

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

Preliminary communication

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(31. VIII. 79)

Summary

The neurotoxin α -kainic acid (**7**) was synthesized from **1** via the thermal key step **5** $\rightarrow$ **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**).

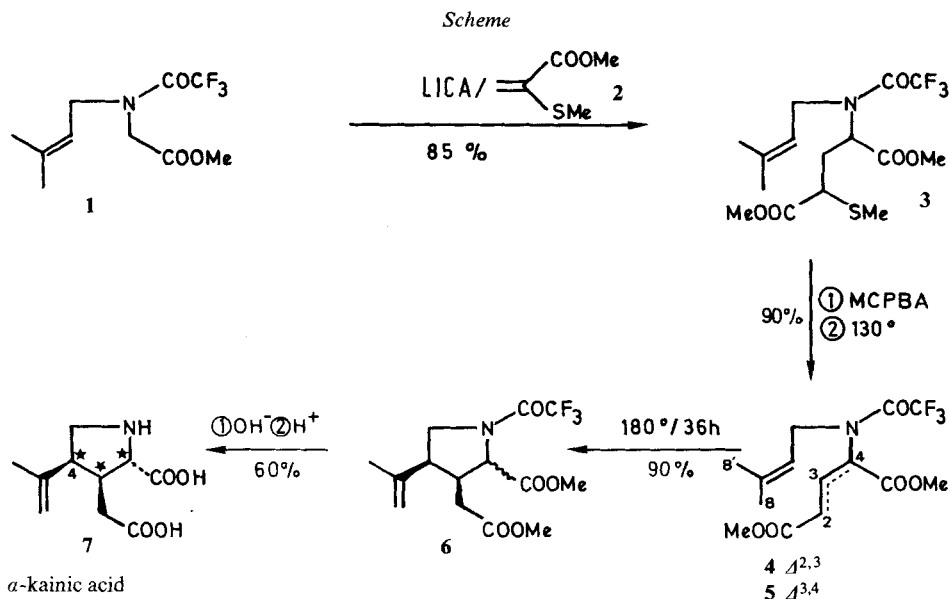
Starting from methyl *N*-trifluoroacetylglucinate [8], *N*-alkylation (NaH/1-bromo-3-methyl-2-butene/HMPT/25°/16 h, work-up with 10% aq. citric acid) gave the amidoester **1**¹⁾ (b.p. 70°/0.01 Torr) in 80% yield. In order to assemble the acyclic key precursor **4**, the remaining three carbon atoms were 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 thioethers **3**¹⁾ in 72 to 97% yield as a mixture of stereoisomers. Oxidation of **3** (*m*-chloroperbenzoic acid/CH₂Cl₂/-78°/30 min) followed by bulb-to-bulb distillation of the chromatographed sulfoxide mixture at 130-150° (bath)/0.01 Torr gave after chromatography (SiO₂, toluene/ethyl acetate) the 1,5-diene **5**¹⁾⁴⁾ in 90% yield.

¹⁾ IR., ¹H-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): $\lambda_{\max}$ = 219 nm ($\log \epsilon$ = 3.9). - ¹H-NMR. (CCl₄, 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* $\times$ *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).



It appears that the initially formed 1,6-diene **4** has isomerized to **5** under the thermal desulfenylation conditions [11]. Anticipating the isomerization **4** $\rightarrow$ **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/H₂O 1:1), isolation of the amino-diacids by treatment with ion exchange resins⁶⁾ and crystallization (H₂O) furnished pure ($\pm$)- 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 H₂SO₄ 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 stereoisomers⁷⁾. Crystallization of ($\pm$)-**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., $[\alpha]_D^{20} = -14.6^\circ$ ($c = 1.46$, H₂O)), identical with natural **7** as confirmed by IR., chiroptic evidence and ¹H-NMR. (100 MHz).

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. NH₄OH; (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%).

We are indebted to Dr. *H. Morimoto* for kindly providing the spectra of **7** and its stereoisomers. Financial support of this work by the *Swiss National Science Foundation, Sandoz Ltd.*, Basel, and *Givaudan SA*, Vernier, is gratefully acknowledged. We thank Mr. *J.P. Saulnier* and Mrs. *F. Klöti* for careful measurements of NMR. and mass spectra.

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