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Stereocontrolled Synthesis of (+)-Methoxyphenylkainic Acid and (+)-Phenylkainic Acid

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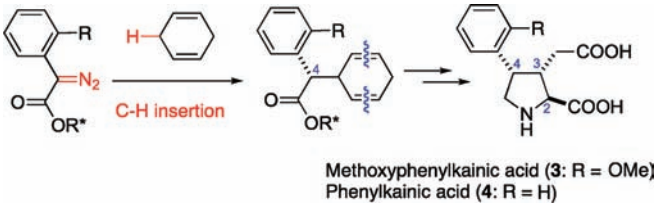
ABSTRACT



The efficient total syntheses of (+)-methoxyphenylkainic acid (3) and (+)-phenylkainic acid (4) were achieved using a rhodium carbenoid-mediated intermolecular C−H insertion reaction. Complete stereoselective construction of the kainoid skeleton was accomplished by utilizing the stereochemistry at the C-4 position as a pivotal stereogenic center.

Recently, kainoids, such as compound **1** (Figure 1), have received significant attention due to their binding affinity for ionotropic glutamate receptors (iGluRs). iGluRs are involved in important neurophysiological processes, such as memory and learning.[1] Although many synthetic investigations of kainoids have been reported to date,[2] efficient synthetic methods are still strongly required. During the pioneering investigations of the potent natural product acromeric acid A (**2**),[3] discovered by the Shirahama group, it was discovered that a synthetic derivative **3** possessed more potent activity than the natural compound **2**.[4] Inspired by this interesting structure−activity relationship, we launched an investigation into the development of efficient synthetic methods for achieving **3** and **4**. Although several synthetic investigations of **3** and **4** have been reported,[5] few investigations have elucidated the mode by which these compounds selectively bind to iGluRs. Detailed biological studies would be assisted by access to an adequate supply of the compounds via an efficient synthetic route.

The heart of our synthetic plan is illustrated in Scheme 1. We envisioned that two carboxylic acid moieties could be

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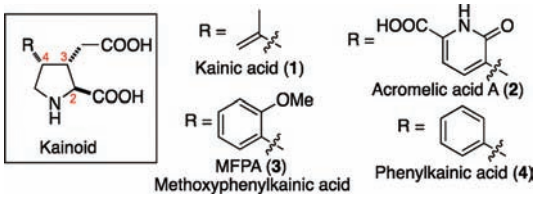
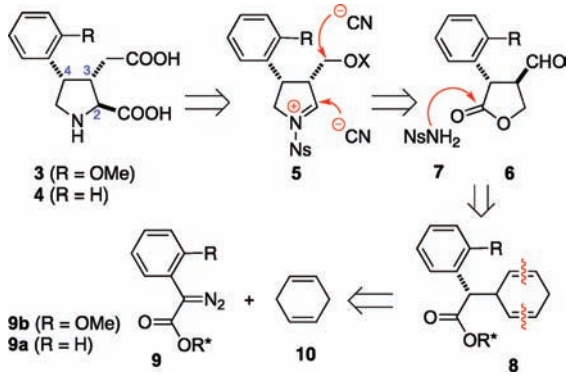


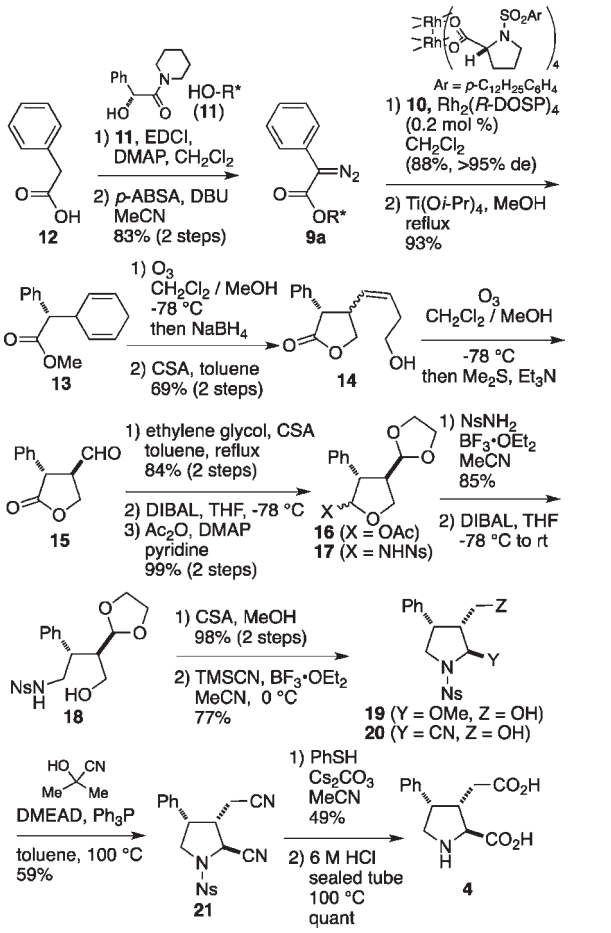
Figure 1. Structures of kainoids **1**, **2**, **3**, and **4**.

Scheme 1. Retrosynthetic Analysis of **3** and **4**



readily elaborated from cyano groups with retention of the oxidation state. The upper and lower nitriles would be incorporated by an S_N2 reaction and the Strecker-type reaction of **5**, respectively. After incorporation of the amine group in **6** by our Ns-amide **7**,[6] ring closure by reaction of the nitrogen atom with the aldehyde would give **5** with the desired stereochemistry. Switching the stereochemistry of the side chain at the C-3 position of **5** by a ring-opening reaction of **6** followed by recyclization would be a crucial step. Because the stepwise oxidative cleavage of **8** would provide a stable *trans*-substituted aldehyde **6**, a stereocontrolled synthesis of **8** would be required. Recently, we developed an efficient rhodium carbenoid-mediated intramolecular C−H insertion[7] of aryldiazoacetate, which possessed a chiral auxiliary.[8,9] We envisioned

Scheme 2. Synthesis of (+)-Phenylkainic Acid (**4**)



that applying this strategy to the intermolecular reaction of **9** and cyclohexadiene **10** would enable construction of **8** with the correct stereochemistry.[10] Although similar C−H insertion reactions of the methyl ester derivatives **9** and **10** have been reported, the enantiomeric excess has not been satisfactory.[9] Thus, our strategy for the synthesis of phenylkainic acid commenced with the incorporation of a chiral auxiliary into the phenylacetic acid.

Preparation of the diazoester **9a** was performed by condensation of phenylacetic acid **12** with the chiral auxiliary **11**[8] and the subsequent diazo transfer reaction (Scheme 2). Upon treatment of **9a** and **10** with 0.2 mol % of the Davies catalyst,[11] the C−H insertion reaction proceeded smoothly to afford, exclusively, a diene **13** in 82% yield. Next, monoselective oxidative cleavage of the diene **13** was accomplished by treatment with ozonolysis at −78 °C. After checking for the disappearance of the starting material by TLC, subsequent addition of $NaBH_4$ gave the corresponding primary alcohol. Without purification, subjection to acidic cyclization provided a lactone

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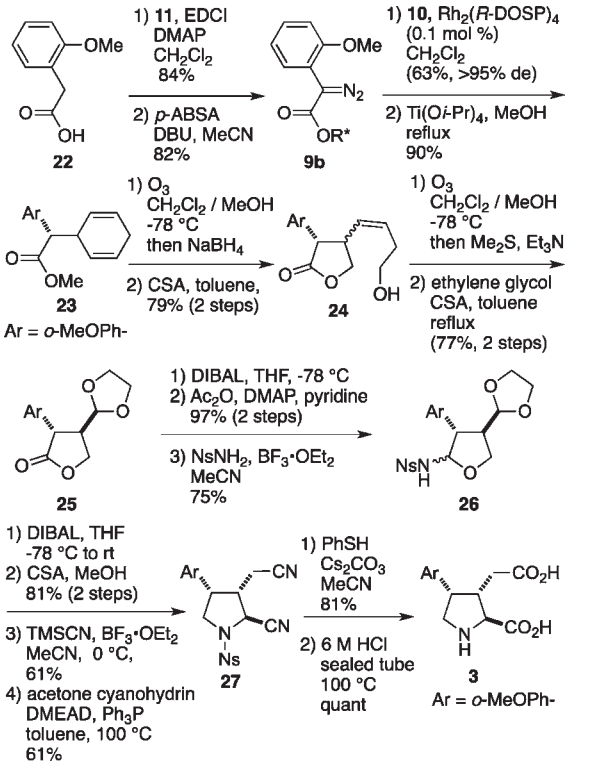
14 as a 1:1 mixture of the diastereoisomers. Next, oxidative cleavage of the olefin **14** proceeded with the concomitant epimerization at the α-position of the aldehyde to give, predominantly, the *trans* lactone **15**. In this reaction, the absence of triethylamine base resulted in a 1:1 mixture of the *cis* and *trans* lactones. After protection of the aldehyde with ethyleneglycol, DIBAL reduction of the lactone and conversion of the lactol to the acetate gave **16**. Upon treatment of **16** with Ns-NH_2 and $BF_3 \cdot OEt_2$ at room temperature, an oxonium cation-mediated amination reaction proceeded smoothly to afford **17** in 85% yield. Selective reduction of the aminal of **17** was performed by treatment with DIBAL to give the desired primary alcohol **18** without loss of the acetal moiety. Treatment of **18** under acidic conditions, alcoholysis of the acetal, and subsequent cyclization with the Ns-amide proceeded smoothly to provide the aminal **19**. Upon treatment of **19** with $BF_3 \cdot OEt_2$ and TMSCN, nucleophilic alkylation of cyanide to the nitrobenzensulfonyliminium ion intermediate occurred from the less hindered *β*-face of the pyrrolidine ring to provide the desired aminonitrile as a single diastereomer. Upon treatment of **20** with acetone cyanohydrine[12] and DMEDA,[13] the desired Mitsunobu reaction proceeded smoothly to afford **21**, which possessed the desired stereochemistry for **4**. After deprotection of the Ns group by treatment with PhSH and base,[14,15] acidic hydrolysis of the cyano groups was carried out in a sealed tube to give the desired phenylkainic acid **4**, the spectral data of which (^{1}H NMR, ^{13}C NMR, IR, and HRMS) were in full agreement with those reported to date.[5e]

Next, we turned our attention to the synthesis of (+)-methoxyphenylkainic acid (MFPA, **3**). As shown in Scheme 3, we employed a similar procedure that was employed for the synthesis of **4**. Starting from methoxyphenylacetic acid (**22**), using an intermolecular C−H insertion, between **9b** and **10**, a stepwise oxidative cleavage of diene **23** and Strecker-type reaction of the Ns-iminium salt derived from **26** as key steps provided **3** in a similar selectivity and yield.[16] Investigations of the biochemistry and biological properties of **3** and **4** are ongoing in our laboratory, and the results will be reported in detail soon.

Scheme 3. Synthesis of (+)-MFPA (**3**)



In conclusion, a stereoselective total synthesis of **3** and **4** was accomplished by an intermolecular Rh-catalyzed C−H insertion between **10** and phenylacetic acid derivatives **9b** and **9a**. The asymmetric center at the benzylic position permitted efficient incorporation of the three sequential stereochemistries on the pyrrolidine ring.

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Supporting Information Available. Experimental details and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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