Application of rhodium-catalyzed cyclohydrocarbonylation to the syntheses of enantiopure homokainoids*

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Abstract: Kainic acid (KA), rigidified (S)-glutamic acid, is a well-known kainite receptor agonist for excitatory transmission in the central nervous system (CNS). Our interest in highly selective kainite ligands prompted us to design a series of new kainic homologs, “homokainoids”, i.e., conformationally rigidified (S)-glutamic acids. For the syntheses of enantiopure novel homokainoids (pipecolino-glutamic acids), we successfully applied the cyclohydrocarbonylation (CHC) reaction, which has been developed in these laboratories. Efficient total syntheses of enantiopure novel homokainoids from (R)-serine feature the highly diastereoselective conjugate addition and the regioselective CHC process in the key steps.

Keywords: cyclohydrocarbonylation; hydroformylation; rhodium-catalyzed; rigidified glutamates; kainic acid; pipecolinoglutamates.

INTRODUCTION

(S)-Glutamate mediates fast excitatory transmission in the majority of the central nervous systems (CNSs) of mammalian synapses and also participates in neuronal plasticity and neurotoxicity [1–3]. Glutamate exerts its effects through activation of ligand-gates cation channels (the ionotropic glutamate receptors, iGluRs) [4] and/or metabotropic glutamate receptors (mGluRs) [5]. GluRs have attracted considerable attention because of their therapeutic potential for the treatment of a range of chronic and acute disorders such as stroke, epilepsy, and Alzheimer’s and Parkinson’s disease. Although glutamate is a nonselective agonist for the GluRs, it was extensively used as templates for the design of selective ligands. Examination of the chemical structures of the GluR ligands reveals that most of them have been developed by the introduction of conformational rigidity, which is a common strategy in medicinal chemistry [6].

Kainic acid (KA) represents a typical example for the concept of Glu rigidification [7,8]: The glutamate structure is embedded within a pyrrolidine ring, with an isopropenyl substituent at the C-4 position for probable additional hydrophobic interaction [9]. Numerous structure–activity relationship studies disclosed that the C-4 stereochemistry, the nature of the substituent, and its conformation play a critical role in its binding to the GluRs [10]. On the basis of this hypothesis, various ligands have

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been developed by modifying the KA structure or the Glu structure for structure–activity relationship studies [11]. A six–membered ring (i.e., piperidine) is conformationally more rigid than the corresponding five-membered ring (i.e., pyrrolidine) due to the relative high energy cost between chair-boat interconversion [12], which should contribute to the discovery of highly selective ligands for the KA receptor with greater stability and entropic gain. In addition, it is reasonable to assume that the introduction of a methyl or a phenyl group at C-4 or C-5 would mimic the isopropenyl appendage in KA. Accordingly, we have designed a series of homokainic acids as homologs of KA as shown in Scheme 1.

![Scheme 1] Kainic acid and homokainic acids.

Our strategy for the syntheses of these homokainates utilizes the diastereoselective conjugate addition [13] to establish the stereochemistry at the C-3 position and the cyclohydrocarbonylation (CHC) reaction to construct the piperidine moiety with proper functional groups [14,15].

RESULT AND DISCUSSION

Synthesis of 3-pipecolinoglutamic acid (1)

Scheme 2 illustrates the synthetic route to (2S,3R)-3-pipecolinoglutamic acid (1). Horner–Wadsworth–Emmons olefination of Garner’s aldehyde 4, readily obtained from R-serine in a four-step sequence [16], with trimethyl phosphonoacetate afforded acrylate 5 in 93 % yield (E/Z = 6/1). Since both E- and Z-isomers of 5 have given the same syn-adduct 6, separation of the two products is unnecessary. Highly diastereoselective conjugate addition of lithium divinylcuprate to 5 gave syn-product 6 exclusively in 88 % yield. The observed stereochemical course of this conjugate addition is consistent with a Felkin–Anh model in that the attack on the Re face should take place to afford the observed product [13]. Deprotection of oxazolidine 6 under acidic conditions followed by acetylation gave the key intermediate 7 in 94 % overall yield. CHC of 7 catalyzed by Rh(acac)(CO)2-BIPHEPHOS (0.25 mol %) proceeded smoothly at 75 °C and 4 atm of CO and H2 (1:1) in toluene for 24 h to give didehydropiperidine 8 in 99 % yield. Hydrogenation of 8 over 5 % Rh/C under 10 atm of hydrogen afforded piperidine 9 in excellent yield. The CHC and hydrogenation steps were performed in a one-pot manner as well, which gave piperidine 9 quantitatively. The Seebach’s transesterification protocol (i.e., MeOH-DBU-LiBr) proceeded smoothly to give the corresponding primary alcohol 10. Subsequent TEMPO-catalyzed [17] oxidation of 10 with sodium hypochlorite gave the desired acid 11, which was methylated with diazomethane to afford dimethyl ester 12 in 92 % yields for three steps. Finally, 12 was refluxed in 6 N-hydrochloric acid, followed by treatment with propylene oxide to give homokainoids 1.
The enantiomer of \( [i.e., (2R,3S)-3-pipecolinoglutamic acid (\text{ent-}1)] \) was synthesized through the same procedure but starting from \((S)\)-serine.

**Synthesis of 5-phenyl-3-pipecolinoglutamic acid (2a)**

Scheme 3 illustrates the synthesis of \((2S,3R,5S)-5\)-phenyl-3-pipecolinoglutamic acid (2a). \((E)-4\)-Phenylbut-3-enylcarbamate \(7a\) was prepared through Heck reaction of 7 with iodobenzene under the standard conditions in 83 % yield.

CHC of \(7a\) was performed using \(\text{Rh(acac)}(\text{CO})_2\cdot\text{P(OPH)}_3\) at 75 °C and 120 atm of CO and \(H_2\) (1:1) to give 5-phenylidihydropiperidine \(8a\) in 96 % isolated yield. The result indicates that the hydroformylation of the styrene moiety afforded exclusively \(\alpha\)-formyl product, which underwent subsequent cyclization and dehydration to give \(8a\). Hydrogenation of \(8a\) over \(\text{Pd(OH)}_2/\text{C}\) at ambient temperature and pressure proceeded with extremely high diastereoselectivity to give \((5S)-\)phenylpiperidine \(9a\) as a single diastereomer. The stereocenter at the C-5 position was assigned unambiguously based on the clear rotating frame Overhauser effect spectroscopy (ROESY) correlation between H-3 and H-5. To complete the synthesis of \(2a\) from \(9a\), the same protocol described for the synthesis of \(1\) was applied through \(12a\), to afford homokainoid \(2a\). This synthesis was achieved in five steps from 7 in 57 % overall yield.
In order to introduce a methyl group at the C-5 position of pipecolinoglutamic acid, we envisioned two possible routes, i.e., (i) CHC of an ω-methyl-

(i) Pd(OAc)$_2$ (5 mol%), PPh$_3$ (10 mol%), Et$_3$N (3 eq) PhI (3 eq), DMF, 75 °C, 4 d (83%). (ii) Rh(acac)(CO)$_2$ (2 mol%), P(OH)$_3$ (8 mol%), toluene, H$_2$ (60 atm) CO (60 atm), 75 °C, 3 d (96%). (iii) Pd(OH)$_2$ (5 mol%), H$_2$, MeOH, RT, (88%). (iv) (a) DBU, LiBr, MeOH, RT, (b) TEMPO, KBr, NaOCl, acetone-\-NaHCO$_3$(aq), 4 °C, (c) CH$_2$N$_2$, MeOH. (87% from 9a). (v) (a) 6 N HCl(aq), RT, overnight. (b) EtOH- propylene oxide, reflux. (94%)

Scheme 3 Synthesis of homokainoid 2a.

**Synthesis of 5-methyl-3-pipecolinoglutamic acid (2b)**

In order to introduce a methyl group at the C-5 position of pipecolinoglutamic acid, we envisioned two possible routes, i.e., (i) CHC of an ω-methyl-7 and (ii) Vilsmeier reaction followed by reduction of the resulting aldehyde. We anticipated that CHC of an internal alkene would result in a regioselectivity problem in the hydroformylation step. Therefore, we chose the Vilsmeier-reduction approach. The Vilsmeier reaction of 5,6-didehydropiperidine was reported to give a 5-formylididehydropiperidine [18]. Scheme 4 illustrates the synthesis of 5-methyl-3-pipecolinoglutamic acid (2b).

Reaction of didehydropiperidine 8 with Vilsmeier reagents followed by treatment with sodium acetate gave aldehyde 13. The formyl group of 13 was converted to 1,3-dithiolane 14. Subsequent desulfurization by Raney-Ni under 50 atm of H$_2$ provided a 3:1 mixture of 5-methylididehydropiperidine 8b and 5-methylpiperidine 9b. After removal of the solid Raney-Ni catalyst, hydrogenation of 8b and 9b was carried out over Pd/C in MeOH-AcOH (30:1) to afford 5-methylpiperidine 12b as a single diastereomer in 68 % overall yield from 13.

Scheme 4 Synthesis of homokainoid 2b.
The configuration at the C-5 position was assigned unambiguously to \( R \) on the basis of the ROESY correlation between H-3 and H-5. Subsequent transformations described for the synthesis of 1 was applied to complete the synthesis of homokainoid 2\( b \) (42 % overall yield from 8).

### 4-Methyl-3-pipecolinoglutamic acid (3)

For the synthesis of 4-methyl-3-pipecolinoglutamic acid (3), we employed CHC of oxazolidine 15 bearing a \textit{gem}-disubstituted alkenyl moiety since the regioselectivity of the hydroformylation of this olefin moiety was guaranteed to be exclusive for the formation of the corresponding terminal aldehyde. However, the diastereoselectivity issue at the C-4 position needed to be addressed by experiment. To synthesize 15, we used Lipshultz’s procedure [19] to generate the corresponding high-order cuprate because transmetallation of tetraisopropenyltin to the corresponding cuprate with MeLi was not successful. Thus, lithium diisopropenylcyanocuprate was prepared by reacting tetraisopropenyltin with freshly prepared Me\textsubscript{2}CuCNLi\textsubscript{2}. Subsequent conjugate addition of acrylate 5 proceeded smoothly to give syn-adduct 15 exclusively in 91 % isolated yield (Scheme 5).

We hypothesized that either improvement of diastereoselectivity of the hydroformylation step or separation of two diastereomers might be possible by rigidifying the substrate for CHC. Accordingly, lactone 16 was prepared by hydrolysis and lactonization under acidic conditions. CHC of lactone 16 was performed using Rh(acac)(CO)\textsubscript{2}-BIPHEPHOS at 75 °C and 120 atm of CO and H\textsubscript{2} (1:1) to give bicyclic didehydropipecolinolactone 17 in nearly quantitative yield as a ca. 1:1 mixture of two diastereomers, which were readily separable by flash column chromatography. Nuclear Overhauser effect (NOE) analyses of the two epimers have revealed that the less polar diastereomer has \( S \) configuration at the C-4 position, i.e., the methyl group is \( \beta \) and equatorial, while the more polar diastereomer has an axial methyl at the C-4 position, i.e., \( R \) configuration. Hydrogenation of lactones 17\( \alpha \) and 17\( \beta \) over Rh/C in methanol at ambient temperature and pressure afforded 18\( \alpha \) and 18\( \beta \), respectively. Subsequent transformations, described for the synthesis of 1, were applied to complete the syntheses of homokainoids 3\( \alpha \) (74 % from 17\( \alpha \)) and 3\( \beta \) (81 % from 17\( \beta \)).

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SUMMARY

We successfully synthesized enantiopure homokainoids, $1$, ent-$1$, $2a$, $2b$, $3\alpha$, and $3\beta$, featuring the extremely diastereoselective syn-conjugate addition of an organocuprate to oxazolidinylacrylate $5$ and the Rh-catalyzed CHC $7$, $7a$, and $17$ in the key steps. Further studies on the biological evaluation of the homokainoids are actively underway in these laboratories.

REFERENCES