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A direct route to 2,2,5-trisubstituted pyrrolidines of relevance to kaitocephalin

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ABSTRACT

2,2,5-Trisubstituted pyrrolidines of relevance to the core of kaitocephalin are readily available by an oxime ring closure using substrates derived from aspartic acid.

Kaitocephalin (**1**) (Fig. 1), isolated from chick telencephalic neurons (10 kg of cell culture gave 9 mg of kaitocephalin),[1] is an unusual and potent AMPA receptor antagonist, exhibiting protection of kainite-induced toxicity at 500 mM at chick primary telencephalic and rate hippocampal neurons with EC_{50} values of 0.68 and 2.4 mM, respectively, with no cytotoxic effects,[2] as well as against AMPA/cyclothiazide (500/50 mM) with EC_{50} values of 0.6 and 0.4 mM, respectively.[2] Although its absolute configuration was established[3] and apparently proven by total synthesis,[4] later work indicated this assignment to be in error,[5] and this was confirmed by further total synthesis;[6,7] a reinvestigation of the original Letter has recently appeared.[8] Kaitocephalin has subsequently been synthesised on several occasions.[9–13] Its core 2,2,5-trisubstituted pyrrolidine unit, which has potential as a medicinally relevant scaffold,[14] offers a considerable challenge for synthesis, and has attracted a high level of attention,[14–24] but of interest to us was the possibility that our recently reported ring closure, based upon enolate attack at activated oximes, might also be of value for its rapid construction.[25] This approach, which proceeds by an intramolecular attack at nitrogen of activated oximes **2**, gives pyrrolines of type **3**, which may in turn be reduced to polysubstituted pyrrolidines **4** (Scheme 1).

Fundamental to the application of this methodology would be to demonstrate that the oxime cyclisation reaction was tolerant of more elaborate chemical functionality, and that selective manipulation of the resulting *gem*-dicarbonyl groups could be achieved. In the first regard, commercially available *N*-Cbz-L-aspartic acid **5** was converted into *N*-Cbz-oxazolidinone **6a** (Scheme 2) using the literature approach.[26–29] Conversion into the acid chloride by treatment with oxalyl chloride/DMF[30–32] gave material which was immediately used for Stille coupling with tributylvinyltin,[33–36] giving the required ketone **6b** in 68% yield. Conjugate addition with diethyl malonate in the presence of base gave adduct **6c** in a good yield of 76%. However, when this was treated with $NH_2OH{\cdot}HCl$ and Et_3N in ethanol, a mixture of products was obtained, including oxime **7**, hydroxamic acid **8a** and oxime **8b**, whose identity were all confirmed by mass spectrometry. Unfortunately, isolation of the desired oxime **7** from this mixture was problematic. This outcome is no doubt due to the high nucleophilicity of hydroxylamine, and since changing the temperature for the reaction gave no improvement in the selectivity, it was clear that the oxazolidine ring system was too sensitive towards ring-opening, and that another protecting strategy would be needed.

To avoid this unwanted opening, acid **6a** was treated with sodium methoxide[28] in MeOH at −10 °C, giving a mixture of products including **9**–**11** (Scheme 2). This mixture was directly treated with oxalyl chloride followed by tributylvinyltin and catalytic $PhCH_2Pd(PPh_3)_2Cl$ to produce the required ketone **12**[33–36] in modest yield, which was in turn used for the conjugate addition reaction with diethyl malonate in the presence of base (anhydrous K_2CO_3 and dry dichloromethane heated to reflux), giving adduct

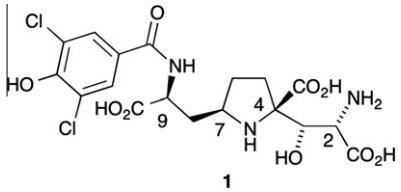

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Figure 1. Kaitocephalin.

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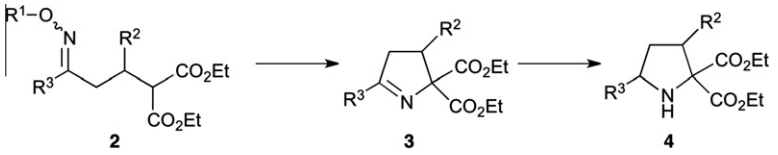
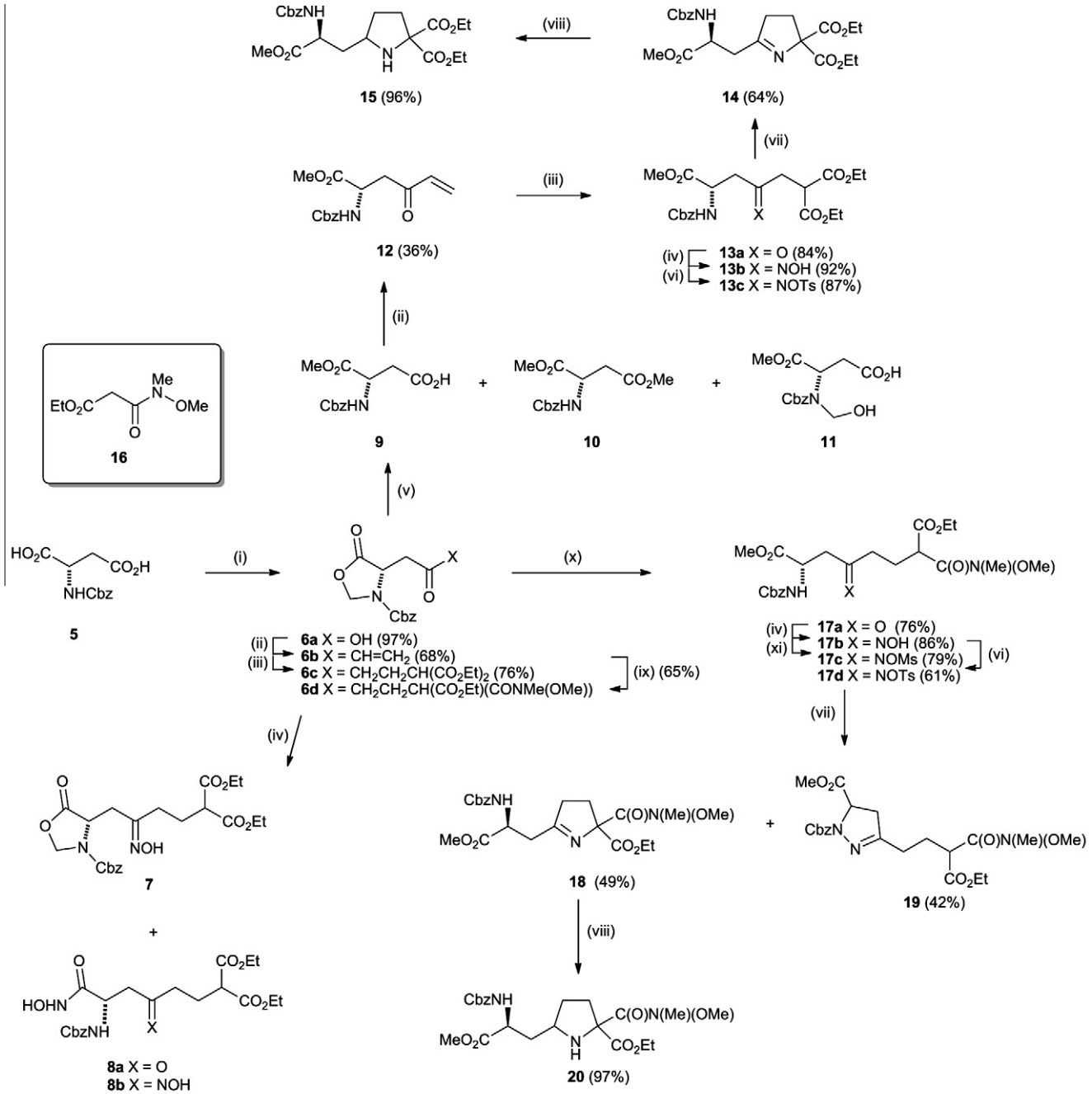


Scheme 1. General strategy for ring closure.



(i) Paraformaldehyde, TsOH, toluene, reflux; (ii) $(COCl)_2$, cat. DMF, toluene then $Bu_3SnCH_2{=}CH_2$, $PhCH_2Pd(PPh_3)_2Cl$; (iii) $CH_2(CO_2Et)_2$, K_2CO_3, CH_2Cl_2, r.t.; (iv) $NH_2OH.HCl$, Et_3N, reflux; (v) MeONa, MeOH, -10 °C; (vi) *p*-TsCl, Et_3N or py, CH_2Cl_2, r.t.; (vii) NaH, THF, reflux; (viii) $NaBH_3CN$, MeOH, 2 M HCl in MeOH, r.t.; (ix) **16**, Cs_2CO_3, CH_2Cl_2, r.t.; (x) 5% $NaHCO_3$, MeOH, reflux; (xi) MsCl, py, CH_2Cl_2, r.t.

Scheme 2. Synthetic scheme for ring closure sequence.

13a in excellent yield. Subsequently it was found that adduct **13a** could be synthesised in quantitative yield directly from **6c** by treatment with 5% $NaHCO_3$ in refluxing MeOH[26–29] followed by esterification with thionyl chloride/MeOH.[37] Adduct **13a** was readily converted into the corresponding oxime **13b** under standard conditions ($NH_2OH{\cdot}HCl$ and Et_3N in ethanol heated to reflux for

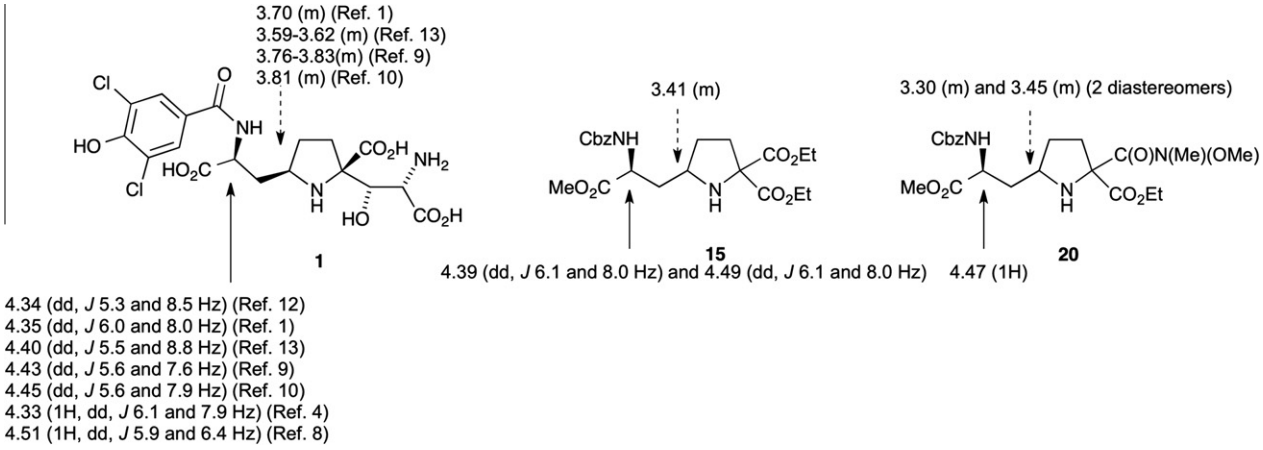


Figure 2. Comparison of NMR data.

1 h) in a very high yield of 92% as inseparable *syn*- and *anti*-isomers. This material was directly treated with *p*-toluenesulfonyl choride and base (Et_3N or pyridine in dry dichloromethane at rt) to afford the tosyl oxime **13c** (87% yield). Treatment of this compound with sodium hydride at reflux gave the desired ring closure product, pyrroline **14** in a good yield of 64%, which when reduced ($NaBH_3CN$, MeOH, 2 M HCl in MeOH, rt) afforded 2,2,5-trisubstituted pyrrolidine **15** (96% yield) with undetermined diastereomeric ratio. This clearly demonstrated that the cyclisation methodology was tolerant of additional system functionality, and the next key goal was to establish a system in which carbonyl group differentiation would be possible.

For this purpose, Weinreb malonamide **16** on conjugate addition with α,β-unsaturated ketone **6b** and base (anhydrous K_2CO_3 in dry dichloromethane at rt) gave adduct **6d** in 65% yield as a mixture of diastereomers (Scheme 2). Since it was now clear that the oxazolidinone ring would not be stable towards oxime formation, it was immediately opened by treatment with 5% $NaHCO_3$ in MeOH, giving ketone **17a** in 76% yield. This material was readily converted into the corresponding oxime **17b** using the standard conditions ($NH_2OH{\cdot}HCl$ and Et_3N in EtOH heated to reflux for 1 h) in a good yield of 86% as inseparable *E* and *Z* isomers. Oxime **17b** was reacted with methanesulfonyl chloride and Et_3N in dry dichloromethane to give the mesyl oxime **17c** in a very good yield of 79% as inseparable *E* and *Z* isomers, and this was immediately treated with NaH in dry THF at reflux for 30 min; however, although the starting material was consumed completely as shown by TLC and the desired cyclised pyrroline **18** could be detected in the mass spectrum, its isolation was very difficult. Instead, conversion of the oxime **17b** into tosyl oxime **17d** by treatment with *p*-toluenesulfonyl chloride with Et_3N or pyridine in dry dichloromethane gave the desired product in 61% yield, and immediate treatment with NaH in dry THF afforded the desired pyrroline **18** in 49% yield with a diastereomeric ratio of approximately 1:2, along with unexpected pyrazole **19** in 42% yield with a diastereomeric ratio of approximately 1:1. This latter product resulted from ring formation by an attack of the proximal carbamate nitrogen on the activated oxime, but both **18** and **19** were easily separated by chromatography. Of interest is that this pyrazole formation is fully analogous to a process previously reported by Black.[38] The pyrroline **18** was readily converted into the 2,2,5-trisubstituted pyrrolidine **20** by treatment with $NaBH_3CN$ in 2 M MeOH to afford a 97% yield with a 1:2 diastereomeric ratio (Scheme 2). Comparisons of the chemical shifts at H-7 and H-9 of kaitocephalin (**1**) and the mimics **15** and **20** are shown in Figure 2; similar chemical shift and coupling patterns were observed in these systems, although the chemical shift of H-7 in both **15** and **20** was about 0.2–0.3 ppm lower than the natural product, most likely as a result of the proximity of the anisotropic carbonyl group at C-4 of the pyrrolidine ring.

In conclusion, we have shown that rapid diastereoselective elaboration of aspartate derivatives into 2,2,5-trisubstituted pyrrolidines is feasible in a short, reliable sequence and in good overall yield, and work to demonstrate its applicability to the synthesis of kaitocephalin is ongoing.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.01.130.

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