Synthesis of Enantiopure Arylkainoids: Preparation of (2S)-Δ^3-4-Phenylkainic Acid

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The kainoid group of pyrrolidinedicarboxylic acids are attractive synthetic targets because of their structural complexity and because they exhibit potent and specific neuroexcitatory activity at glutamate receptors.[1,2] Growing interest in glutamate pharmacology currently demands improved methodology to synthesize these receptor ligands for use as tools to study glutamate-mediated neurochemistry in order to develop memory-enhancing and neuroprotective therapeutics.[3] In addition, the powerful excitatory action at insect neuromuscular junctions that is exhibited by kainoid derivatives has attracted interest in their synthesis for use as potential pesticides in agricultural chemistry.[4]

The neuroexcitatory activity of the kainoids is contingent on the combination of their glutamate-like structure, 4-position substituent, and ring-substituent stereochemistries.[3] For example, *trans*-2-carboxy-3-pyrrolidineacetic acid **2** (Figure 1) possesses the glutamate core structure characteristic of α-kainic acid and exhibits agonist activity at kainate-type and *N*-methyl-D-aspartate-type receptors.[5] (−)-Domoic acid, the causative agent of toxicity in cultured blue mussels responsible for outbreaks of food poisoning in Canada, possesses a conjugated diene at the 4-position and exhibits potent excitatory activity.[1a,4,6] Modification of the aromatic 4-position substituents of the acromelic acids has led to 4-arylkainoids having greater excitatory activity than α-kainic acid.[2] On the other hand, inversion of the 4-position stereochemistry manifests reduced neuroexcitatory activity in allokainic acid.[3]

Recent reports of the use of 4-hydroxyproline to prepare arylkainoids prompted us to reveal our approach to synthesize enantiopure kainoid derivatives.[2a,d] Our route provides 4-arylkainoids via regioselective enolization of a 4-oxoproline, *C*-alkylation, *O*-triflylation, and Pd(0)-catalyzed cross-coupling to an arylboronic acid. We have synthesized (2*S*)-Δ^3-4-phenylkainic acid (**1**) in eight steps from (2*S*,4*R*)-4-hydroxyproline in 39% overall yield and >99% enantiomeric purity. Although the stereochemistry at the 3- and 4-positions influences both the potency and the receptor selectivity of kainoid analogues,[3] to our knowledge, we are the first to prepare a Δ^3-kainoid

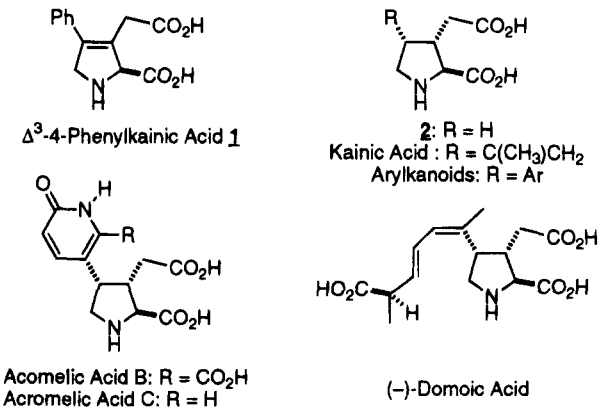

Figure 1. Representative kainoid analogues.

analogue. By restricting the conformations of both the 3- and 4-position substituents on a rigid vinylglycine structure, we have synthesized **1** as a novel probe for exploring glutamate receptors. In light of the efficient methodology to stereoselectively reduce double bonds,[7] Δ^3-analogues should be useful intermediates for the synthesis of isomers in order to study the relationships between kainoid stereochemistry and bioactivity.

Our strategy begins with hydroxyproline as a chiral educt that is submitted to a sequence of esterification,[8] phenylfluorenation,[9] and oxidation[10] in order to furnish benzyl 4-oxo-*N*-(9-(9-phenylfluorenyl))prolinate (**4**) in 77% overall yield (Scheme 1, 9-(9-phenylfluorenyl) = PhFl). Our experience with *N*-(PhFl)-α-amino ketones suggested that regioselective enolization and alkylation of **4** could be used to obtain 3-alkylprolines in high yields without racemization of the chiral α-center.[11] By providing a direct means to alkylate the 3-position, this improved approach eludes the formation of an oxoproline-derived enamine as well as the low to moderate yields from enamine alkylation.[2d,12] We obtained a 2:1 diastereomeric mixture of benzyl 3-((methoxycarbonyl)methyl)-4-oxo-*N*-(PhFl)prolinates **5** in 91% yield after enolization of **4** at −78 °C with $KN(SiMe_3)_2$ (200 mol %) in a 0.06 M THF:DMPU (9:1) solution and treatment with methyl bromoacetate (220 mol %).[13]

We examined three approaches in order to synthesize 4-arylprolines. Initially, benzyl 4-hydroxy-*N*-(PhFl)prolinate (**3**) was converted into tosylate **6** on treatment with TsCl and pyridine. Although arylcuprates add to 4-(tosyloxy)-*N*-(acyl)prolines providing 4-arylprolines with retention of configuration,[2a,14] we could not obtain benzyl 4-phenyl-*N*-(PhFl)prolinate using this chemistry on **6**. We then tried to add organometallic reagents to ketone **4**. Arylcerium reagents react with 4-oxo-*N*-(acyl)prolines in

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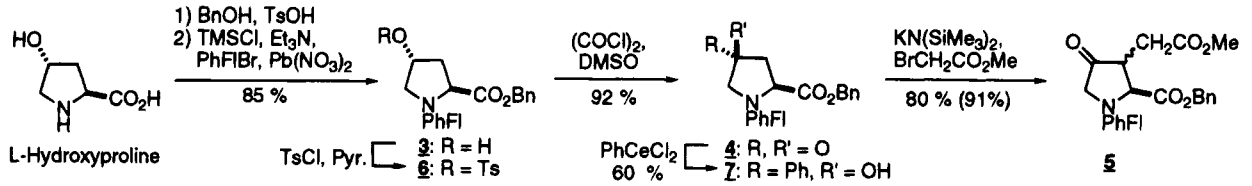
Scheme 1. Alkylation and Nucleophilic Addition onto 4-Oxoproline 4

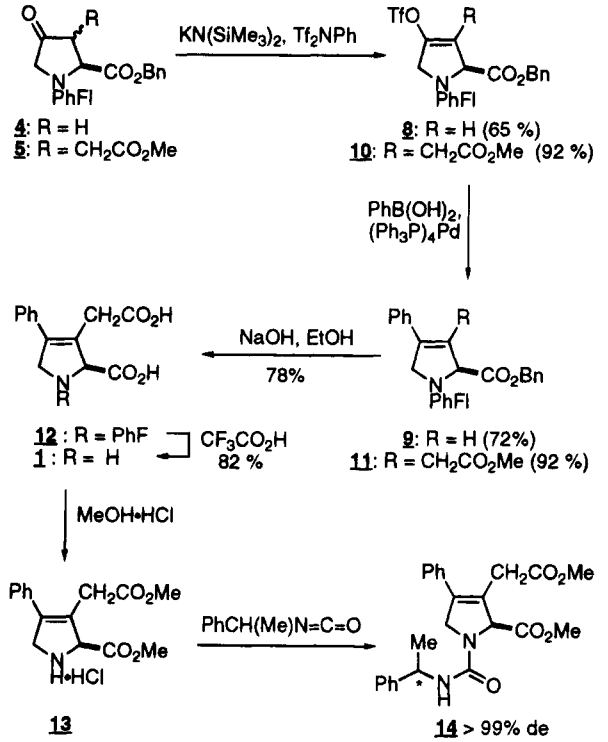


better yields, providing cleaner products than aryllithium and arylmagnesium reagents.[2d,15,16] In our hands, 4-oxo-*N*-(PhFl)proline **4** reacted diastereoselectively with $PheCeCl_2$ (150 mol %) in THF at −60 °C and (2*S*,4*R*)-4-phenyl-4-hydroxyproline **7** was isolated in 60% yield. The 4*R* stereochemistry was assigned initially on observation of the hydroxyl group ^1H NMR signal which was downfield shifted due to hydrogen bonding to the ester carbonyl. Additional support for the *cis* relationship between the phenyl ring and α-proton was obtained from consideration that the α-proton shared vicinal and W coupling constants with the downfield shifted β- and δ-protons. The 3-alkyl substituent had a detrimental affect on the addition of $PheCeCl_2$ to **5** and benzyl 3-((methoxycarbonyl)methyl)-4-phenyl-4-hydroxy-*N*-(PhFl)prolinate was not isolated. Since Pd(0)-catalyzed cross-coupling of arylboronic acids and vinyl triflates furnishes styrenes possessing amino groups and tetrasubstituted olefins,[17] we explored this third alternative to synthesize 4-arylprolines.

Vinyl triflate **8** was prepared in good yield by enolization of 4-oxo-*N*-(PhFl)proline **4** with $KN(SiMe_3)_2$ in THF and *O*-acylation with $PhN(Tf)_2$ (Scheme 2).[17a] Palladium-catalyzed cross-coupling of **8** with $PhB(OH)_2$ (110 mol %) was performed using 5 mol % of $Pd(PPh_3)_4$ in a two-phase system of DME and 2 N Na_2CO_3 with LiCl (300 mol %) at 70 °C for 1 h and gave styrene **9** in 72% yield.[17c] The vinyl proton signal in the spectrum of styrene **9** is shifted 0.3 ppm downfield from its position in the spectrum of triflate **8**. The stage was set to see if tetrasubstituted olefin **11** could be prepared from 3-((methoxycarbonyl)-methyl)-4-oxo-*N*-(PhFl)proline (**5**). Vinyl triflate **10** was prepared from **5** using the above conditions in 92% yield. At first, the cross-coupling did not furnish **11** and triflate **10** was recovered unchanged. Protected Δ³-phenylkainoid **11** was obtained in 92% yield by changing from DME to toluene and heating with $PhB(OH)_2$ (300 mol %) at 95 °C for 6 h.[17f] Deprotection of **11** was accomplished in two steps. The esters were first hydrolyzed using 2 N sodium hydroxide (2500 mol %) in aqueous EtOH at 55 °C for 24 h to provide (2*S*)-Δ³-4-phenyl-*N*-(PhFl)kainic acid (**12**) in 78% yield after chromatography. Finally, solvolysis of the PhFl group using a 0.02 M solution of 1:1:40 TFA:anisole:CH_2Cl_2 at rt for 24 h provided **1** as a white solid in 82% yield after removal of the hydrocarbon impurities by trituration with hexane.[18]

The enantiomeric purity of **1** was ascertained after conversion to (*R*)- and (*S*)-*N*-(α-methylbenzyl)urea dimethyl esters **14**. Esterification of **1** with MeOH·HCl and evaporation provided dimethyl ester hydrochloride **13** that was acylated quantitatively with either (*R*)- or (*S*)-

Scheme 2. Synthesis of Δ³-4-Phenylkainic Acid (1) via Pd-Catalyzed Cross-Coupling on Vinyl Triflate 10



α-methylbenzyl isocyanate in THF with triethylamine.[19] Observation of the diastereomeric methyl ester singlets by 300 MHz ^1H NMR spectroscopy in C_6D_6 during incremental additions of the opposite isomer demonstrated **14** to be of >99% de. Hence **1** is presumed to be of >99% enantiomeric purity.

We have developed an efficacious method to synthesize enantiopure arylkainoid derivatives. (2*S*)-Δ³-4-Phenylkainic acid (**1**) was synthesized in eight steps and 39% overall yield from (2*S*,4*R*)-4-hydroxyproline. Rapid assembly of the trisubstituted pyrrolidine is achieved by regioselective enolization of 4-oxo-*N*-(PhFl)prolinate **4**, *C*-alkylation, *O*-triflylation, and Pd(0)-catalyzed cross-coupling to an arylboronate. We are now examining diastereoselective olefin reduction as well as the bioactivity of the Δ³-4-phenylkainate derivatives. Because a variety of alkyl halides and arylboronic acids can be employed in this strategy, our method exhibits great potential for the study of glutamate-mediated neurotransmission.

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Supplementary Material Available: Experimental details as well as ^1H and ^{13}C NMR spectra of **1**, **5**, and **7**−**12** and ^1H NMR spectra of **13** and **14** (23 pages).

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