Bioorganic & Medicinal Chemistry Letters, Vol 2, No.12, pp. 1519-1522, 1992
Printed in Great Britain

0960-894X/92 $5.00 + .00

SYNTHESIS OF THE ω-PHOSPHONIC ACID ANALOGUE OF KAINIC ACID

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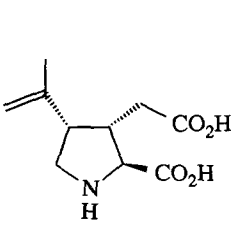
(*Received* 14 *August* 1992)

Abstract: The ω-phosphonic acid analogue of kainic acid was synthesised from the naturally occurring carboxylic acid in nine steps and 6% overall yield.

(-)-α-Kainic acid **1**, isolated from the marine alga *Digenea Simplex*,[1] is the parent member of an unusual class of pyrrolidine dicarboxylic acids known as the kainoids which includes domoic acid **2** and acromelic acid A **3**.



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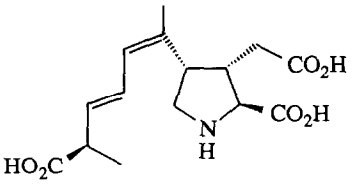

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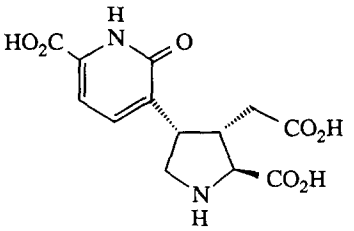
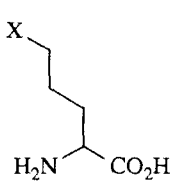


3

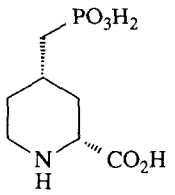
Kainic acid has attracted considerable attention as it has been shown to be an extremely powerful neuroexcitant,[2,3] and also shows anthelmintic and insecticidal properties.[1]

The neuroexcitant properties of the kainoids are probably associated with the ability of these compounds to act as conformationally restricted analogues of (S)-glutamate which itself plays an important role as an excitatory neurotransmitter in the vertebrate CNS.[4] Abnormalities in the function of the receptors that mediate synaptic excitation elicited by excitatory amino acids such as glutamate may be responsible for neurological disorders such as epilepsy and spasticity. They have also been implicated as contributing factors in neurodegenerative conditions such as Alzheimer's disease.[5]

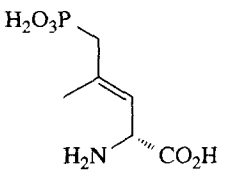
The subtype of glutamate receptor selective for the agonist N-methyl-D-aspartate (NMDA) has been extensively studied. Since the discovery that replacement of the ω-carboxylic acid of α-aminoadipic acid **4** with the phosphonic acid group gave a compound **5** with an increase in potency and selectivity at the NMDA receptor,[6] ω-phosphono-α-carboxylic amino acids have received much attention. Several such compounds are now known which are potent antagonists with affinity constants in the nanomolar range e.g. CGS19755 and CGP37849 which are useful pharmacological probes and offer promise as drugs.[7,8]



4 X=CO_2H
5 X=PO_3H_2



(±)
CGS19755



(±)
CGP37849

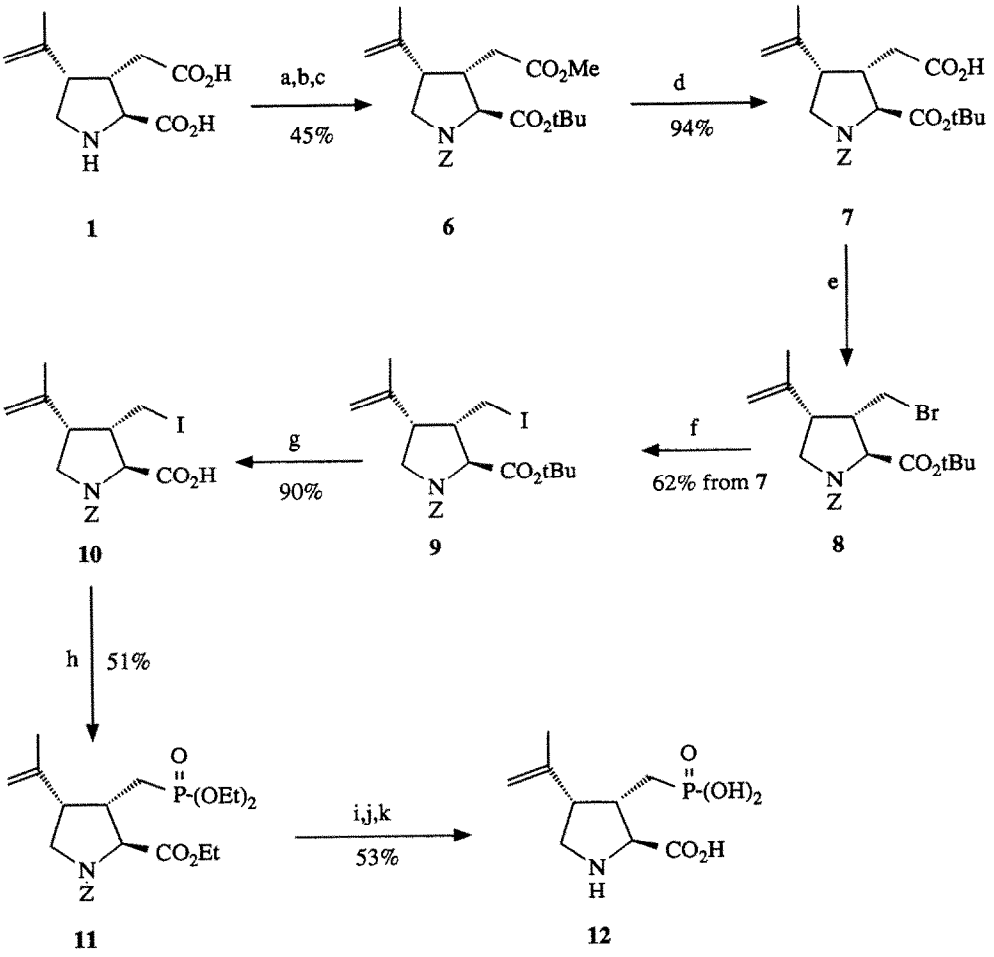
Whilst the NMDA receptor has been well characterised, a lack of potent and selective antagonists has hampered exploration of the kainate receptor.

As part of a continued interest in excitatory amino acid agonists and antagonists, and in view of the success of the ω-phosphono-α-amino carboxylic acids as antagonists at the NMDA receptor, we became interested in preparing the ω-phosphonic acid analogue of kainic acid. Moreover, the need to preserve the (S)-configuration at the amino acid carbon and the requirement for unsaturation at C-4 of a defined spatial geometry for activity at the kainate binding site made this compound an attractive synthetic target.[9,10]

We chose to start the synthesis of this compound from naturally occurring kainic acid **1**.[11] The protected amino acid **6** was obtained in 45% yield by selective esterification of the terminal carboxylic acid with thionyl chloride in methanol, protection of the amine as its benzyloxycarbonyl derivative and conversion of the α-amino acid to a *tert*-butyl ester.[12,13] Treatment of **6** with aqueous sodium hydroxide in methanol provided the carboxylic acid **7** which we hoped to manipulate using the halogenative decarboxylation method of Barton.[14] Thus, irradiation of a bromotrichloromethane solution of the *O*-acyl thiohydroxamate derived from carboxylic acid **7** and *N*-hydroxy-2-thiopyridone led smoothly to the bromide **8**. The bromide was not readily separated from the trichloromethylpyridyl sulfide by-product. However, after treatment of the crude product with an excess of sodium iodide in acetone, the iodide **9** could be isolated in a pure state in 62% yield for the two steps.[15] Compound **9** did not undergo Arbuzov reaction with a range of trialkylphosphites and could be recovered unchanged from the reaction mixture in good yield. However, after conversion of the *tert*-butyl ester to the acid **10** this compound underwent the desired reaction with triethylphosphite with concomitant esterification to give the phosphonate **11** in 51% yield after chromatography.[16] Sequential treatment of **11** with iodotrimethylsilane then barium hydroxide, followed by ion exchange chromatography gave the desired amino acid **12**.[17]

Compound **12** showed 77% inhibition of kainate binding at 10 μM.[18] This indicates that **12** has a lower affinity for the receptor of 1 - 2 orders of magnitude relative to kainic acid.

Acknowledgements: The skilled experimental contribution of Mrs A. Lambert is gratefully acknowledged. Thanks are due to Dr G. E. Fagg, Ciba Geigy, Basle for carrying out the binding assay.



Reagents

a) MeOH, $SOCl_2$ b) $PhCH_2OCOCl$, $NaHCO_3$ c) isobutylene, H_2SO_4, CH_2Cl_2

d) NaOH, MeOH e) i)EtOCOCl, N-methylmorpholine, THF ii) N-hydroxy-2-thiopyridone, Et_3N

iii) $BrCCl_3$, hν f) NaI, acetone g) $HCl_{(g)}$, ether h) $P(OEt)_3$, 156°C i) Me_3SiI, $CHCl_3$

pyridine j) $Ba(OH)_2$ k) DOWEX 50Wx2

References and Notes:

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11. Kainic acid was purchased from Sigma.
12. All new compounds showed satisfactory analytical data ^{1}H, ^{13}C NMR, IR and MS.
13. The ^{1}H and ^{13}C NMR spectra were complicated by the lack of free rotation around the carbon nitrogen bond of the benzyloxycarbonyl group.
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15. We were unable to convert 7 directly to **9** using the iodoform and cyclohexene system described; Barton, D. H. R.; Crich, D.; Motherwell, W. B. *Tetrahedron*, **1985**, 3901.
16. The steric effects of the *tert*-butyl ester may be responsible for the failure of the Arbusov reaction with compound **9**.
17. Selected data for compound **12** δ_H (400 MHz; D_2O) 1.38 (1H, ddd, J 17, 15.5 and 12 Hz, one of CH_2P), 1.60 (1H, ddd, J 20, 15.5 and 2.5 Hz one of CH_2P), 1.77 (3H, s, CH_3), 2.95-2.99 (2H, m, C=C-C*H* and *H*CCH_2P), 3.39 (1H, apparent t, J 11.7 Hz, one of CH_2NH), 3.62 (1H, dd, J 11.7 and 7.3 Hz one of CH_2NH), 4.48 (1H, br s, $CHCO_2H$), 4.72 (1H, br s, one of $=CH_2$), 5.07 (1H, br s, one of $=CH_2$); δ_C (100 MHz; D_2O) 24.9 (CH_3), 28.2 (CH_2P, $J_{C\text{-}P}$ 132 Hz), 42.2 ($CHCH_2P$, $J_{C\text{-}P}$ 2.1 Hz), 48.2 (CH_2N), 49.4 ($CHCH_2N$, $J_{C\text{-}P}$ 14.9 Hz), 68.5 ($CHCO_2H$), 115.7 ($C=CH_2$), 142.7 ($C=CH_2$), 176.5 (CO_2H); δ_P 23.0; $[\alpha]_D^{24}$ -6.8° (c=1, H_2O)
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