 °C for 20 min, the rearrangement cleanly took place to afford trichloroacetamide **11** in 75% yield.[21] It is important to note that when the reaction was conducted at lower temperature (< 140 °C), the yield was dramatically diminished to 40% or less because it required the longer reaction time resulting in appreciable decomposition of **10** or **11**. Palladium-catalyzed conditions[22] were also found to be less effective in this rearrangement and led to a complex mixture. The rearranged product **11** thus obtained was then converted to

(11) (a) Espino, C. G.; Du Bois, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 598–600. (b) Espino, C. G.; Wehn, P. M.; Chow, J.; Du Bois, J. *J. Am. Chem. Soc.* **2001**, *123*, 6935–6936. (c) Espino, C. G.; Fiori, K. W.; Kim, M.; Du Bois, J. *J. Am. Chem. Soc.* **2004**, *126*, 15378–15379. (d) Fiori, K. W.; Du Bois, J. *J. Am. Che. Soc.* **2007**, *129*, 562–568. (e) Zalatan, D. N.; Du Bois, J. *J. Am. Chem. Soc.* **2009**, *131*, 7558–7559.

(12) For reviews, see: (a) Zalantan, D. N.; Du Bois, J. *Top. Curr. Chem.* **2010**, *292*, 347–378. (b) Du Bois *Org. Process Res. Dev.* **2011**, *15*, 758–762.

(13) (a) Johnson, C. R.; Braun, M. P. *J. Am. Chem. Soc.* **1993**, *115*, 11014–11015. (b) Curran, T. T.; Hay, D. A.; Koegel, C. P.; Evans, J. C. *Tetrahedron* **1997**, *53*, 1983–2004.

(14) Deardorff, D. R.; Windham, C. Q.; Craney, C. L. *Organic Syntheses*; Wiley: New York, 1998; Collect. Vol. IX, pp 487−492.

(15) Luche, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 2226–2227.

(16) For a review, see: Hughes, D. L. *Org. React.* **1992**, *42*, 335–656.

(17) Kozikowski, A. P.; Wu, J.-P. *Tetrahedron Lett.* **1987**, *28*, 5125–5128.

(18) For a review, see: Chemler, S. R.; Trauner, D.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 4544–4568.

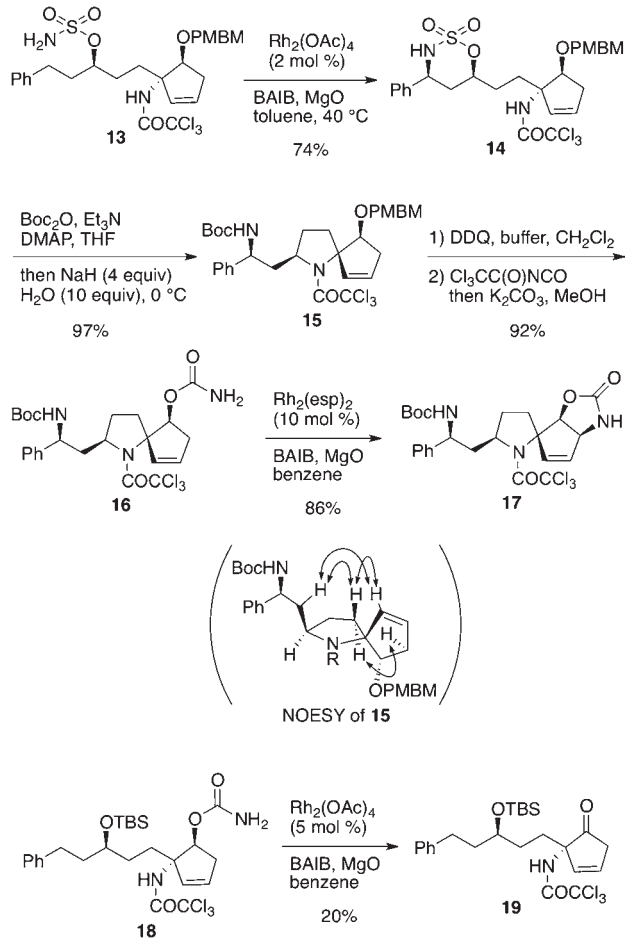
(19) (a) Uenishi, J.; Fujikura, Y.; Kawai, U. *Org. Lett.* **2011**, *13*, 2350–2353. (b) Reddy, D. K.; Shekhar, V.; Prabhakar, P.; Babu, B. C.; Siddhardha, B.; Murthy, U. S. N.; Venkateswrlu, Y. *Eur. J. Med. Chem.* **2010**, *45*, 4657–4663.

(20) For a review, see: Overman, L. E. *Acc. Chem. Res.* **1980**, *13*, 218–224.

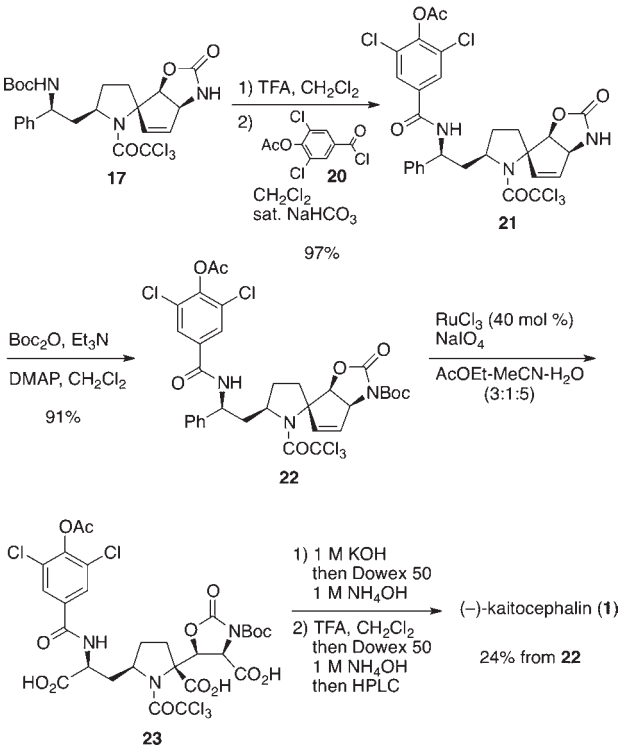
(21) Nishikawa, T.; Asai, M.; Ohyabu, N.; Isobe, M. *J. Org. Chem.* **1998**, *63*, 188–192.

(22) Schenck, T. G.; Bosnich, B. *J. Am. Chem. Soc.* **1985**, *107*, 2058–2066.

Scheme 3. Preparation of Key Intermediate **17**



Scheme 4. Synthesis of (−)-Kaitocephalin



sulfamate **13** by desilylation followed by sulfamation in 72% yield.

We next examined the assembly of the pyrrolidine core starting with rhodium-catalyzed C−H amination[11] of **13** (Scheme 3). When sulfamate **13** was treated with 2 mol % of $Rh_2(OAc)_4$, bis(acetoxy)iodobenzene (BAIB), and MgO in CH_2Cl_2 at 40 °C according to the procedure[11b] reported by Du Bois and co-workers, an oxidative C−H amination took place at the benzylic position regio- and stereoselectively to give cyclic sulfamate **14** in 74% yield, and no other isomers were detected. Although a pyrrolidine synthesis via intramolecular displacement of a cyclic sulfamate with a nitrogen atom was unprecedented, we were pleased to find very effective conditions for this transformation. Thus, after selective *tert*-butoxycarbonylation of the sulfamate nitogen of **14**, the resulting *N*-Boc derivative was successively treated with NaH and water in the same flask at 0 °C to instantaneously provide pyrrolidine **15** in 97% yield via stereoselective cyclization in S_N2 fashion. When 5 M NaOH was used in place of NaH−water, **15** was also obtained in good yield (89%) although the cyclization became somewhat sluggish. Interestingly, when NaH was used alone without addition of water, no cyclization occurred. The stereostructure of **15** was well supported by the NOESY spectrum.

For another rhodium-catalyzed C−H amination on the cyclopentene ring, **15** was converted to carbamate **16** by deprotection of the PMBM group with DDQ followed by carbamoylation in 92% yield. Upon treatment of **16** with 10 mol % $Rh_2(OAc)_4$, BAIB, and MgO in CH_2Cl_2[11b] at room temperature, the desired allylic C−H amination proceeded to give cyclic carbamate **17** in 60% yield. This reaction was markedly improved by employing 10 mol % of $Rh_2(esp)_2$[11d] in benzene, and **17** was obtained in 86% yield. It is important to add that all attempts to effect an allylic C−H amination prior to a benzylic C−H amination failed. For example, $Rh_2(OAc)_4$-catalyzed reaction of **18** did not give the corresponding cyclic carbamate and ketone **19** was obtained in 20% yield instead.

The final stage of the synthesis of kaitocephalin (**1**) involved fomation of the 3,5-dichloro-4-hydroxybenzamide moiety, oxidative cleavage of the phenyl group and the cyclopentene ring generating three carboxylic acids, and removal of all protecting groups (Scheme 4). Thus, after removal of the Boc group of **17**, the resulting amine was subjected to amidation with **20**[23] under Schotten−Baumann conditions to give amide **21** in 97% yield. At this point, we initially attempted the RuO_4 oxidation[24] of **21** using a catalytic amout of $RuCl_3$ and $NaIO_4$;

(23) Hirata, K. WO 2008/062740.

(24) (a) Carlsen, P. H. J.; Katsuki, T.; Martín, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936–3938. (b) Matsuura, F.; Hamada, Y.; Shioiri, T. *Tetrahedron* **1993**, *49*, 8211–8222. (c) Clayden, J.; Knowles, F. E.; Baldwin, I. R. *J. Am. Chem. Soc.* **2005**, *127*, 2412–2413.

however, the desired triacid was not obtained at all. It turned out that the cyclic carbamate moiety does not survive under the oxidation conditions. After several discouraging results, we found that *N*-Boc cyclic carbamate **22**, derived from **21** in 91% yield, successfully underwent RuO_4-mediated oxidative cleavage to afford triacid **23**. Furthermore, we could unambiguously determine the absolute structure of **22** by X-ray crystallographic analysis.[25] Finally, without purification, **23** was successively subjected to saponification and deprotection of the *N*-Boc group to furnish (−)-kaitocephalin (**1**) in 24% overall yield from **22** after Dowex 50WX4 treatment, reversed-phase chromatography, and HPLC. The synthetic substance was identical with an authentic sample by spectroscopic (^1H and ^{13}C NMR) and chromatographic (reversed-phase TLC and HPLC) comparisons.

In conclusion, we have accomplished the highly stereocontrolled total synthesis of (−)-kaitocephalin (**1**) from readily available **5** in 21 steps and 4% overall yield. The present work provides here a new methodology for the stereoselective construction of substituted pyrrolidines utilizing a rhodium-catalyzed C−H amination.

Acknowledgment. This work was supported by a Grant-in-Aid for Scientific Research (A) (22249001) and Grant-in-Aid for Young Scientists (B) (23790015) from JSPS and a Grant-in-Aid for Scientific Research on Innovative Areas "Reaction Integration" (No. 2105) (22106538) from MEXT. We thank Prof. Ohfune and Prof. Shinada (Osaka City University) for providing us with an authentic sample of kaitocephalin and valuable information.

Supporting Information Available. Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(25) The crystallographic data (CCDC 859724) can be obtained free of charge from the Cambridge Crystallographic Data centre via www.ccdc.cam.ac.uk/data_request/cif.

The authors declare no competing financial interest.