Pergamon

Tetrahedron Letters 42 (2001) 7893–7897

TETRAHEDRON LETTERS

Synthetic studies toward kaitocephalin

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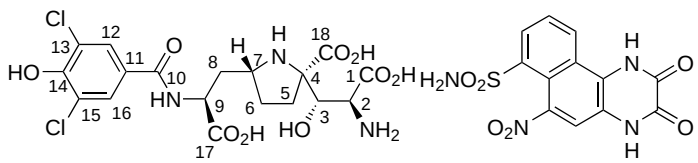
Received 11 June 2001; revised 15 August 2001; accepted 30 August 2001

Abstract—Synthetic studies toward the total synthesis of kaitocephalin **1**, whose stereochemical assignment was undetermined at the time of commencement, were undertaken in an attempt to provide a general methodology to gain access to any one of all 32 possible stereoisomers. An interesting, unexpected, result was observed in the anticipated stereoselective key aldol reaction.

The function of L-glutamate as the chief excitatory neurotransmitter in the mammalian central nervous system (CNS) is by now well-established, being attributed to over 70% of the fast excitatory CNS synapses.[1,2] The very fact that excitatory amino acid (EAA) receptors enjoy ubiquitous occurrence contributes to their alleged roles in a wide diversity of brain functions and abnormalities, having been implicated in such disorders as epilepsy,[3] Huntington's chorea,[4] Alzheimer dementias,[5] AIDS-related dementia, schizophrenia and Parkinsonism.[6] It is believed that L-glutamate antagonists, in particular those belonging to the AMPA subclass, can prospectively prevent brain damage immediately following a stroke. Drugs which are developed on this principle have been put on clinical trials, while new agents are greatly sought after.[7]

Kaitocephalin (**1**, Fig. 1) is a novel L-glutamate receptor antagonist, which is shown to protect chick telencephalic neurons as well as rat hippocampal neurons from kainate toxicity.[8] The isolation and characterization of this highly functionalized pyrrolidine, produced by a solid medium culture of *Eupenicillium shearii* PF1191, was first reported by Kazuo et al. in late 1997.[8,9] More importantly, considerable interest in the use of AMPA/KA receptor antagonists as an effective means of treating ischaemia–reperfusion injury as a stroke arises, following a report on the ability of a well-known synthetic AMPA/KA receptor antagonist NBQX (2,3-dihydroxy-6-nitro-7-sulfamoyl-benzo[f]-quinoxaline, **2**) in protecting neuronal cells from ischaemia injury even when administered after an ischaemic attack.[10]

The basic planar skeletal structure of kaitocephalin **1** was deduced via a combination of HRFAB-MS, IR, one dimensional ^{1}H and ^{13}C NMR, phase-sensitive DQF, ^{1}H–^{13}C HMBC and ^{1}H–^{15}N HMBC measurements. At the time we decided to embark upon the synthesis of kaitocephalin, the absolute and relative stereochemistries about the five stereogenic carbons C-2, C-3, C-4, C-7 and C-9 had yet to be elucidated. Hence, synthetic studies toward the total synthesis of kaitocephalin were undertaken in an attempt to provide a general methodology whereby a judicious choice of relatively cheap and readily available enantiomerically pure starting materials would grant access to any one of all 32 possible stereoisomers. The absolute stereochemical assignment of kaitocephalin **1** was disclosed very recently by Seto et al.[11]



1 **2**

Figure 1. Structures of kaitocephalin **1** and NBQX **2**.

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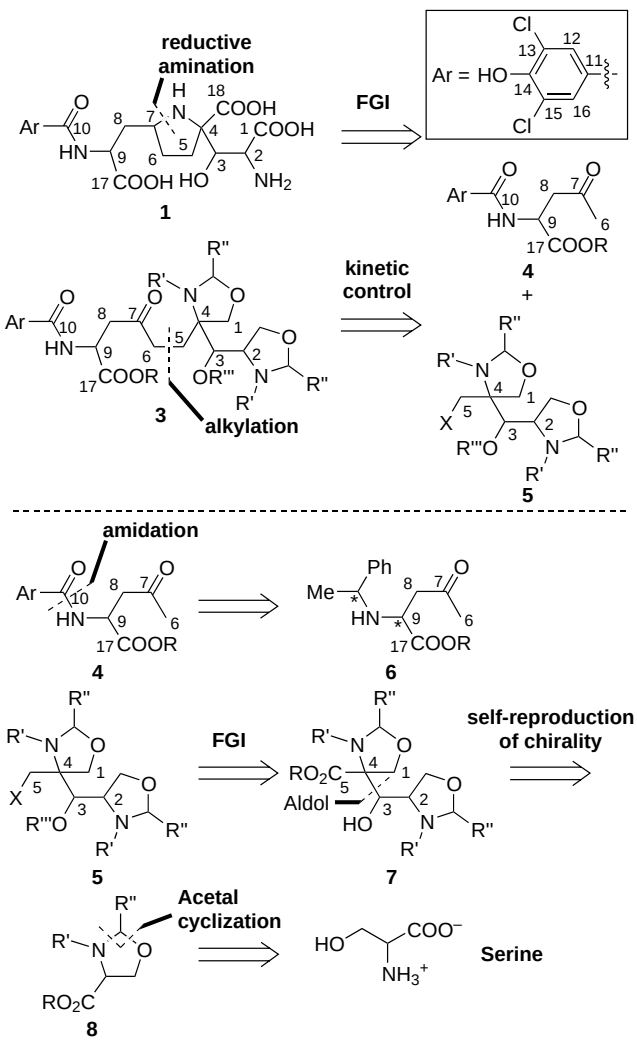
0040-4039/01/$ - see front matter © 2001 Published by Elsevier Science Ltd.
PII: S0040-4039(01)01631-8

Any serious attempts at the synthesis of kaitocephalin **1** will have to address the challenges put forward by assembly of the five stereogenic centers on the highly functionalized pyrrolidine, of which three are contiguous with an α,α-disubstituted amino acid pattern on C-4. In addition to this, there are three amino acid motifs, the remaining two being tertiary α-monosubstituted centers, of which C-2 and C-4 are to be achieved by employing an enantiomerically pure form of the amino acid, serine, as starting material in the envisaged retrosynthetic route (Scheme 1). By so doing, the synthesis is readily amenable to producing any of the diastereomers of kaitocephalin, simply by commencing with either the D- or L-isomer. It is noteworthy at this point that kaitocephalin had yet to succumb to any total synthesis and neither have any synthetic studies been reported so far.

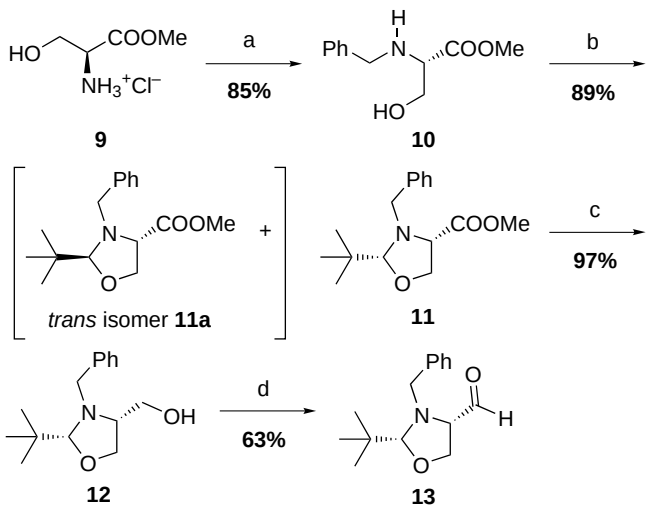
An efficient stereoselective route to fragment **6** was developed by our group earlier during the course of exploration toward the total synthesis of dysiherbaine.[12] As such, our focus was first targeted at the synthesis of key intermediate **7** via a stereocontrolled aldol reaction. Since neither the absolute, nor relative stereochemistries about the five stereogenic centers of kaitocephalin **1** were not known at the time of commencement, preliminary investigative work was carried out using readily accessible L-serine methyl ester hydrochloride **9**, for which substantial precedents exist in the literature for stereoselective derivatization of its tertiary stereogenic α-carbon by means of Seebach's principal of self-reproduction of chirality.[13]



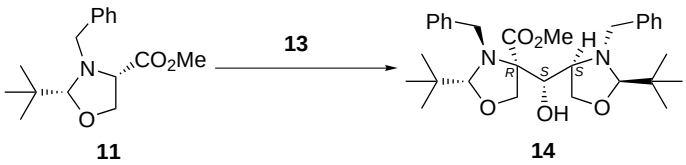
Scheme 1. Retrosynthetic analysis of kaitocephalin **1**.

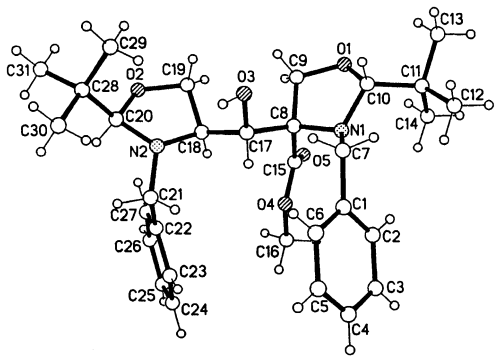
Adopting Corey's 1,3-oxazolidine **11**[13d] (Scheme 2) as the chiral template in our synthetic studies, commercially available L-serine methyl ester hydrochloride **9** was first mono-*N*-benzylated via reductive amination to afford **10** in 85% yield. Ensuing cyclization with pivalaldehyde was implemented by a Dean–Stark trap to give the desired 1,3-oxazolidine **11** in a much shorter period of time, although with a slight compromise in the yield (89%). As demonstrated previously by Corey and Reichard, **11** is formed alongside with the *trans*-isomer **11a**, equilibrating to the thermodynamic 9:1 ratio of *cis*:*trans* isomers upon heating to 80°C, as determined by HPLC analysis. Mild reduction of ester **11** with $NaBH_4$ in MeOH/THF (88:12) gave the primary carbinol **12** in excellent yield. A subsequent Swern oxidation ($DMSO/(COCl)_2/Et_3N$) to the aldehyde **13** in 64% yield set the stage for the anticipated stereoselective key aldol union with ester **11** (Scheme 3).

With the ester **11** and aldehyde **13** to hand, an initial trial was conducted using LDA (1.5 equiv.) at −78°C for 2 h. Unfortunately, the yield of the desired aldol key intermediate **14** was less than 5% (Table 1, entry 1). The addition of LiBr salt was found to more than double the yield (entry 2). Upon changing to the more bulky LiHMDS base (entries 3–5), much higher yields were obtained, but here the addition of LiBr serves



Scheme 2. Setting the stage for the key aldol reaction. (a) Et_3N, PhCHO, MeOH, 0°C, 3 h, then $NaBH_4$; (b) ^{t}BuCHO, *p*-TsOH, PhMe, Δ, 4 h; (c) $NaBH_4$, MeOH/THF (88:12); (d) $(COCl)_2$/DMSO, CH_2Cl_2, −78°C, then Et_3N, to rt.





Scheme 3. Anticipated key stereoselective aldol reaction.

Table 1. Optimization of the conditions for the key aldol reaction

Entry	Conditions[a]	Yield[b] (%)	Selectivity[c]
1	LDA, −78°C, 2 h	<5	–
2	LDA, 5 equiv. LiBr, −78°C, 2 h	11	–
3	LiHMDS, −78°C, 2 h, then overnight at rt	17[d]	–
4	LiHMDS, 5 equiv. LiBr, −78°C, 2 h	27	92:8
5	LiHMDS, −−78°C, 2 h	28	92:8

[a] A solution of the base (1.5 equiv.) in THF was cooled to −78°C, followed by the addition of ester **11** (1.2 equiv.) and the mixture was stirred for $1\frac{1}{2}$ h prior to the addition of aldehyde **13** (1.0 equiv.).
[b] Isolated yield of serine aldol **14**.
[c] Selectivity refers to the ratio of *isolated* **14** as compared to that of *all* the other diastereomers formed in the reaction.
[d] Reaction became complex as indicated by the crude ^{1}H NMR spectrum.

little purpose (entry 4). In addition, other diastereomers[14] were also observed with a selectivity of 92: 8, in favor of **14**.

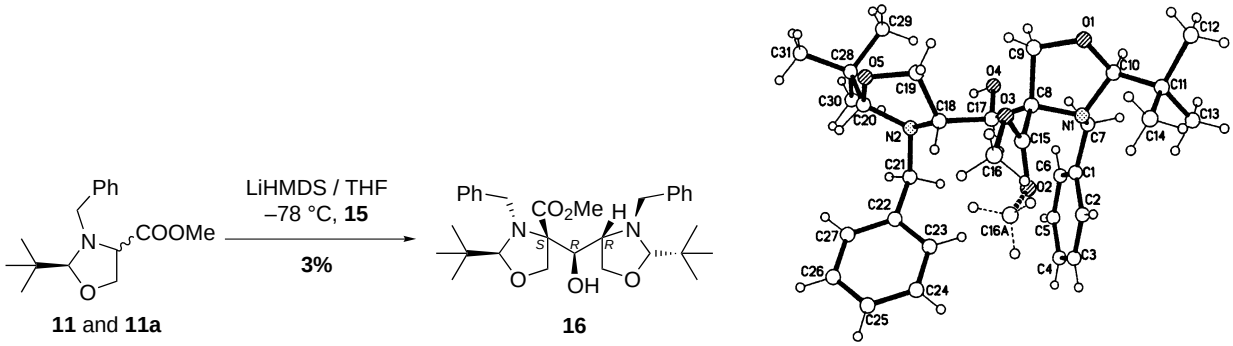
Employing the conditions in entry 5 as the basis, another series of optimizations were carried out (Table 2). As a general trend, increasing the concentration and amount of base used increases the yield of serine aldol **14** (entries 1, 2, 4 and 7). Also, changing the counterion from Li^+ to K^+ does not have any significant effect (entry 8). However, the effect of increased reaction time appears to vary with the amount of base used (entries 3, 5 and 6). Finally, the conditions in entry 7 were chosen for a scale-up preparation of aldol **14**. Unfortunately, the scale-up synthesis of **14** only proceeded in 10% yield, plausibly due to difficulty in reproducing the exact conditions used during the small-scale optimization.

The absolute configuration of serine aldol **14** was established by means of a single-crystal X-ray diffraction analysis, using the known absolute configuration (*S*) about C-18 (Scheme 3) as a reference, the result of which is in accordance with a Zimmerman–Traxler[15] transition state. Upon comparison with the recently revealed stereochemistry of kaitocephalin **1**, it was found that the chirality at C-3 (C-17 of **14**) and C-4 (C-8 of **14**) are correct, but that at the C-2 (C-18 of **14**)

Table 2. Optimization of the condition for the key aldol reaction continued[a]

Entry	Base used	Base (equiv.)	Vol. of THF (mL)	Time[b]	Yield[c] (%)
1	LiHMDS	1.5	1.0	2 h	6
2	LiHMDS	1.5	0.0	2 h	28
3	LiHMDS	1.5	0.0	1 day	15
4	LiHMDS	3.0	0.0	2 h	40
5	LiHMDS	3.0	0.0	1 day	48
6	LiHMDS	3.0	0.0	1 week	Reaction complex
7	LiHMDS	5.0	0.0	2 h	51
8	KHMDS	1.5	0.0	2 h	27

[a] A solution of the base in THF was cooled to −78°C, followed by the addition of ester **11** (33.6 mg, 0.121 mmol, 1.2 equiv.) transferred with 0.1 mL of anhydrous THF and the mixture was stirred for $1\frac{1}{2}$ h prior to the addition of aldehyde **13** (25.0 mg, 0.101 mmol, 1 equiv.) transferred with 1.0 mL of THF, together with the conditions listed for each entry.
[b] All reactions were conducted and maintained at −78°C for the whole duration of the experiment.
[c] Determined using the intensity ratio of the methyl ester methoxy ^{1}H NMR signal in **14** (3.37 ppm, s, 3H) compared to that from **11** (3.47 ppm, s, 3H), as observed in the crude ^{1}H NMR spectrum.



Scheme 4. Cross aldol reaction.

α-carbon is opposite to the natural product. In addition, our initial derivatization of aldol **14** which entails functionalization of the ester at C-8 of **14** would invert the stereochemistry about C-4 of **1**, rendering the chirality incorrect. In order to circumvent this problem, we would have to employ the enantiomeric D-serine instead, so as to get the enantiomer of serine aldol **14**, although the stereochemistry about C-3 would be incorrect in this case. Nevertheless, post-aldol oxidation and stereoselective reduction should afford the desired stereochemically 'correct' isomer.

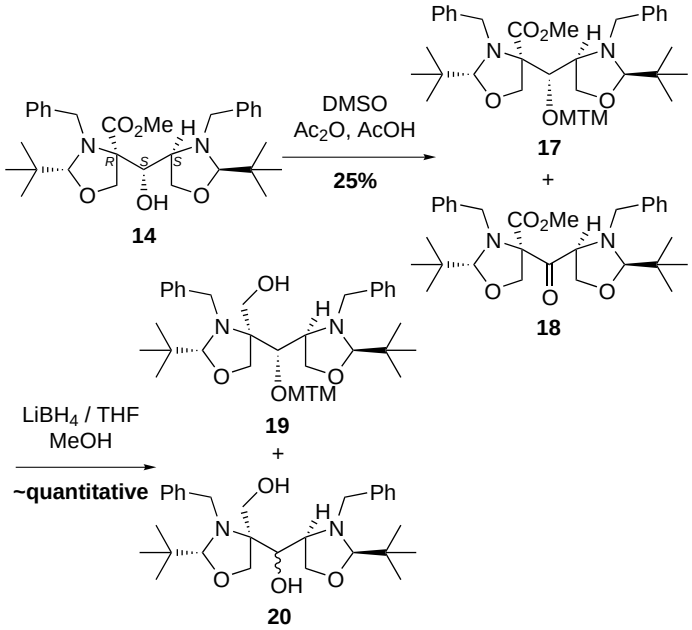
In our initial effort to establish the versatility of this route for the synthesis of all the possible stereoisomers of kaitocephalin, the enantiomeric aldehyde **15** was synthesized in the same way as for **13** by commencing from D-serine methyl ester hydrochloride (Scheme 4). Surprisingly, the cross aldol reaction between **15** and ester **11** was found to give a major product with *relative* stereochemistry *identical* to aldol **14**, as revealed by a single-crystal X-ray diffraction analysis of the cross aldol product **16** (Scheme 4). In an attempt to rationalize this unexpected observation, it was noticed that the yield of **16** (3%) is much lower than that of **14**. Also bearing in mind that the 1,3-oxazolidine ester used is a 9:1 mixture of diastereomeric *cis*:*trans* isomers, the isolated product **16** may have been formed from the reaction of **15** with the (*Z*)-enolate derived from the *trans*-substituted 1,3-oxazolidine **11a**, that is **16** is the desired enantiomer of **14**. This is also supported by the fact that the selectivity of serine aldol **16** toward *all* the other diastereomers decreased drastically from 92:8 in the case of **14**, to 67:33.[14] The aldol reaction for reasons not very clear at this moment, plausibly the stereochemical-controlled conformational match of the two reacting molecules exhibits a preference for **14** or **16**.

As we were initially unaware of the absolute configuration of natural kaitocephalin **1**, subsequent synthetic work was carried out on **14**. Continuing with the synthetic studies, our next task is to protect the newly formed C-3 secondary hydroxyl of **14**, prior to reduction of the ester function. The benzyl group was chosen initially, but again to our surprise, upon treating **14** with NaH followed by BnBr the crude ^{1}H NMR indicated clearly the presence of signals from the ester **11**, with no signs of the bis-oxazolidine skeleton of **14**. Apparently, a *retro-aldol* cleavage had occurred to regenerate **11**. Subsequent trials with silyl based TIPS (TIPSOTf, 2,6-lutidine) and TMS (TMSCN; TMSCl, Mg) failed with recovery of starting material, presumably due to steric encumbrance about the C-3 hydroxyl. Finally, the MTM (methylthionylmethyl) group proved successful. However, due to the similarity of the conditions used (DMSO/AcOH/Ac_2O) with that of Swern oxidation, an approximately 50:50 mixture of MTM protected **17** and the ketone side-product **18** was obtained (Scheme 5). The mixture was then subjected to $LiBH_4$ reduction in MeOH/THF, to give the primary alcohol **19** and the diol **20** quantitatively, which were then separated by silica gel column chromatography. Unfortunately, ensuing efforts to transform the primary hydroxyl into a good leaving group by both sulfonylation (MsCl, pyr; TsCl, pyr) and bromination (NBS, CBr_4) proved futile.

In conclusion, we succeeded in the key aldol reaction of oxazolidine based ester **11** and aldehyde **13**, both derived from serine methyl ester hydrochloride, for the construction of the C-1–C-5 fragment of kaitocephalin **1**. Unfortunately, further derivatization for coupling with the known C-6–C-9 fragment **6** via an anticipated enolate addition met with some difficulties and further work toward the second key step is currently in progress in our laboratory. In addition, the absolute configuration of kaitocephalin **1** was unveiled very recently, which dictates a post-aldol oxidation–reduction sequence in order to generate the correct stereochemistries in the C-1–C-4 fragment, while commencing from D-serine instead.

Acknowledgements

We gratefully acknowledge the National University of Singapore for the generous financial support. We would also like to thank A/P Jagadese J. Vittal and Ms. Tan Geok Kheng of the X-ray Diffraction Laboratory, National University of Singapore, for determining the X-ray structure for serine aldols **14** and **16**.



Scheme 5. Further transformation of serine aldol **14**.

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14. Interestingly on TLC, the spot due to **14** (R_f=0.38, hexane:ethyl acetate=10:1×2) stands out from the rest of the diastereomers, *all* of which appeared in a *single* spot lower (more polar, R_f=0.25) than that of **14**, inseparable by sgc.
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