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PROGRESS IN THE SYNTHESIS OF (−)-α-KAINIC ACID

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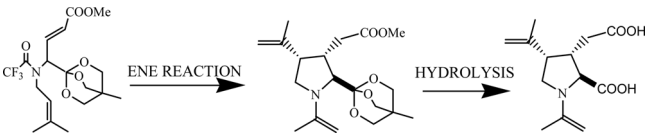
GRAPHICAL ABSTRACT



Abstract *Causing neuronal death, kainic acid and its derivatives are toxic to several known animal species, including rats. Kainic acid and its derivatives have been shown to cause neuroexcitatory activity observed in several neurological disorders. In this research project, a synthetic route that involves control of the stereochemistry to synthesize a pure stereoisomer of kainic acid is proposed. The pure stereoisomer possesses certain medical properties of interest to pharmacological companies. This laboratory synthesis is gaining popularity and increasing importance all over the world because extraction from seaweeds, where kainic acid is found, does not produce reasonable yields. This laboratory procedure will attempt to synthesize kainic acid using an ENE reaction in the final step of the 12 steps as shown in the graphical abstract.*

Keywords ENE reaction; kainic acid; OBO protecting group

INTRODUCTION

β-Hydroxy α-amino acids are an important class of compounds because of their inherent biological activities.[4] They are structural components of many complex biomolecules, such as D-allo-threonine, found in antibiotics such as katanosins and accuminatum. They have also been used as intermediates in the synthesis of many other compounds.[5] Kainic acid is a natural product that was first isolated from red algae found in Japan.[7] This structure is analogous to L-glutamate, an excitatory amino acid, which causes permanent structural adjustments to several brain regions as shown by hippocampal malfunction in adult rats. Administration of this toxic substance can cause seizure activity such as kindling in rats, neuronal loss, and rearrangement of synaptic associations. It also induces heightened neuronal stimulation, causing hyperexcitability.[1] This compound has been used in studying several neurological disorders including, but not limited to, epilepsy, Alzheimer's,

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and Huntington's diseases.[7] Despite its many harmful side effects, pure stereoisomers of kainic acid can be used in treatment of the previously mentioned diseases as well as other neurological disorders.[1,7]

OBJECTIVE

The goal of this project is to use L-serine, a β-hydroxy α-amino acid, to synthesize a pure stereoisomer of kainic acid that has limited harmful side effects in which pharmacological means may enable the treatment of neurological diseases. An attempt is under way to synthesize kainic acid in the laboratory in 12 steps as shown in Scheme 1. The key step for this scheme is the synthesis of the enantiomerically pure N-protected L-serine-4-methyl-2,6,7-trioxabicyclo[2.2.2] ortho ester (OBO) (**7**) to prevent epimerization at the α-carbon in **6** during allylation at the nitrogen atom[5] followed by the ene reaction.[6,7]

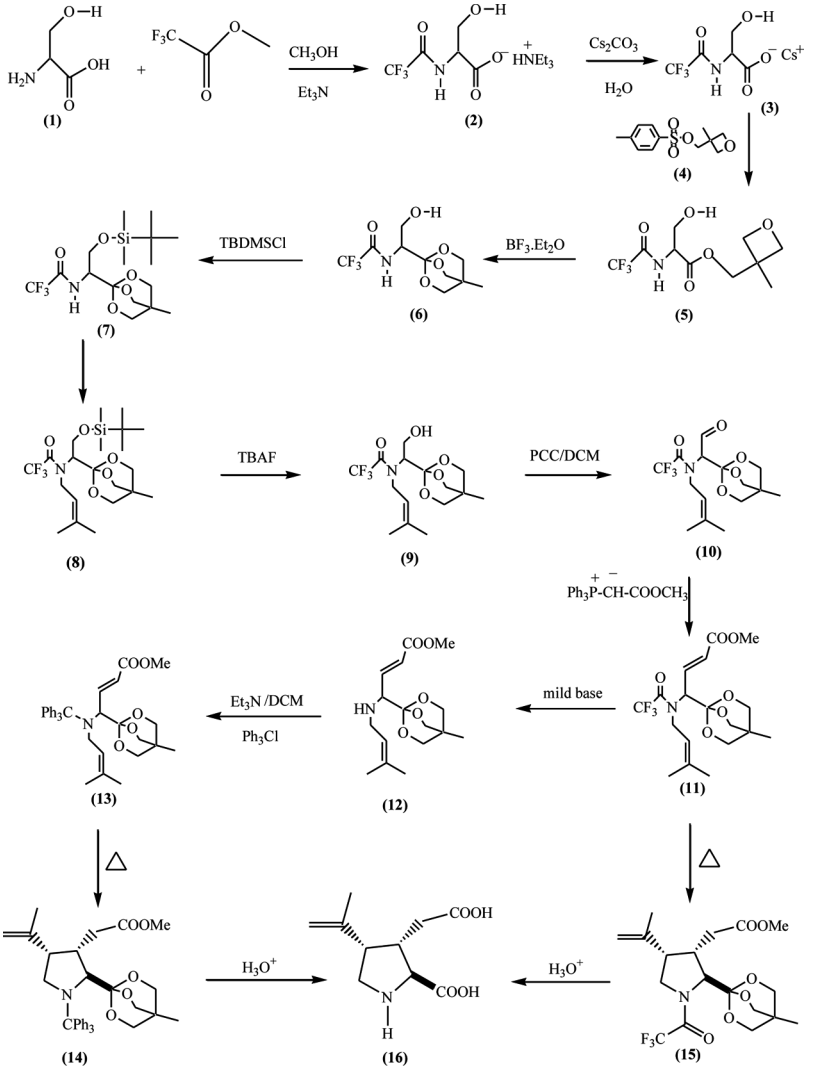
EXPERIMENTAL

Melting points were obtained on a Kofler hot-stage apparatus. ^{1}H NMR spectra were obtained on a Varian Mercury 400-MHz instrument, using $CDCl_3$ solutions with tetramethylsilane (TMS) as internal reference, unless otherwise indicated. δ values are given in parts per million (ppm), and coupling constants are given in hertz (Hz). Subscript letters refer to the hydrogen assignments as noted in the numbered structures. Thin-layer chromatography (TLC) was carried out on 0.25-mm GF60A silica plates, and column chromatography utilized Sorbisil silica. Solvent ratios are in volumes prior to mixing. Dichloromethane (DCM) solvent was dried over calcium chloride and then distilled. Reaction solvents were purified and dried according to literature methods.[8] Extraction solvents were removed under reduced pressure using the rotary evaporator. Petroleum ether refers to the fraction of boiling range between 40 and 60 °C.

Triethyl Ammonium-N-trifluoroacetyl-L-serinate (2)

Triethylamine (9.62 g, 0.1 mol) and methyl trifluoroacetate (15.24 g, 0.12 mol) were added dropwise to a finely ground suspension of L-serine (**1**) (10 g, 0.1 mol) in dry methanol (50 mL), over a period of an hour. Extra care was taken as methyl trifluoroacetate is volatile and the fumes are poisonous upon inhalation. So, this reaction was carried out in a well-ventilated fume hood. The resulting mixture was stirred at room temperature under dry nitrogen for 15 h, which gave a colorless solution. After this time, the solvent was removed in vacuo, which gave the triethyl ammonium salt of N-trifluoroacetylserine (**2**) as a colorless oil, which then crystallized as a yellowish white solid on standing[9] (23.5 g, 78%); mp 30 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.25 (9 H, t), 3.20 (6 H, q), 3.90 (2 H, m), 4.10 (1 H, m), 4.20 (br, s, 1 H, O*H*, exch. with D_2O), 8.10 (1 H, d, exch. with D_2O). ^{19}F NMR ($CDCl_3$, 400 MHz): δ −73.118.



Scheme 1. Proposed total synthesis of kainic acid.

Cesium-N-trifluoroacetyl-L-serinate (3)

The triethyl ammonium salt of N-trifluoroacetylserine (**2**) (15.1 g, 0.05 mol) was dissolved in DMF (30 mL), and cesium carbonate (19.3 g, 0.1 mol) was added and stirred for 1 h. After that time, a white solid, which is the cesium salt of N-trifluoroacetylserine (**3**), was obtained (10.5 g, 63%).

^{1}H NMR (CD_3CN, 400 MHz): δ 3.80–3.94 (m, 2H, β-C*HH*), 4.26 (m, 1 H, α −C*H*), 7.40 (br, s, 1 H, O*H*), 9.02 (br, s, 1 H, N*H*). ^{1}H NMR (H_2O, 400 MHz): δ 3.65–3.67 (m, 2 H, β-C*HH*), 3.88 (t, $J = 4.6$ Hz 1 H, α-C*H*). ^{13}C NMR (D_2O, 400 MHz): δ 178.69, 164.88, 162.06, 63.27, 58.90.

3-Methyl-3-(tosylate)oxetane (4)

Freshly recrystallized toluenesulfonyl choride (28 g, 0.15 mol) was added to a solution of 3-methyl-3-(hydroxymethyl)oxetane (10.0 g, 0.1 mol) in freshly distilled dry pyridine (150 mL), and the resulting mixture was stirred at room temperature under nitrogen for 2.5 h. After that time, the mixture was poured onto ice water (400 mL) and stirred again for 1 h, which gave a white precipitate. This was collected by vacuum filtration and washed copiously with cold water to give the tosyl oxetane ester (**4**) as a white solid. This was dried in a vacuum desiccator over phosphorus pentoxide (20.48 g, 80%); mp 54–55 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.25 (3 H, s), 2.5 (3 H, s), 4.10 (2 H, s), 4.4 (4 H, s), 7.4 (2 H, d), 7.8 (2 H, d).

N-Trifluoroacetyl-3-methyl-3-oxetane-L-serinate (5)

The cesium salt of N-trifluoroacetylserine (**3**) (6.00 g, 0.018 mol) was suspended in dry DMF (30 mL), and the tosyl oxetane ester (**4**) (4.61 g, 0.018 mol) was added, followed by sodium iodide (15 g, 0.1 mol). The mixture was stirred at room temperature under dry nitrogen for 80 h.

After that time, the solvent was removed in vacuo to leave an orange residue (**5**). This was partitioned between ethyl acetate (50 mL) and distilled water (50 mL). The organic layer was washed with saturated aqueous sodium hydrogen carbonate (2 × 30 mL) and brine (2 × 30 mL). The organic layer was dried with anhydrous sodium sulfate, and the solvent was removed in vacuo to give yellow oil (**5**) (3.05 g, 63%); $[\alpha]_D^{25}$ −4.5 °, (c = 1.00, EtOAc). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.30 (s, 3 H, oxetane C*H*$_3$), 3.20–3.54 (dd, J = 1.8, 2.0 Hz, 1 H, *OH*, exch. with D_2O), 3.97–3.92 (m, 1 H, β-C*H*H), 4.25–4.10 (m, 2 H, α-C*H*, β-C*H*H), 4.78–4.48 (m, 6 H, 3 oxetane C*H*$_2$O), 7.50 (br, d, J = 6.75 Hz, 1 H, N*H*, exch. with D_2O). ^{13}C NMR ($CDCl_3$, 400 MHz): δ 171.37, 169.03, 157.26, 79.29, 69.17, 61.88, 54.98, 39.49, 20.82. ^{19}F NMR ($CDCl_3$, 400 MHz): δ −76.227.

N-Protected L-Serine-4-methyl-2,6,7-trioxabicyclo[2.2.2]ortho Ester (OBO) (6)

Compound **5** (0.92 g, 3.2 mmol) was dissolved in 15 mL freshly distilled dichloromethane and cooled to 0 °C, and a solution of $BF_3 \cdot Et_2O$ (53.2 μL) was then added. The mixture was stirred for 8 h and allowed to reach room temperature.

After that time, triethyl amine (100 μL) was added to the solution and then evaporated to dryness. The residue was purified by flash column using 3:1 ethyl acetate/hexane loaded in dichloromethane.

Finally, the product was recrystallized using ethyl acetate/hexane, which gave colorless crystals of the N-protected L-serine-4-methyl-2,6,7-trioxabicyclo[2.2.2] ortho ester (OBO) (**6**) (0.61 g, 67%); mp 130–132 °C; $[\alpha]_D^{25}$ −17.5 ° (c = 1.00, EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.90 (s, 3 H, ortho C*H*$_3$), 3.00 (br, dd, J = 8.5, 4.0 Hz, 1 H, *OH*, exch. with D_2O), 3.74–3.64 (m, 1H β-C*H*H), 3.95 (s, 6 H, 3 ortho C*H*$_2$O), 4.00–3.90 (m, 2 H, α-C*H*, β-C*H*H), 6.50 (br, d, J = 9.0 Hz 1 H, N*H*).

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