# A Direct Route to Biologically Active Kainic Acid Analogs

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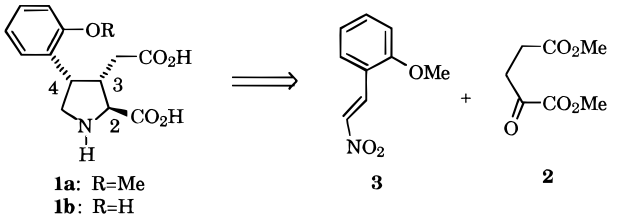
The synthesis of kainic acid, acromelic acid, and related compounds such as domoic acid has been the subject of considerable investigation.[1] The observation by Shirahama that **1a** and **1b** have potent neurophysiological activity has spawned intense synthetic attention toward C-4 aryl analogs.[2] Control of the C-3/C-4 stereochemistry is important, since the isomer bearing the opposite stereochemistry exhibits little biological activity. Most of the synthetic routes to C-4 aryl analogs begin from 4-hydroxyproline.[3] Most notable among these routes is a recent contribution by Baldwin and co-workers wherein the crucial C-3/C-4 stereochemistry was introduced by a hydroxyl-directed hydrogenation.[4] As part of a program to better understand the interplay between the structure, activity, and toxicological profiles of kainoids, we required a direct route to the kainoid skeleton.[5] We report herein a very direct route to racemic **1a** from the dimethyl ester of α-keto glutaric acid (**2**) and nitrostyrene **3**.



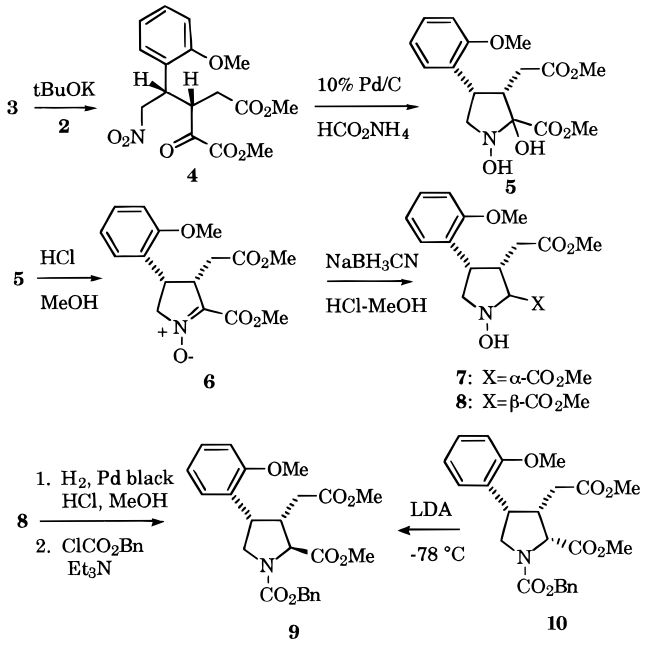

**1a**: R=Me
**1b**: R=H

**3** **2**

The Michael addition of the enolate of diester **2** with nitrostyrene **3** was investigated under a variety of reaction conditions. The enolate of **2** generated from LDA in THF at temperatures ranging from −78 to −20 °C was unstable, affording reaction mixtures containing self-condensation products and much unreacted **3**. Potassium *tert*-butoxide appeared promising and was studied in solvents such as acetonitrile, diethyl ether, THF, 1,2-dimethoxyethane, 2-methyl-2-butanol, and DMF. The optimal conditions (*t*-BuOK, THF) furnished a 45% isolated yield of nitro diester **4** as a 14:1 mixture of diastereomers. The *anti* configuration of **4** was tentatively assigned on the basis of analogy with γ-nitro ketones prepared by Seebach.[6] The assignment was confirmed by its conversion to known compound **9**.

The reduction of **4** with palladium on carbon with ammonium formate in methanol at 25 °C produced a 89% yield of **5**. The proton NMR and a resonance at 92.8 ppm (C-2) in the $^{13}C$ NMR spectrum supported the assigned structure.[7] Compound **5** could be generated from **4** by treatment with zinc and $NH_4Cl$ in aqueous THF,[8] but the yield was low. Compound **5** was unstable. In practice, it was converted without purification into nitrone **6**. Initially, **5** was subjected to dehydration using $POCl_3$ and triethylamine, providing nitrone **6** in 42% yield. Subsequently, it was found that treatment of **5** with HCl in methanol afforded **6** in 73% yield.

While reduction of nitrone **6** with sodium borohydride at 0 °C furnished a complex mixture of compounds, reduction with sodium cyanoborohydride in acidic media (HCl in MeOH) provided a mixture of hydroxyamino diesters **7** and **8** in 71% and 4% yields, respectively, from **6**. Compound **8** was reduced to the amino diester with palladium black in acidic media,[9] and the amine was protected with benzyl chloroformate and triethylamine to afford **9** in 89% yield. The structure of **9** was confirmed by comparison of its proton NMR spectra with the authentic NMR spectrum of **9** kindly supplied by Dr. Shirahama. Compound **9** has already been converted by Shirahama into **1a** by hydrolysis and deprotection.[10] Using a procedure similar to that used for **8**, compound **7** was converted into **10**. Compound **10** could be epimerized into **9** by reaction with 2.6 equiv of LDA at −78 °C for 1 h. The ratio of **9** to **10** was 7:1.[11]

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(3) Reference 1, 4165−4168. Remuzon, P. *Tetrahedron* **1996**, *52*, 13803.
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(6) Brook, M. A.; Seebach, D. *Can. J. Chem.* **1987**, *65*, 836. The methylene α to the nitro group in **4** was a doublet rather than two doublets of doublets (a pattern often observed in the *syn*-isomers).
(7) Attempts to convert **4** directly into **7** or the amino diester with hydrogen and Ra-Ni in THF, MeOH, or EtOAc led to mixtures of very polar materials.
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(9) Murahashi, S.-I.; Shiota, T. *Tetrahedron Lett.* **1987**, *28*, 6469.
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(11) Compounds **9** and **10** contain two rotamers in a 1:1 ratio. In **9**, the methine proton at C-2 appears as two doublets at 4.13 and 4.17 with $J = 5.7$ Hz. In **10**, the methine proton at C-2 appears as two doublets at 4.62 and 4.65 with $J = 7.2$ Hz.

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Our approach controls the C-3/C-4 stereochemistry without having to reduce the carbonyl group at C-2. Either isomer at C-2 is readily available.[12] Our synthesis should be quite flexible with regard to substitution on the Michael acceptor. Extension to more diverse C-4 aryl analogs and to other kainoids will be reported in due course.

**Acknowledgment.** We thank Professor Haruhisa Shirahama for an NMR spectrum of **9**. We thank Iowa State University for a postdoctoral position for H.M.

**Supporting Information Available:** Experimental procedures and proton and $^{13}C$ NMR data (19 pages).

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