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A concise [C+NC+CC] coupling-enabled synthesis of kaitocephalin

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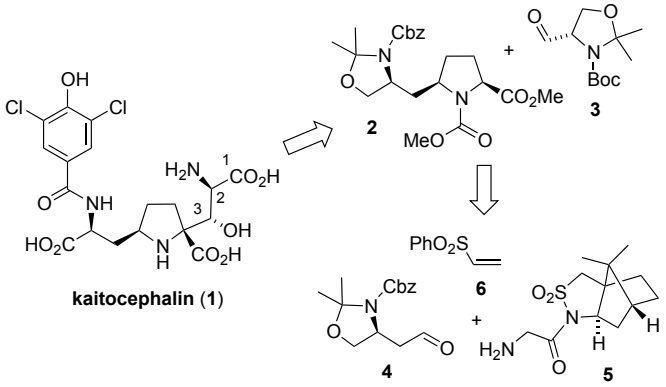
A 15-step synthesis of the iGluR antagonist kaitocephalin from aspartic acid is reported. The linchpin pyrrolidine ring of the target molecule is efficiently assembled with in a single operation via an asymmetric [C+NC+CC] reaction.

Kaitocephalin is a natural product isolated from the fungus *Eupenicillium shearii* that was found to be a potent competitive antagonist of ionotropic glutamate receptor (iGluR) activity.[1] This property is of interest because glutamate receptors are the major excitatory neurotransmitter receptors in the vertebrate brain and are involved in both normal and pathological neuronal functions.[2] Drugs targeting glutamate receptors may have considerable potential for treating such diverse disorders as epilepsy, amyotrophic lateral sclerosis, ischemic brain damage, major depression, drug abuse, and neuropathic pain. Glutamate receptors have also been implicated in non-neurological diseases such as diabetes[3] and cancer.[4] Many of these disease states are associated with the selective expression of iGluR subtypes, which are broadly classified according to their selective activation by NMDA (N-methyl-D-aspartate), AMPA (2-amino-3-(3-hydroxy-5-methyl-isoxazol-4-yl)propionate), or kainate. Kaitocephalin displays differential affinity for iGluR subtypes in the order NMDA > AMPA >> kainate,[5] and is thus of interest as a scaffold for drug design.[6] Recently, the crystal structure of kaitocephalin bound to an iGluR was determined and provides clues for the development of subtype-specific antagonists.[7] As a first step towards this goal, we report a concise total synthesis of kaitocephalin. Our approach is distinguished from prior syntheses[8a-g] of kaitocephalin by its effective use of the asymmetric [C+NC+CC] coupling reaction to assemble the target's core pyrrolidine ring.

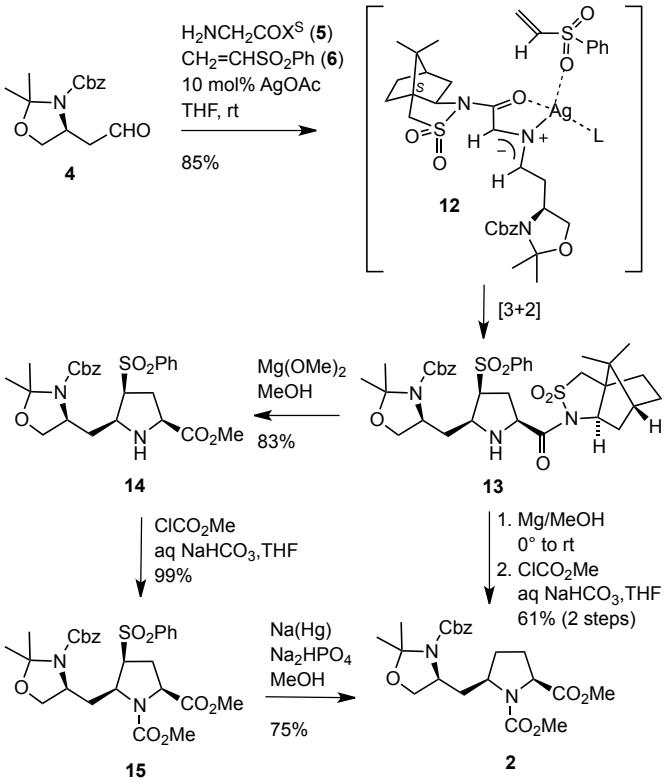
Our key retrosynthetic analysis of kaitocephalin (**1**, Scheme 1) began with the introduction of the C1-C3 moiety via the union of **2** with the serine-derived aldehyde **3** following an established aldol tactic (references 8a and 8e). The pyrrolidine precursor of **2** comprising the remaining contiguous carbon skeleton of **1** would be assembled via a Ag(I)-catalyzed asymmetric [C+NC+CC] coupling of the aspartic acid-derived aldehyde **4**, (*S*)-glycyl sultam **5**, and vinyl sulphone **6**.[9] The key C-C bond-forming step involves a [3+2] cycloaddition of a metalated azomethine ylide (formed in situ from **4** and **5**) with an electronically-activated dipolarophile **6**. The advantage of [C+NC+CC] coupling over other [3+2] cycloaddition methodology stems from the ability to employ aliphatic aldehydes such as **4** without enolization or enamine formation that would result in undesired side reactions. This limitation precludes the application of existing [3+2] dipolar cycloaddition technology to the kaitocephalin pyrrolidine problem. While essential for activating the dipolarophile in the underlying cycloaddition process, the phenylsulfonyl moiety would be removed reductively at a subsequent stage in the synthesis.[10]



Scheme 1 Retrosynthetic analysis of **1**.

Reduction of this plan to practice began with the synthesis of the key pyrrolidine **2** (Scheme 2). The [C+NC+CC] coupling of **4**,[11] **5**,[12] and **6**[13] proceeded cleanly at ambient temperature in the presence of Ag(I) ion to give the endo-cycloadduct **13** in 85% isolated yield.[14] The pyrrolidine ring stereochemistry of this cycloadduct was

expected based on the (endo-Si) pre-TS ensemble **12** and was supported by the successful conversion of **13** to the natural product **1**. Although the stereochemistry of the phenylsulphonyl group at C6 is inconsequential because this functional group is removed downstream, we believe that it is endo based on our previous experience with the Ag(I)-catalyzed [C+NC+CC] coupling reaction.[15] Post [C+NC+CC] coupling adjustment of the pyrrolidine substitution pattern began with methanolysis of the acyl sultam using $Mg(OMe)_2$ to give the pyrrolidine ester **14** which was N-carbamoylated with methyl chloroformate to provide the methyl carbamate **15**. Chemoselective reductive cleavage of the phenylsulfonyl group was accomplished with sodium amalgam to provide **2** in 62% overall yield from **13** concluding the 3-step sequence. Alternatively, the cycloadduct **13** could be converted to **2** in just two steps in comparable overall yield by exposing **13** to excess magnesium metal in MeOH to produce the methyl ester (desulphonation and methanolysis) followed by N-carbamoylation to afford **2**.

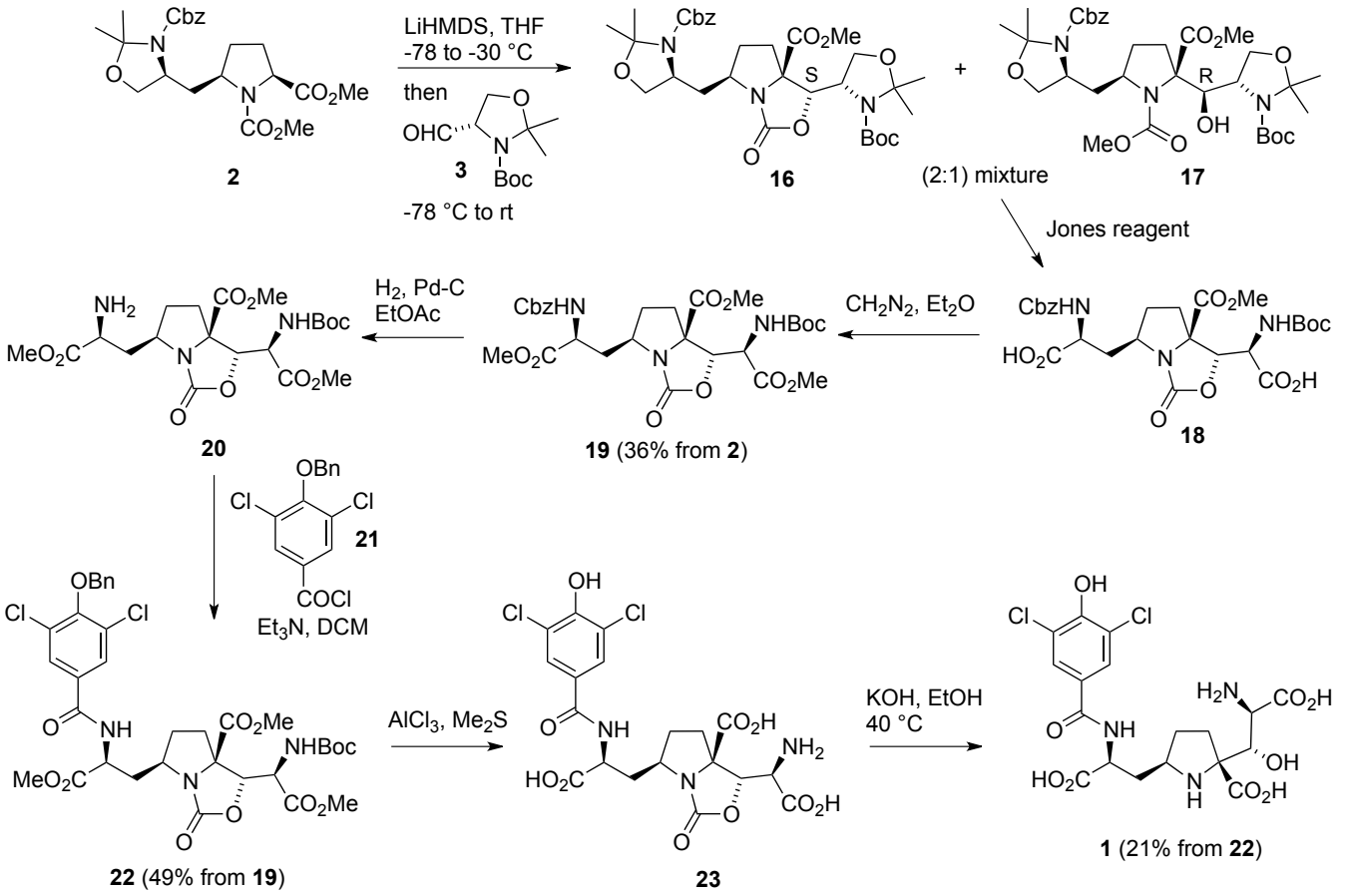


Scheme 2 Synthesis of Pyrrolidine **2**.

With the pyrrolidine **2** in hand, we were poised to complete the synthesis of kaitocephalin (Scheme 3). We found that the lithium enolate of **2** reacted with the serinal derivative **3** to give a 2:1 mixture of oxazolidinone **16** and undesired (*3R*) aldol diastereomer **17** in 83% combined yield. Presumably, **16** arose from the preferential cyclization of the major (*3S*) aldolate. This result was in line with Ma's report (reference 8e). Because of the difficulty in separating **16** from **17**, the mixture was used for the next reaction. Following Dondoni's protocol,[16] exposure of this mixture to Jones reagent resulted in clean conversion of both N-protected oxazolidines to their N-protected α-amino acids. The resulting diacid **18** was treated directly with excess diazomethane to give the triester **19** in 36% overall yield from **2**. This three-step reaction sequence accomplished a total of five synthetic transformations (aldol addition, oxazolidinone formation, bis-oxazolidine hydrolysis, diol oxidation, and bis-esterification), affording pure **19** after a single chromatography.[17] Hydrogenolysis of **19** released the amine **20**, which was acylated with the known acid chloride **21** to give the amide **22** in good overall yield. Synthesis of **22** constituted a formal synthesis of the target molecule **1** (reference 8e). Removal of the Boc, benzyl ether, and three methyl ester protecting groups was effected by treating **22** with the Fujita reagent[18] to afford **23**. This was followed by hydroxide-mediated hydrolysis of the oxazolidinone to give kaitocephalin (**1**). Our material was identical to an authentic sample of **1**.

This short (15 steps from aspartic acid) total synthesis of kaitocephalin demonstrates the value of the asymmetric [C+NC+CC] coupling reaction for the construction of complex pyrrolidine structures and paves the way for the generation of novel kaitocephalin analogues for biological studies.

Our research was supported by a grant from the National Science Foundation (CHE-1149327). We thank Vertex Pharmaceuticals for a supply of **5**•HCl and the Ohfune lab at Osaka City University for providing us with a sample of kaitocephalin for comparison.



Scheme 3 Kaitocephalin end-game.

Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental procedures and characterization data for all new compounds are provided. See DOI: 10.1039/x0xx00000x

‡ This paper is dedicated to Professor Yasufumi Ohfune on the occasion of his retirement from Osaka City University.

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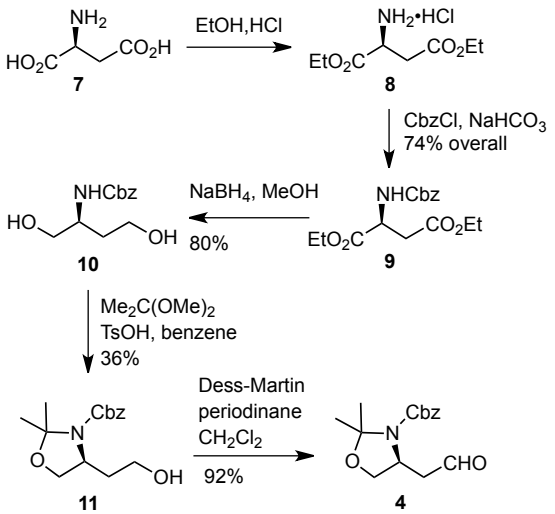
10 A related approach to **1** had been suggested but never implemented, apparently due to the poor yield and stereoselectivity associated with the underlying azomethine ylide cycloaddition (Kudryavtsev, K. V.; Nukolova, N. V.; Kokoreva, O. V.; Smolin, E. S. *Russ. J. Org. Chem.* **2006**, *42*, 412).

11 Aldehyde **4** was synthesized from aspartic acid **7** as shown below.



12 Glycyl sultam **5** can be prepared by a route involving azide reduction (Kaniskan, H. Ü.; *A Formal Total Synthesis of Bioxalomycin Beta 2*, Ph.D dissertation, Case Western Reserve University, **2007**) or the Delépine reaction (Isleyen, A.; Gonsky, C.; Ronald, R. C.; Garner, P. *Synthesis* **2009**, 1261).
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14 This multicomponent reaction could be performed on a 10 g scale (aldehyde **4** is the limiting reagent) but with a slight reduction in yield of **13** to 70%.
15 Indirect evidence for the endo-stereochemistry in **13** comes from the fact that the Cu(I)-catalyzed [C+NC+CC] coupling of **4**, **5** and **6**, conditions that favour the exo-product (Garner, P.; Hu, J.; Parker, C. G.; Youngs, W. J.; Medvetz, D. *Tetrahedron Lett.* **2007**, *48*, 3867), produced a cycloadduct that was isomeric to **13**. (See Supplementary Information.)
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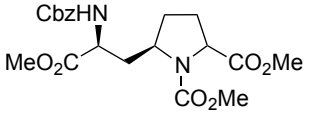
17 Compound **25** was also isolated in 11% yield, presumably arising from a retro-aldol reaction at some stage during the reaction sequence.



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