Pergamon

Bioorganic & Medicinal Chemistry Letters 10 (2000) 309–311

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

Novel C-4 Heteroaromatic Kainoid Analogues: A Parallel Synthesis Approach

Jack E. Baldwin,* Andrew M. Fryer and Gareth J. Pritchard

The Dyson Perrins Laboratory, South Parks Road, Oxford OX1 3QY, UK

Received 28 October 1999; accepted 9 December 1999

Abstract—New C-4 thiazole **4**, **5** and aminothiazole **6**, **7** kainoid analogues were efficiently synthesised in five steps from commercially available (−)-α-kainic acid **1** and exhibited strong binding to the kainate receptors. A reactive α-bromoketone **10** was generated and reacted with thioamides and thioureas to form thiazole and aminothiazole heterocycles **11**–**14**. Deprotection gave the new kainoid amino acids **4**–**7** in excellent yield.

The kainoids are a unique family of non-proteinogenic amino acids, isolated from several marine algal and fungal sources.[1] In addition to their complex structure, the kainoids also possess interesting biological properties. In particular, they display potent neuroexcitatory activity in the mammalian central nervous system (CNS) and act at the kainate subclass of ionotropic glutamate receptors.[2] Ligands that show selective agonist or antagonist activity at these specific receptors are in high demand for use as tools in experimental neuropharmacology.[3,4] (−)-α-Kainic acid (**1**) is the parent member of the kainoid family and was first isolated from the Japanese marine red alga *Digenea simplex* in 1953.[5] Acromelic acid A **2** is the most potent naturally occurring kainoid and was isolated along with several other related acromelic acids from a toxic Japanese mushroom *Clitocybe acromelalga*.[6–8] Since then, a number of unnatural C-4 aryl analogues of the acromelic acids have been synthesised and their neuroexcitatory activity evaluated.[1,9,10] The *o*-anisyl analogue **3** was shown to be the most highly neuroexcitatory kainoid known to date (Fig. 1).[11]

Herein, we report a rapid and efficient, parallel synthesis of new C-4 thiazole **4**, **5** and aminothiazole **6**, **7** analogues of the acromelic acids starting from commercially available (−)-α-kainic acid (**1**). Although we have recently developed concise and versatile syntheses of both natural[12,13] and unnatural[9,10] kainoids from *trans*-4-hydroxy-L-proline, we have chosen **1** as our starting material here due to its availability and because all of the required stereochemistry around the pyrrolidine ring is in place.

Our aim was to convert the C-4 isopropylidene substituent into a reactive unit that could be readily transformed by simple cyclisation reactions into a variety of aromatic heterocycles. A related approach was used by Shirahama and co-workers in the first syntheses of acromelic acid A (**2**) and acromelic acid B.[6] They functionalised the C-4 substituent of **1** for constructing the pyridone rings of the acromelic acids. For the present study, an α-bromoketone was chosen as the reactive unit since α-bromoketones can react with thioamides and thioureas to form thiazoles (Hantzsch synthesis) and aminothiazoles, respectively.[14] After initial investigations into different protective group strategies, it was found that *tert*-butyl esters for the carboxylic acids and a benzoyl group for the secondary amine were the most robust protecting groups for the subsequent chemistry. Protection of **1** was therefore carried out by treatment with isobutylene and concentrated sulfuric acid in 1,4-dioxane followed by Schötten Baumann acylation of nitrogen using aqueous sodium hydroxide and benzoyl chloride to give the diester **8** in good yield (Scheme 1).

Ozonolysis of **8** in a mixture of MeOH and DCM at −78 °C followed by a reductive work up with triphenylphosphine gave methyl ketone **9** in essentially quantitative yield. A regiospecific bromination was accomplished by the in situ generation of a silyl enol ether from **9** using LiHMDS and TMSCl in THF at −78 °C followed by treatment of the silyl enol ether with phenyltrimethylammonium perbromide at 0 °C.[15]

Keywords: alkaloids; amino acids and derivatives; natural products; neurologically active compounds.

*Corresponding author. Tel.: +44-1865-275671; fax: +44-1865-275632; e-mail: jack.baldwin@chem.ox.ac.uk

0960-894X/00/$ - see front matter
PII: S0960-894X(99)00690-3

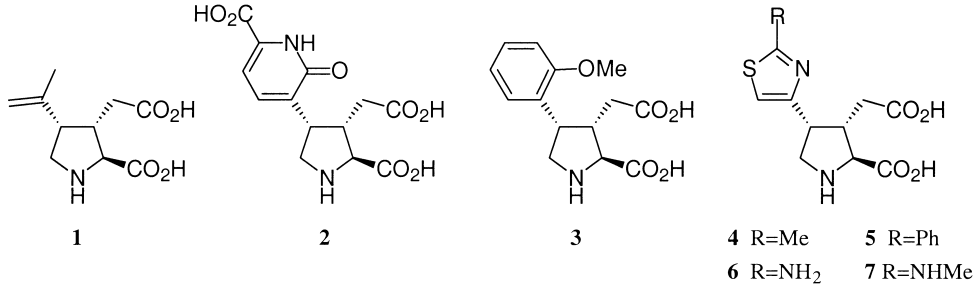
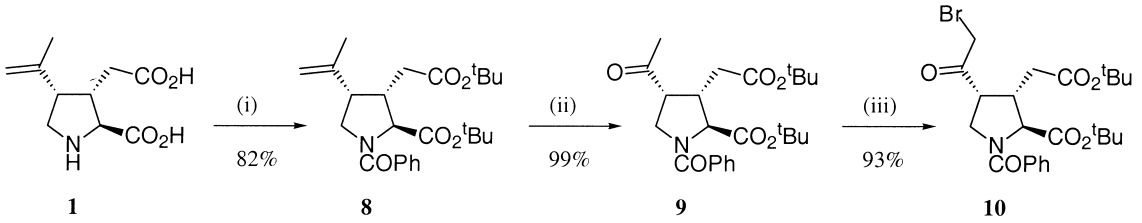


Figure 1.



Scheme 1. Reagents: (i) isobutylene, c. H_2SO_4 then NaOH, PhCOCl; (ii) O_3, MeOH, CH_2Cl_2, −78 °C then PPh_3, to rt; (iii) LiHMDS, TMSCl, −78 °C then $PhNMe_3Br_3$, to rt.

Bromoketone **10** was obtained in excellent yield as a white, crystalline solid after purification by silica gel chromatography.

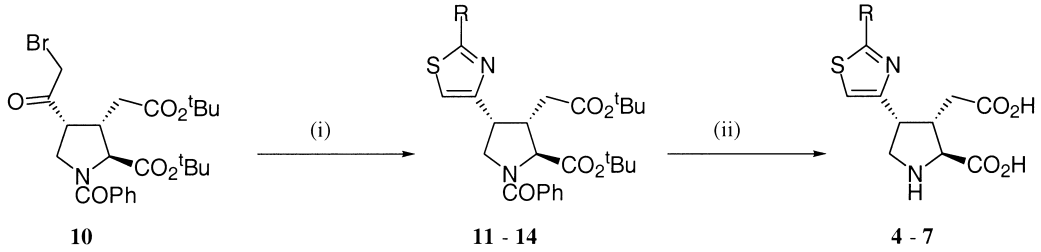
Cyclisation reactions were then performed with **10** using a number of representative condensing reagents, namely thioacetamide, thiobenzamide, thiourea and *N*-methylthiourea (Scheme 2). The reactions proceeded cleanly, giving the thiazole **11**, **12** and aminothiazole derivatives **13**, **14** in excellent yields (see Table 1). Deprotection of **11**–**14** was performed by treatment with 6 M hydrochloric acid under reflux. Purification with Dowex® 50WX8 ion-exchange resin furnished the free amino acids **4**–**7** in high yields.

Confirmation of the correct 4*S* stereochemistry was gained by ^{1}H NMR NOE experiments with **4** and **5** and by comparison of the spectral data of **4**, **6** and **7** with their C-4 epimers which were synthesised by an analogous route. This work will be reported in detail in due course. All new compounds gave satisfactory analytical and spectroscopic data.

In summary, C-4 thiazole and aminothiazole kainoid amino acids **4**–**7** have been synthesised in five high yielding steps from commercially available (−)-α-kainic acid (**1**). This route should allow the preparation of a number of C-4 heteroaromatic kainoid analogues by parallel cyclisation reactions with bromoketone **10**. Such compounds will be extremely valuable for neuropharmacologists as new tools for probing the kainate receptors and their function in the CNS. New kainoids **4**–**7** are currently undergoing biological evaluation, initial results have shown that compounds **4** and **6** are the twice as active as **3** and are thus the most potent neuroexcitatory kainoids known. The synthesis of different reactive units at the C-4 position and cyclisation reactions giving other heteroaromatic kainoid analogues are currently under investigation.

Table 1. Cyclisation and deprotection reactions

R	Cyclised product	Yield (%)	Deprotected kainoid	Yield (%)
Me	**11**	99	**4**	100
Ph	**12**	91	**5**	100
NH_2	**13**	100	**6**	97
NHMe	**14**	100	**7**	100



Scheme 2. Reagents: (i) $RCSNH_2$, $NaHCO_3$, EtOH, Δ; (ii) 6 M HCl (aq), Δ then Dowex® 50WX8.

Acknowledgements

We would like to thank the EPSRC for a studentship to AMF and the EPSRC mass spectrometry service (Swansea) for high resolution mass spectra. We also thank L. Hoffmann-La Roche for biological evaluation of compounds **4**–**7**.

References

1. For a review see: Parsons, A. F. *Tetrahedron* **1996**, *52*, 4149.
2. Cantrell, B. E.; Zimmerman, D. M.; Monn, J. A.; Kamboj, R. K.; Hoo, K. H.; Tizzano, J. P.; Pullar, I. A.; Farrell, L. N.; Bleakman, D. *J. Med. Chem.* **1996**, *39*, 3617, and references cited therein.
3. Mayer, M. *Nature* **1997**, *389*, 542.
4. Clarke, V. R. J.; Ballyk, B. A.; Hoo, K. H.; Mandelzys, A.; Pellizzari, A.; Bath, C. P.; Thomas, J.; Sharpe, E. F.; Davies, C. H.; Ornstein, P. L.; Schoepp, D. D.; Kamboj, R. K.; Collingridge, G. L.; Lodge, D.; Bleakman, D. *Nature* **1997**, *389*, 599.
5. Murakami, S.; Takemoto, T.; Shimizu, Z. *J. Pharm. Soc. Jpn.* **1953**, *73*, 1026.
6. Konno, K.; Hashimoto, K.; Ohfune, Y.; Shirahama, H.; Matsumoto, T. *J. Am. Chem. Soc.* **1998**, *110*, 4807.
7. Fushiya, S.; Sato, S.; Kanazawa, T.; Kusano, G.; Nozoe, S. *Tetrahedron Lett.* **1990**, *31*, 3901.
8. Fushiya, S.; Sato, S.; Kera, Y.; Nozoe, S. *Heterocycles* **1992**, *34*, 1277.
9. Baldwin, J. E.; Bamford, S. J.; Fryer, A. M.; Rudolph, M. P. W.; Wood, M. E. *Tetrahedron* **1997**, *53*, 5233.
10. Baldwin, J. E.; Fryer, A. M.; Spyvee, M. R.; Whitehead, R. C.; Wood, M. E. *Tetrahedron* **1997**, *53*, 5273.
11. Hashimoto, K.; Horikawa, M.; Shirahama, H. *Tetrahedron Lett.* **1990**, *31*, 7047.
12. Baldwin, J. E.; Fryer, A. M.; Pritchard, G. J.; Spyvee, M. R.; Whitehead, R. C.; Wood, M. E. *Tetrahedron Lett.* **1998**, *39*, 707.
13. Baldwin, J. E.; Fryer, A. M.; Pritchard, G. J.; Spyvee, M. R.; Whitehead, R. C.; Wood, M. E. *Tetrahedron* **1998**, *54*, 7465.
14. Metzger, J. V. *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R.; Rees, C. W.; Potts, K. T., Eds. 1st ed.; 1984; Vol. 6, p. 294.
15. Corey, E. J.; Gross, A. W. *Tetrahedron Lett.* **1984**, *25*, 495.