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THE TOTAL SYNTHESIS OF α-ALLOKAINIC ACID

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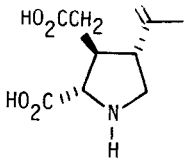
Summary - The aminoacid α-allokainic acid was synthesized in eight steps from thiazolidine **2**.

The aminoacid α-allokainic acid (**1**) was isolated from the marine algae Digenea simplex Ag.[1] Other members of this class include α-kainic acid,[2] an isomer of **1** in which the isopropenyl and the acetic acid groups are cis, and domoic acid.[3] Although **1** shows



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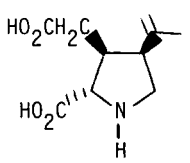
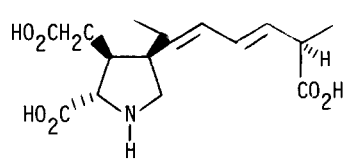


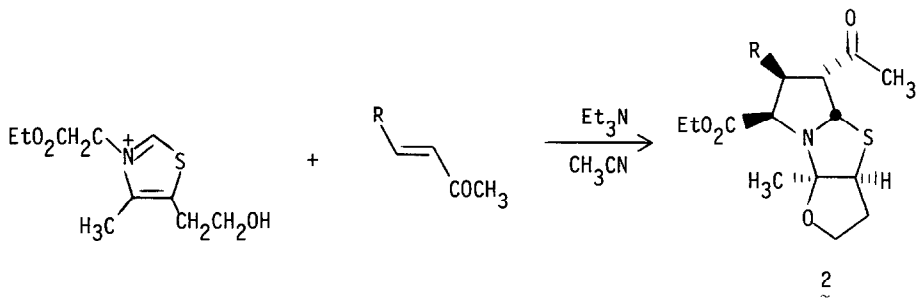
α-kainic acid



domoic acid

antihelmintic properties, its potent neurophysiological activity in mammals[4] has attracted considerably more attention. Earlier syntheses were nonstereospecific but served to elucidate the structure. Recently, Oppolzer has communicated an elegant synthesis of **1** based on an intramolecular ene reaction.[5]

We recently reported a 1,3-cycloaddition route that produced the functionalized pyrrolidine **2** and demonstrated that the cycloaddition was stereospecific.[6] Additionally, the



2

300 MHz proton NMR spectrum indicated that the ratio of endo- to exo-adducts was greater than 10:1. The relative stereochemistry of **2** (R = CH_2CH_2OBn) was determined by x-ray crystallography. In order to exploit this strategy for the synthesis of pyrrolidine-based natural products we undertook the synthesis of **1**. The successful outcome of our efforts is the subject of this paper.

The transformation of **2** (R = $CH_2CH_2OCH_2Ph$)[7] into **1** is shown in Scheme 1. Initially, we found that desulfurization agents such as RaNi or lithium in ammonia produced complex mixtures of products. The vinylogous amide **3** could be prepared by the reaction of **2** with potassium t-butoxide in the presence of methyl iodide[8] followed by reaction with hydrochloric acid in anhydrous ethanol (r.t., 3h). Common procedures for the reduction of vinylogous amides afforded mixtures of aminoketones and aminoalcohols. However, a reaction involving o-silylation with trimethylsilyl triflate[9] followed by reduction of the resulting iminium salt with sodium cyanoborohydride in ethanol, protection and DBU epimerization furnished **4** in good yield. Recently the synthetic sequence has been streamlined by use of a two step procedure involving desulfurization with one equivalent of tributyltin hydride[10] followed by acid hydrolysis (HCl, anhyd EtOH', r.t.) and protection[11] of the aminoketone. Hydrogenolysis of the benzyl group (H_2, Pd/C, 18 psi) produces a hemiketal which in turn is oxidized to ketoacid **5** with Jones reagent (r.t., 15 min.). A Wittig reaction (Ph_3PCH_3I, nBuLi, THF, 0°C) on the ester derived from **5** affords **6**. The structure of this intermediate is supported by NMR absorptions at 1.69 δ (brs) and 3.67(s). Ester hydrolysis (KOH, CH_3OH)

and removal of the protecting group[12] produces an isomer of **1** as evidenced by the x-ray structure. We initially anticipated that epimerization would occur during ester hydrolysis. However, no epimerization was observed. Epimerization to **1** did occur when the acid was heated with an excess of base for 1h at 155°C. The synthesis of **1** from **2** proceeds in 11% yield. We intend to use this strategy for the synthesis of dolomic acid, α-kainic acid and other alkaloids containing the pyrrolidine subunit.

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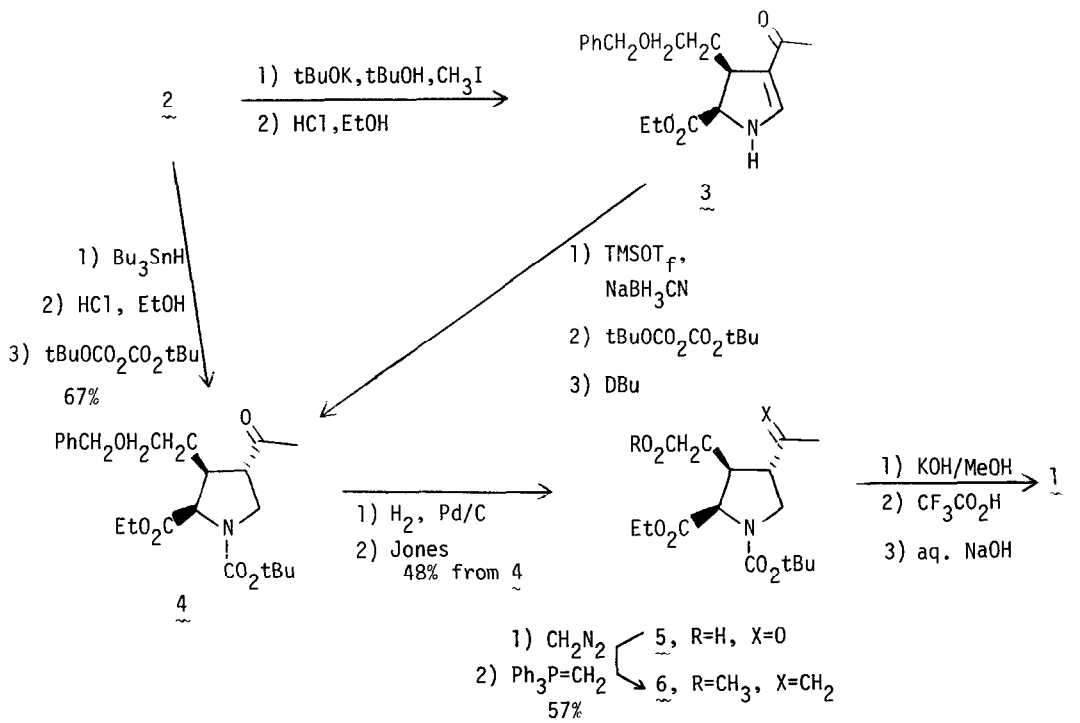
Scheme 1



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7. The structure needed for the α-allokainic acid synthesis was prepared from the reaction of the appropriate thiazolim ylid (see ref. 6) with 6-benzyloxy-3-hexen-2-one in 65% yield. The enone was prepared by a Wittig reaction on 3-benzyloxy-propionaldehyde. All intermediates exhibited PMR, CMR, IR and high resolution mass spec data in accord with the assigned structures.
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