233. A Total Synthesis of α-Kainic Acid by an Intramolecular Ene Reaction

Preliminary communication

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Summary

The neurotoxin α-kainic acid (**7**) was synthesized from **1** *via* the thermal key step **5** → **6** in 41% overall yield.

α-Kainic acid, isolated from the marine algae *Digenea simplex Ag.* [1] and *Centroceras clavulatum* [2] has been assigned structure **7** based on chemical [3] and X-ray studies [4]. This cyclic amino diacid has attracted considerable medicinal interest owing to its potent neurobiological activity [5]. Former multistep syntheses furnished **7** in low yield [6]. In connection with our recent synthesis of its C(4)-epimer α-allokainic acid [7] we now wish to report a new stereoselective approach to α-kainic acid (**7**).

Starting from methyl *N*-trifluoroacetylglycinate [8], *N*-alkylation (NaH/1-bromo-3-methyl-2-butene/HMPT/25°/16 h, work-up with 10% aq. citric acid) gave the amidoester **1**[1]) (b.p. 70°/0.01 Torr) in 80% yield. In order to assemble the acyclic key precursor **4**, the remaining three carbon atoms were introduced using 2-methylthio-acrylate (**2**)[2]) as a *Michael* acceptor [10]. Because of the instability of the ester enolate of **1**[3]), lithium *N*-isopropylcyclohexylamide (1.1 mol-equiv.) was added dropwise to a mixture of **1** and **2** (1.05 mol-equiv.) in THF at −78° over a period of 30 min. The reaction was quenched with acetic acid at −78° to give after aqueous work-up and distillation (130°(bath)/0.001 Torr) the thio-ethers **3**[1]) in 72 to 97% yield as a mixture of stereoisomers. Oxidation of **3** (*m*-chloro-perbenzoic acid/CH_2Cl_2/−78°/30 min) followed by bulb-to-bulb distillation of the chromatographed sulfoxide mixture at 130–150° (bath)/0.01 Torr gave after chromatography (SiO_2, toluene/ethyl acetate) the 1,5-diene **5**[1])[4]) in 90% yield.

[1]) IR., ^{1}H-NMR. and MS. are in full agreement with the assigned structure.

[2]) The acrylate **2** was prepared in analogy to the corresponding 2-phenylthio acrylate [9].

[3]) Complete decomposition of the ester enolate of **1** was observed even at −78° within 15 min.

[4]) UV. (MeOH): λ_{max} = 219 nm ($\log\varepsilon$ = 3.9). – ^{1}H-NMR. (CCl_4, 100 MHz, internal standard tetramethylsilane (δ = 0 ppm), *s* = singlet, *d* = doublet, *t* = triplet, *J* = spin-spin coupling constant, Hz): 1.64 (*s*, 3 H); 1.70 (*s*, 3 H); 3.24 (*d*, *J* = 7.5, 2 H); 3.3–4.2 (1 H); 3.70 (*s*, 3 H); 3.83 (*s*, 3 H); 4.35 (*d* × *d*, *J* = 7.5 and 14.5, 1 H); 5.21 (*t*, *J* = 7.5, 1 H); 7.26 (*t*, *J* = 7.5, 1 H).

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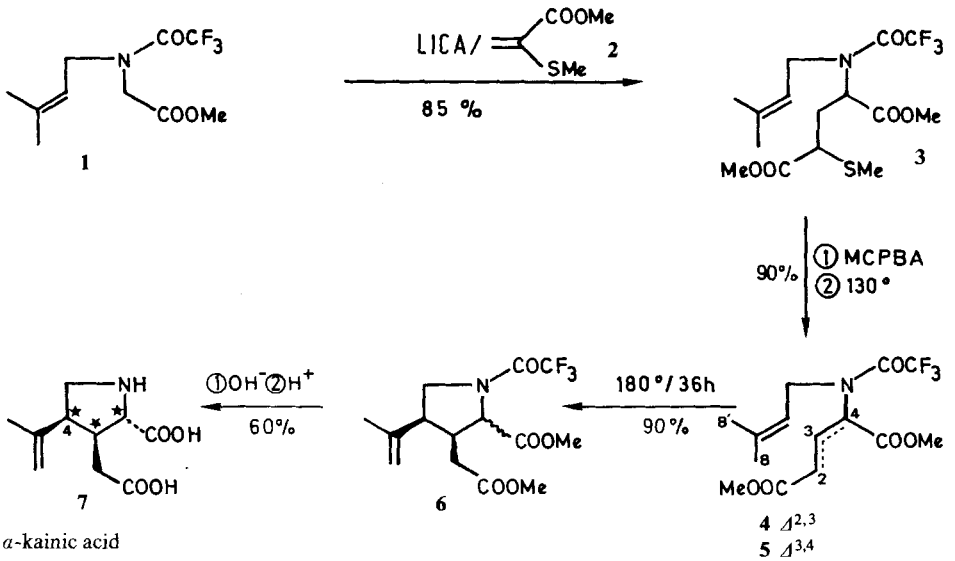
Scheme



It appears that the initially formed 1,6-diene **4** has isomerized to **5** under the thermal desulfenylation conditions [11]. Anticipating the isomerization **4**→**5** to be reversible at high temperature, the 1,5-diene **5** was heated to 180° for 35 h (5% solution in toluene under argon) to afford, presumably *via* the ene-reaction of **4**[5]), the cyclized pyrrolidine **6**[1]) in over 90% yield. Saponification of the crude diester amide **6** (9 mol-equiv. of 2N NaOH, 4 h reflux in MeOH/H_2O 1:1), isolation of the amino-diacids by treatment with ion exchange resins[6]) and crystallization (H_2O) furnished pure (±)-α-kainic acid (**7**) (m.p. 230–260°, dec., 51.5% yield). Further **7** was precipitated as its barium salt on addition of sat. aq. $Ba(OH)_2$ to the mother liquor; after treatment of this salt with H_2SO_4 and crystallization, another portion of pure **7** was obtained (60.5% total yield). Careful analysis of the remaining mother liquor, after liberation of the aminoacids from their barium salts, showed the presence of **7** together with other stereoisomers[7]). Crystallization of (±)-**7** with (+)-ephedrine (EtOH) furnished a salt (m.p. 208–213°, dec.) which, after treatment with weakly acidic ion exchange resin (*Merck* IV) and crystallization (EtOH), afforded the enantiomerically pure (−)-α-kainic acid (m.p. 235–243°, dec., $[\alpha]_D^{20} = -14.6°$ ($c = 1.46$, H_2O)), identical with natural **7** as confirmed by IR., chiroptic evidence and ^{1}H-NMR. (100 MHz).

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[5]) The alternative, less likely mechanism involving direct cyclization of **5** by H-transfer from C(8) to C(4) is not rigorously excluded. For a recent review on intramolecular ene-reactions see [12].

[6]) (i) Absorption of **7**, its isomers and the sodium ions on strongly acidic ion exchange resin (*Merck* I); (ii) elution of the amino-diacids with 1N aq. NH_4OH; (iii) evaporation of the eluate, addition of water, filtration of the solution through a weakly acidic ion exchange resin (*Merck* IV) and evaporation of the filtrate.

[7]) α-Kainic acid (**7**, 11%), β-kainic acid (6%), α-allokainic acid (8%), and β-allokainic acid (14.5%).

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