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Neuroexcitatory amino acids: phosphonic analogue of kainic acid

Short Communication

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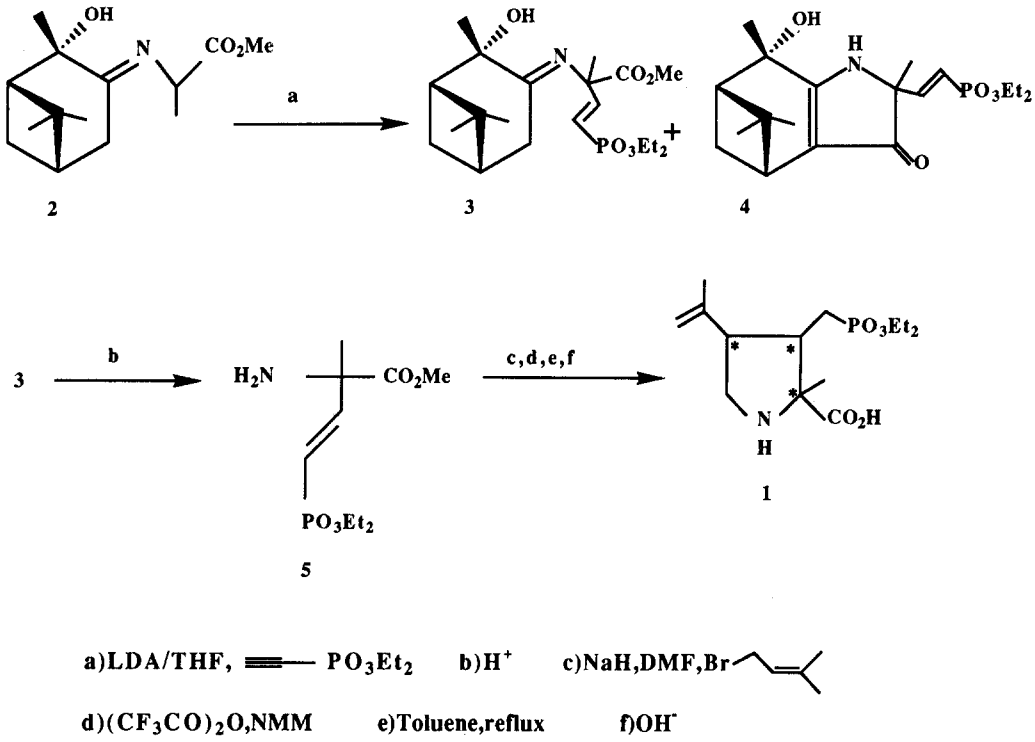
Summary. The enantioselective synthesis of phosphonic analogue of kainic acid is described.

Keywords: Amino acids – Asymmetric synthesis – 2-Hydroxypinan-3-one – Kainic acid – Phosphonic analogue

Introduction

L-glutamic acid is one of the major neurotransmitters in the mammalian central nervous system and peripheral neurons of invertebrate. Recent studies demonstrated that the receptors of L-Glu took part in the acquirement of memory and learning: Collingridge (1990). Neurodegeneration sickness and Huntington's and Alzheimer's diseases could arise from the abnormal function of the glutamatergic systems: Maragos (1987). Development of selective agonists and antagonists allowed the classification of excitatory aminoacid receptors into four ionotropic receptors: NMDA (N-methyl D Aspartate), kainate, AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid), L-AP4 (L-2-amino-4-phosphonobutanoate) and a metabotropic type receptor. In these subtypes, kainate type receptor was relatively unexplored (in comparison to NMDA receptor) and modifications of structure of kainic acid affected positions 3 and 4. We planned to prepare several analogues of kainic acid and we describe here the diastereoselective synthesis of the analogue of kainic acid having a methyl substituent in position 2 and a distal phosphonic acid function. Indeed, structure activity studies by Watkins (1988) showed that good competitive NMDA antagonists were obtained if the distal acidic function was a phosphonic one.



Results

The precursor of choice to obtain the compound **1** is the aminoester **5** which can be easily prepared. 1,4 addition of the chiral Schiff base **2** obtained from (1S, 2S, 5S) 2-hydroxypinan-3-one and alanine methyl ester, with acetylenic phosphonic acid diethyl ester in the presence of LDA at −80°C in THF afforded Schiff base 3 in 51% yield. Near **3** was obtained compound 4 in 12% yield which arises from the protonation of the intermediate vinyl anion by the proton α to the $C = N$ linkage, formation of a new anion which cyclizes on the carboxylic ester function and migration of the double bond. **3** was isolated as a single diastereomer with *E* geometry of the double bond (as detected by ^1H NMR, 250 MHz). The configuration of the α carbon [*R* configuration assigned according to previous work: Elachqar (1988)] is under investigation by *RX* diffraction. Hydrolysis with 1N HCI compound 5 was obtained in 14% yield, under sonication the yield was raised to 57%. Boric acid (1M, pH = 6, 6.5) gave the aminoester **5** in 71% yield. **5** was N-alkylated in dimethyl formamide with 1-bromo 3-methyl 2-butene in 58% yield. After N-protection with trifluoroacetic anhydride, (quantitative yield) thermal ene reaction (Toluene, reflux 18 h, under N2, 80% yield) and deprotection, the phosphonic analogue of 2 methyl kainic acid was obtained.

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