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Rhodium-Catalyzed Cyclohydrocarbonylation Approach to the Syntheses of Enantiopure Homokainoids

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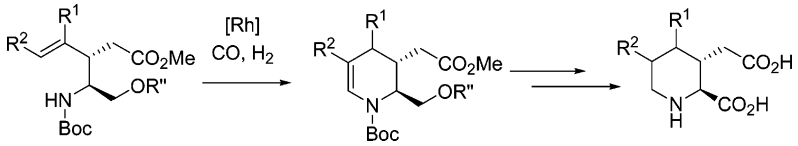

Homologues of kainic acid, a naturally occurring potent glutamate receptor agonist, were designed based on a rigidified pipecolinoglutamic acid structure and can be regarded as homokainoids for their potential activities in the central nervous system. These novel homokainoids in an enantiomerically pure form were synthesized from enantiopure (*R*)- and (*S*)-Garner's aldehyde, featuring (i) the highly diastereoselective addition of alkenylcuprates to the acrylate intermediates and (ii) the Rh-catalyzed cyclohydrocarbonylation of homoallylic amine intermediates to construct the functionalized piperidine moiety in the key steps. For the introduction of a substituent at the 4- or 5-position of pipecolinoglutamic acid, a few different strategies were used, which successfully led to the formation of enantiopure homokainoids.

Introduction

L-Glutamic acid (Glu) mediates fast excitatory transmission at the majority of the central nervous system (CNS) synapses and also participates in neuronal plasticity and neurotoxicity.[1−4] Accordingly, Glu is involved in many brain functions such as motor control, vision, learning, and memory. Glu, when synaptically released, exerts its effects via activation of ligand-gate cation channels (the ionotropic glutamate receptors: iGluRs)[5] and/or metabotropic glutamate receptors (mGluRs),[6] which modulate intracellular second messengers through G protein-coupled processes. Glu receptors have attracted considerable attention because of their therapeutic potential for the treatment of a range of chronic and acute CNS disorders such as stroke, epilepsy, and Alzheimer's disease. iGluRs are defined, on the basis of subtype selective agonists, as *N*-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazolypropionic acid (AMPA), or kainate (KA) subtypes.[5,7] On the other hand, mGluRs are coupled with GTP binding that activates various second-messenger cascades.[6] To date, eight mGluRs receptor subtypes have been divided into three classes on the basis of amino acid homology, agonist pharmacology, and the signal transduction pathway to which they are coupled.[6,8] Glu itself is a nonselective agonist for both iGluRs and mGluRs but was extensively used as a template for the design of selective ligands for either class of receptors. Examination of the chemical structures of the ligands for the iGluRs or mGluRs reveals that most of them have been developed by the introduction of conformational rigidity, which is a common strategy in medicinal chemistry.[9] In these ligands, the Glu template has been embedded in cyclic frames or substituted by lipophilic appendages on its carbon backbone.[10,11]

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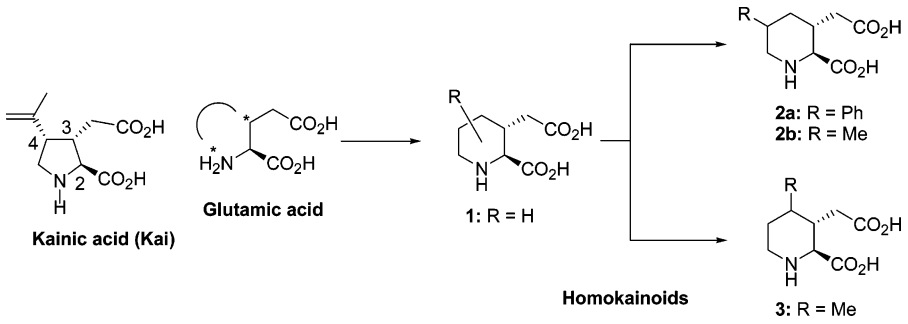
SCHEME 1. Kainic Acid (Kai) and Homokainoids



Kainic acid (Kai) is an agonist for the KA subtype and a typical example of Glu rigidification:[12,13] the Glu structure is frozen within a pyrrolidine ring, and an isopropenyl residue is present at the C-4-position of the five-membered ring, probably responsible for additional hydrophobic interactions.[14] Numerous structure−activity relationship studies have disclosed that the stereochemistry at the C-4-position, the nature of the C-4 substituent, and its conformation play a critical role in its binding to the receptor.[15] Furthermore, KA ligands are excellent tools for studying the neuronal loss in brain dysfunctions as KA activation has been shown to produce neuronal death in the brain of vertebrates, which is attributed to Glu neurotoxicity. Therefore, it has been hypothesized that the use of KA antagonists might be an approach to treat senile dementia.[16] On the basis of this hypothesis, several groups have designed and developed various ligands by modifying the Kai structure or the Glu scaffold for structure−activity relationship studies.[17−31]

Our interest in highly selective KA ligands[32] prompted us to design a series of new Kai homologues, homokainoids (**1**, *ent*-**1**, **2a**,**b**, and **3a**,**b**), shown in Scheme 1.

The rationales for the design of these homokainoids are (i) to the best of our knowledge, homokainoids bearing a pipecolinoglutamic acid framework are unprecedented in chemical literature; (ii) a six-membered ring (i.e., piperidine) is conformationally more rigid than the corresponding five-membered ring (i.e., pyrrolidine) because of the relatively high energy cost between chair−boat interconversion, which should contribute to the discovery of highly selective ligands for the KA receptor with a greater stability and entropic gain;[33] and (iii) we have developed an efficient synthetic method that is applicable for the synthesis of enantiopure pipecolinoglutamic acids with variations at the C-4- or C-5-positions of the piperidine ring.

Molecular modeling studies of homokainoids **1**−**3** on the basis of the X-ray crystal structure of Kai-bound iGluR using the InsightII 2000 program have revealed that (i) homokainoids bind to the Kai binding site with three major hydrogen bonding interactions with the critical amino acid residues Pro^{478}, Arg^{485}, and Thr^{655} as well as hydrophobic interactions with Tyr^{450} in a closely similar manner as Kai in spite of the fact that the C2-CO_2H and C3-CH_2CO_2H groups are at equatorial positions in the piperidine ring (Figures 1 and 2); (ii) there is a hydrophilic open channel (right side in Figure 1) and also flexible open space sufficient to accommodate rather large substituents on the piperidine ring of homokainoids without bumping into amino acid residues near the core binding site (Figure 1); and (iii) homokainoid **3a** (C4-β-methyl) appears to be the closest mimic of Kai, but all other homokainoids are quite interesting to explore possible new interactions with iGluR, which may lead to the discovery of new KA agonists or antagonists (Figure 2).

Our strategy for the synthesis of an enantiopure pipecolinoglutamic acid framework is based on two reactions, i.e., (i)

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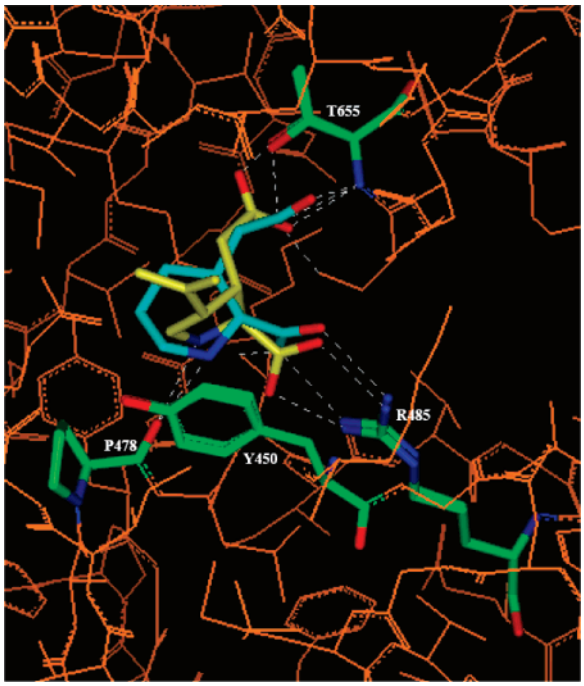

FIGURE 1. Overlay of Kai (yellow) with homokainoid **1** (cyan) in the iGluR binding pocket based the X-ray crystal structure.[14]

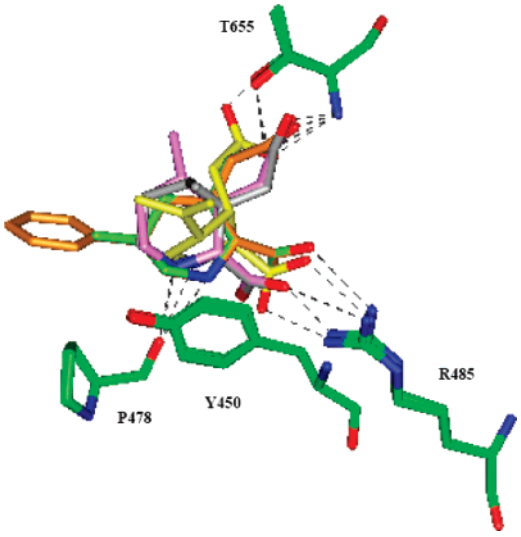

FIGURE 2. Overlay of Kai (yellow) and homokainoids **1** (cyan), **2a** (orange), **2b** (green), **3a** (gray), and **3b** (magenta).

a diastereoselective 1,4-addition of an sp^2 organocuprate to oxazolidinylacrylate **A** derived from Garner's aldehyde[34] to form homoallylic amine **B** and (ii) an extremely regioselective cyclohydrocarbonylation (CHC)[23,35−38] of **B** to construct the piperidine moiety with proper functional groups[39] (Scheme 2).

Results and Discussion

Synthesis of (2*S*,3*R*)-3-Pipecolinoglutamic Acid (1). We started our syntheses of a series of homokainoids from 3-pipecolinoglutamic acid (**1**: R = H), which is the simplest compound with no substituent at the C4- or C5-position, in accordance with our retrosynthetic analysis shown in Scheme 2. Scheme 3 illustrates the synthetic route to **1**. For the preparation of the first key intermediate **A** in Scheme 2, we carried out the Horner−Wadsworth−Emmons olefination[40,41] with Garner's aldehyde **4**,[34] which was readily obtained from *R*-serine in a known four-step sequence.[42] Thus, the reaction of **4** with trimethyl phosphonoacetate afforded oxazolidinylacrylate **5** (**A**: R^1 = Boc) in 93% yield (E/Z = 6:1). Highly diastereoselective[41,43,44] conjugate addition of lithium divinylcuprate to **5** gave syn adduct **6** exclusively in 88% yield. In this reaction, the use of salt-free vinyllithium through transmetalation of tetravinyltin to methyllithium (salt-free) was crucial to generate active lithium divinylcuprate and to make this process clean, high yielding, and reproducible. Since both E and Z isomers of **5** have given the same syn adduct **6**, separation of these geometrical isomers is unnecessary. Deprotection of **6** under acidic conditions followed by acetylation gave **7**, which is the second key intermediate in Scheme 2 (**B**: R = H, R^1 = Boc, and R^2 = Ac), in 94% yield. Cyclohydrocarbonylation of homoallylic carbamate **7** catalyzed by Rh(acac)$(CO)_2$-BIPHEPHOS (0.25 mol %) proceeded smoothly at 75 °C and 4 atm of CO and H_2 (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**, which is the final key intermediate in Scheme 2 (**C**: R = H, R^1 = Boc, and R^2 = Ac), in 95% yield. The cyclohydrocarbonylation and hydrogenation steps were performed in one pot as well, which gave **9** quantitatively.

Removal of the acetyl group from **9**, followed by oxidation and deprotection, should give the target homokainoid **1**. However, attempts to remove the acetyl group of **9** by methanolysis using bases such as LiOH, NaOH, KOH, K_2CO_3, and $KHCO_3$ gave bicyclic oxazolidinone **11**. These results indicate that the primary alkoxide **12** generated undergoes a facile cyclocondensation with the Boc protecting group (Scheme 4.)

To circumvent this problem, we used Seebach et al.'s transesterification protocol.[45] Thus, transesterification of acetate **9** to the corresponding primary alcohol and methyl acetate was carried out using a MeOH−DBU−LiBr system. Then, subsequent TEMPO-catalyzed oxidation of the primary alcohol with sodium hypochlorite[46−48] gave the desired carboxylic acid, which was methylated with diazomethane to afford dimethyl pipecolinoglutamate **10** in 92% yield (for 3 steps). Finally, **10** was refluxed with 6 N hydrochloric acid, followed by a treatment with propylene oxide to give (2*S*,3*R*)-3-pipecolinoglutamic acid (**1**) (Scheme 3). Thus, the efficient first synthesis of homokainoid **1** was achieved in 7 steps from Garner's aldehyde **4** in 55% overall yield. The enantiomer of **1** (i.e., (2*R*,3*S*)-3-pipecolinoglutamic acid (*ent*-**1**)) was synthesized through the same procedure, but starting from *S*-serine.

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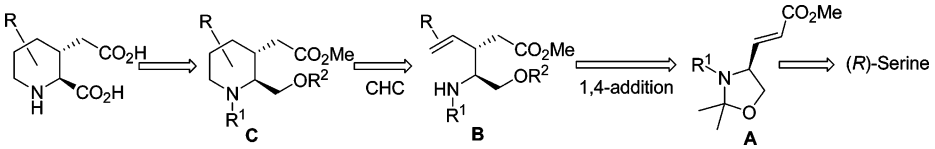
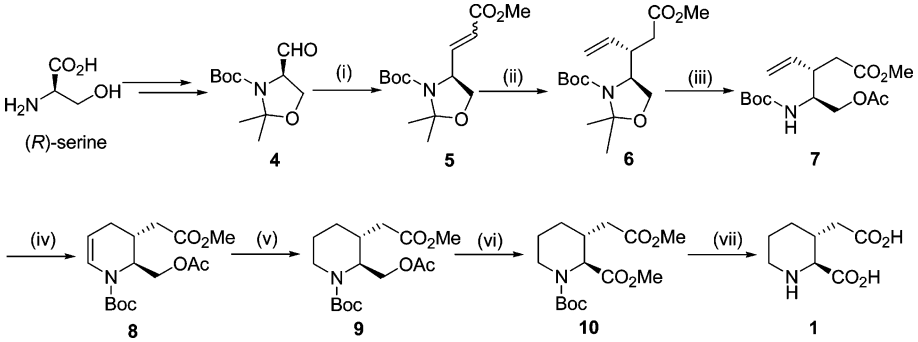
SCHEME 2. Retrosynthetic Pathway for Construction of Pipecolinoglutamic Acids

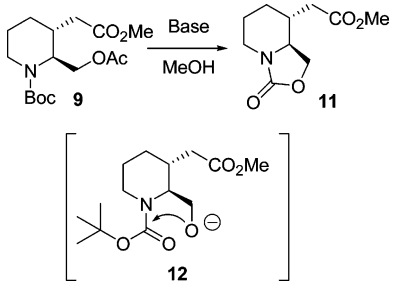


SCHEME 3. Synthetic Route to Pipecolinoglutamic Acid (1)[a]

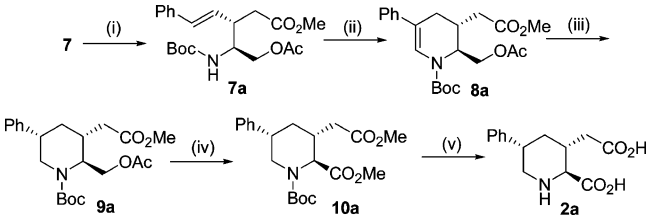


[a] (i) $(MeO)_2POCH_2CO_2Me$, TBAI, K_2CO_3, rt (93%); (ii) $LiCu(CH{=}CH_2)_2$, TMSCl, Et_2O, −78 °C to rt (88%); (iii) (a) PTSA, MeOH, rt and (b) excess Ac_2O-pyridine (94%); (iv) $Rh(acac)(CO)_2$ (0.25 mol %), BIPHEPHOS (0.50 mol %), toluene, H_2 (2 atm), CO (2 atm), 75 °C (99%); (v) 5% Rh-C, H_2 (10 atm), MeOH, rt (95%); (vi) (a) DBU, LiBr, MeOH, rt; (b) TEMPO, KBr, NaOCl, acetone-$NaHCO_3$(aq), 4 °C; and (c) CH_2N_2, MeOH (92%); and (vii) (a) HCl(aq), reflux and (b) EtOH-propylene oxide (83%).

SCHEME 4



SCHEME 5[a]

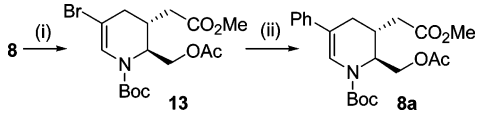


[a] (i) $Pd(OAc)_2$ (5 mol %), PPh_3 (10 mol %), Et_3N (3.0 equiv), PhI (1.2 equiv), DMF, 75 °C, 4 days (83%); (ii) $Rh(acac)(CO)_2$ (2 mol %), $P(OPh)_3$, (8 mol %), CO (60 atm), H_2 (60 atm), 75 °C, toluene, 3 days (96%); (iii) $Pd(OH)_2$/C (5 mol %), H_2, MeOH, rt (88%); (iv) (a) DBU, LiBr, MeOH, rt; (b) TEMPO, KBr, NaOCl, acetone-$NaHCO_3$(aq), 4 °C; and (c) CH_2N_2, MeOH (87%); and (v) (a) HCl(aq), reflux and (b) EtOH-propylene oxide (94%).

Building upon the successful synthesis of homokainoid **1**, we moved to the syntheses of C5-substituted analogues **2** as well as C4-substituted analogues **3**, using the cyclohydrocarbonylation in the key step.

Synthesis of (2*S*,3*R*,5*S*)-5-Phenyl-3-pipecolinoglutamic Acid (2a). The synthesis of homokainoid **2a** was achieved using the cyclohydrocarbonylation of homoallylic carbamate **7a** in the key step in a manner similar to the synthesis of homokainoid **1** described above. Scheme 5 illustrates the synthetic route to **2a**. Homoallylic carbamate **7a** was prepared through a Heck reaction of **7** (Scheme 5) with iodobenzene under standard conditions

SCHEME 6[a]



[a] (i) (a) Br_2, CH_2Cl_2, −78 °C and (b) DIPEA, CH_2Cl_2 −78 °C to rt (93%) and (ii) $Pd(dppf)Cl_2$ (3.3 mol %), $PhB(OH)_2$, Tl_2CO_3, DMF, 85 °C, 4 days (65%).

in 83% yield after recrystallization from *n*-heptane. The reaction gave the trans product exclusively. Cyclohydrocarbonylation of **7a** was carried out using a $Rh(acac)(CO)_2$-$P(OPh)_3$ catalyst at 75 °C at 120 atm of CO and H_2 (1:1) in toluene to give didehydropiperidine **8a** in 96% isolated yield. Thus, the result indicates that the hydroformylation step was extremely regioselective. It is worth mentioning that, in this reaction, the use of unmodified $Rh_4(CO)_{12}$ gave **8a** in 80% yield under the same conditions, while the reaction using the $Rh(acac)(CO)_2$-BIPHEPHOS catalyst was so sluggish that it required more than 1 week to reach an appreciable conversion. Thus, the classical $Rh(acac)(CO)_2$-$P(OPh)_3$ catalyst gave the best results so far.

An alternative route to didehydropiperidine **8a** was also studied, which included regioselective bromination of **8**, followed by Suzuki coupling (Scheme 6). Reaction of didehydropiperidine **8** with bromine at −78 °C followed by the addition of Hünig's base gave 5-bromo-5,6-didehydropiperidine **13** in 93% yield.[49] Suzuki coupling of **13** with phenylboronic acid catalyzed by $Pd(dppf)Cl_2$ afforded 5-phenyldidehydropiperidine **8a** in 65% yield. It should be noted that cyclic vinyl bromide **13** serves as a versatile intermediate for the synthesis of various C5-substituted pipecolinoglutamic acids (i.e., homokainoids) through Pd-catalyzed coupling reactions.[50,51]

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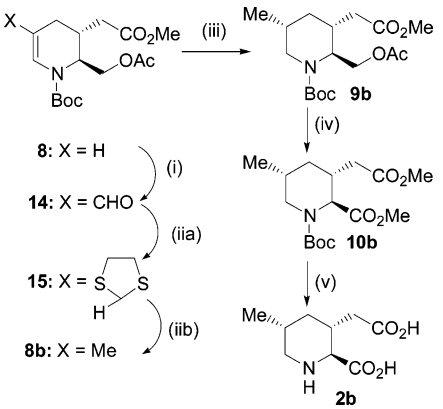
SCHEME 7 [a]



[a] (i) (a) DMF (6 equiv), $POCl_3$ (6 equiv), $ClCH_2CH_2Cl$, rt and (b) NaOAc(aq) reflux (83%); (ii) (a) $HSCH_2CH_2SH$ (1.1 equiv), PTSA (10 mol %), $CHCl_3$, rt and (b) Raney-Ni H_2 (50 atm), MeOH, rt; (iii) 10% Pd-C (5 mol %), H_2 (10 atm), MeOH/AcOH (30:1), rt (68%); (iv) (a) DBU, LiBr, MeOH, rt; (b) TEMPO, KBr, NaOCl, acetone-$NaHCO_3$(aq), 4 °C; and (c) CH_2N_2, MeOH (82%); and (v) (a) HCl(aq), reflux and (b) EtOH-propylene oxide (91%).

Hydrogenation of **8a** over $Pd(OH)_2/C$ at ambient temperature and pressure of hydrogen proceeded with extremely high diastereoselectivity to give (5*S*)-phenylpiperidine **9a** as a single diasteromer (Scheme 5). As the hydrogenation catalyst, $Pd(OH)_2/C$ was found to be the most active catalyst among Pd/C, $Pd(OH)_2/C$, Rh/C, and Pt/C. The S configuration at the C5-position of **9a** was assigned unambiguously based on the clear ROESY (rotational nuclear Overhauser effect spectroscopy) correlation between H-3 and H-5. In addition, the large $^1H-^1H$ coupling constants ($^3J_{4,5}$ = 10.0 Hz and $^3J_{3,4}$ = 10.0 Hz) observed for H-3(β)/H-4(α) and H-4(α)/H-5(β) indicate trans diaxial arrangement between these hydrogens, which is consistent with the ROESY result.

The synthesis of (2*S*,3*R*,5*S*)-5-phenyl-3-pipecolinoglutamic acid (**2a**) was completed using the same protocol as that described for the synthesis of homokainoid **1** via fully protected phenylpipecolinoglutamic acid **10a**, in 82% from **9a**. The overall yield from **7** was 57% in 5 steps.

Synthesis of (2*S*,3*R*,5*R*)-5-Methyl-3-pipecolinoglutamic Acid (2b). For the introduction of a methyl group to the C-5-position of pipecolinoglutamic acid, a few methods can be easily envisioned (e.g., cyclohydrocarbonylation of ω-methyl-**7**, methylation of **13**, Vilsmeier reaction followed by reduction of the resulting aldehyde, etc.). However, the regioselectivity in the cyclohydrocarbonylation approach (i.e., hydroformylation in the first step) is anticipated to be difficult to control because the substrate is essentially an internal alkene without a critical stereoelectronic factor for favorable regioselectivity. The cross-coupling of **13** with methylating agents lacks a reliable method. Accordingly, we chose the Vilsmeyer−reduction approach. The Vilsmeier−Haack reaction of 5,6-didehydropiperidine was reported to give 5-formyl-5,6-didehydropiperidine.[52] Scheme 7 illustrates the synthesis of homokainoid **2b** from **8**.

Reaction of didehydropiperidine **8** with Vilsmeier reagents (6 equiv) at room temperature, followed by treatment with sodium acetate under reflux, gave 5-formyldidehydropiperidine **14** in 83% yield. The formyl group of **14** was converted to the corresponding 1,3-dithiolane with 1,2-ethanedithiol in the presence of PTSA (10 mol %)[53] to give **15**. Subsequent desulfurization of crude **15** with Raney-Ni under 50 atm of hydrogen afforded a 3:1 mixture of 5-methyldidehydropiperidine **8b** and 5-methylpiperidine **9b**. After removal of the Raney-Ni catalyst, the hydrogenation of the mixture of **8b** and **9b** was carried out over Pd/C in MeOH/AcOH (30:1) to afford 5-methylpiperidine **9b** as a single diastereomer in 68% yield from **14**. Thus, the hydrogenation of the olefinic moiety of **8b** (and possibly **15** for Raney-Ni) over Raney-Ni and Pd/C was extremely diastereoselective as in the case of **8a**. The stereochemistry at the C5-position was unambiguously determined to be R based on the clear ROESY correlation between H-3 and H-5 as well as the large $^1H-^1H$ coupling constants ($^3J_{4,5}$ = 9.0 Hz and $^3J_{3,4}$ = 9.0 Hz) observed for H-3(β)/H-4(α) and H-4(α)/H-5(β), which confirms trans diaxial arrangement for these hydrogens. The extremely high diastereoselectivity observed in the hydrogenation of **8a** and **8b** on heterogeneous $Pd(OH)_2/C$ or Raney-Ni/Pd-C indicates that there should be a critical difference between the two diastereofaces of the olefin moiety (C5−C6). The molecular dynamics and molecular mechanics calculations using the Chem3D program (MM2) clearly indicate that the C2-CH_2-OAc and C3-CH_2CO_2Me groups are in the axial positions because of the eminent $A^{1,3}$-allylic strain between the *t*-Boc group and the C2-CH_2OAc group. In this 2,3-diaxial conformation, it can be said that the supported metal catalyst surface overwhelmingly prefers the C2-CH_2OAc group over the C3-CH_2CO_2Me group for adsorption based on the observed results. Also, the very hydrophobic and bulky *t*-butyl group is slightly pushed toward the C3-CH_2CO_2Me side face, which may contribute to the observed extremely high diastereoselectivity as well.

The same procedure as that described for the synthesis of **1** was successfully applied to complete the synthesis of (2*S*,3*R*,5*R*)-5-methyl-3-pipecolinoglutamic acid (**2b**) via 1-Boc-5-methylpipecolinoglutamate **10b** in 75% yield from **9b**. The overall yield from **8** was 42% in 5 steps.

Synthesis of 4-Methyl-3-pipecolinoglutamic Acids (3-α and 3-*β*). For the synthesis of homokainoid **3** bearing a methyl group at the C4-position of pipecolinoglutamic acid, we employed cyclohydrocarbonylation of 3-methylhomoallylic carbamate **17** since the regioselectivity of the hydroformylation of this *gem* disubstituted olefin was guaranteed to be exclusive for the formation of the corresponding terminal aldehyde. However, the diastereoselectivity issue at the C4-position needed to wait for experimental results.

Our first challenge was the synthesis of 3-methylhomoallylic carbamate **17** via 3-isopropenyl-4-oxazolidinylpropanoate **16** from oxazolidinylacrylate **5** through conjugate addition of an isopropenylcopper reagent. The attempted preparation of lithium diisopropenyl cuprate failed because the generation of isopropenyl lithium via transmetalation of tetraisopropenyltin[54] with methyllithium was not successful. Accordingly, we tried Lipschutz et al.'s procedure[55] to generate the corresponding higher-order cuprate, which was successful. Thus, lithium

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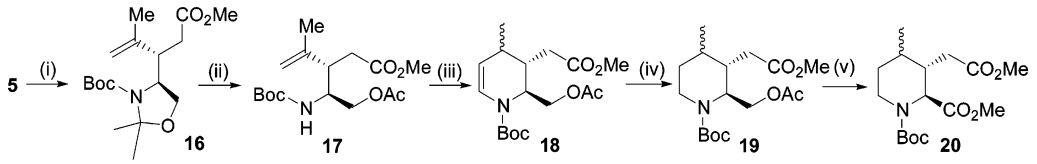
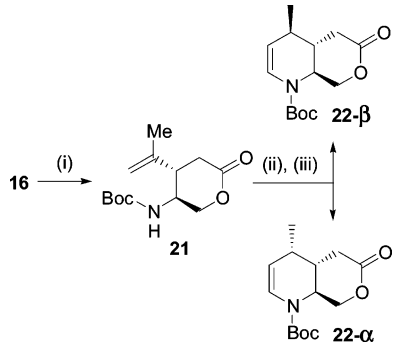
SCHEME 8 [a]



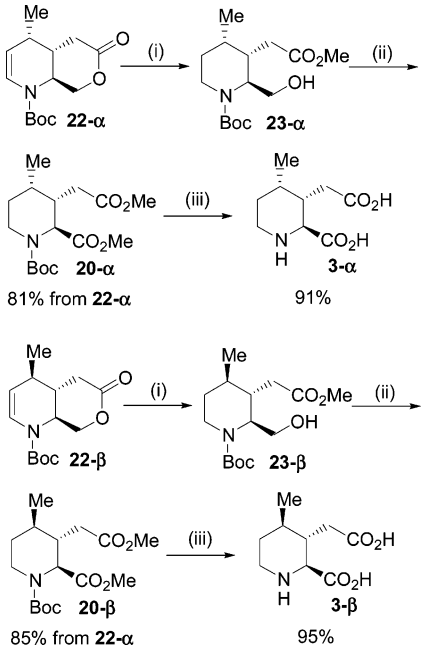
[a] (i) $Li_2CuCN(CMe{=}CH_2)_2$, THF, −78 °C to rt (91%); (ii) (a) PTSA, MeOH, rt and (b) excess Ac_2O-pyridine (80%); (iii) $Rh(acac)(CO)_2$, CO (60 atm), H_2 (60 atm), toluene, 75 °C, 5 days (85%); (iv) 5% Rh-C, H_2 (10 atm), MeOH, rt (99%); (v) (a) DBU, LiBr, MeOH, rt; (b) TEMPO, KBr, NaOCl, acetone-$NaHCO_3$(aq), 4 °C; and (c)CH_2N_2, MeOH (84%).

SCHEME 9 [a]



[a] (i) (a) PTSA, MeOH, rt and (b) PTSA, Dean−Stark (87%); (ii) $Rh(acac)(CO)_2$ (5 mol %), BIPHEPHOS (10 mol %), CO (60 atm), H_2 (60 atm), 75 °C, toluene, 2 days (quantitative); and (iii) chromatographic separation: **22-**α, 44% and **22-***β*, 46%.

SCHEME 10 [a]



[a] (i) 5% Rh-C, H_2 (10 atm), MeOH, rt; (ii) (a) TEMPO, KBr, NaOCl, acetone-$NaHCO_3$ (aq), 4 °C and (b) CH_2N_2, MeOH; and (iii) (a) 6 N HCl, reflux and (b) EtOH, propylene oxide.

diisopropenylcyanocuprate, $(H_2C{=}CMe)_2CuCNLi_2$, was prepared by reacting tetraisopropenyltin with freshly prepared $Me_2CuCNLi_2$. Subsequent conjugate addition of this higher-order cuprate to **5** proceeded smoothly to give the syn adduct **16** exclusively in 91% yield (Scheme 8). Then, the hydrolysis−acetylation protocol used for the conversion of **6** to **7** (Scheme 3) was employed to give 3-methylhomoallylic carbamate **17** in 80% yield (Scheme 8).

Cyclohydrocarbonylation of **17** was carried out using a Rh catalyst (2 mol %) at 75 °C and 120 atm of CO and H_2 (1:1) for 5 days to give 4-methyldidehydropiperidine **18** in 78−85% yield as a ca. 2:1 mixture of two epimers at C4: $Rh(acac)(CO)_2$-BIPHEPHOS (78%, 2.1:1), $Rh(acac)(CO)_2$ (85%, 2:1), and $RhCl(PPh_3)_3$ (85%, 2.3:1). Subsequent transformations, the same as those used for the synthesis of other homokainoids described above, afforded 1-Boc-4-methylpipecolinoglutamate **20** in 83% overall yield from **18** (Scheme 8). However, the two C4 epimers of **18**−**20** were, unfortunately, inseparable by column chromatography on silica gel (for the ^1H and ^{13}C NMR spectra of **18**−**20**, see the Supporting Information). Thus, this route was abandoned.

We thought that either improvement of the diastereoselectivity of the hydroformylation step or separation of two diastereomers might be possible by rigidifying the substrate for cyclohydrocarbonylation. Accordingly, *δ*-lactone **21** was prepared by deprotection and intramolecular lactonization of **16** under acidic conditions (Scheme 9). Cyclohydrocarbonylation of 4-isopropenyl-5-Boc-amino-*δ*-lactone **21** catalyzed by $Rh(acac)(CO)_2$-BIPHEPHOS at 75 °C and 120 atm of CO and H_2 (1:1) gave bicyclic didehydropipecolinolactone **23** in nearly quantitative yield as a ca. 1:1 mixture of two diastereomers. The lack of diastereoselectivity in this CHC reaction can be attributed to the fact that the isopropenyl group of **23** can still freely rotate, and the reaction was run under high pressure of CO, which would disfavor a possible chelation control, involving *N*-Boc, Rh, and the olefin moiety. Gratifyingly, we were able to separate the two diastereomers of **22** by flash chromatography on silica gel, although almost no diastereoselectivity was observed. The 1-D difference NOE NMR analyses of these two diastereomers have revealed that the less polar diastereomer **22-***β* (R_f 0.66, EtOAc/*n*-hexane = 1:3 to 1:1, 46% yield) has an S configuration at C4 (i.e., the methyl group is *β* and equatorial), while the more polar diastereomer **22-**α (R_f 0.62, EtOAc/*n*-hexane = 1:3 to 1:1, 44% yield) has an axial (α) methyl group at C4 (i.e., R configuration at C-4) (Scheme 9).

Hydrogenation of **22-**α and **22-*β*** over Rh/C in methanol at ambient temperature and pressure of hydrogen gave the corresponding ring-opened 4-methylpiperidines bearing a hydroxy ester moiety, **23-**α and **23-*β***, respectively. Subsequent oxidation−methylation of **23-**α and **23-*β*** afforded 1-Boc-4-methylpipecolinoglutamates **20-**α (81% from **22-**α) and **20-*β*** (85% from **22-*β***), respectively. The ROESY analyses of **20-**α and **20-*β*** between the H3 hydrogen and the C4 methyl group confirmed the integrity of the stereochemistry at C4 (i.e., no change from **22-**α and **22-*β***). Finally, deprotection of **20-**α and **20-*β*** gave **3-**α and **3-*β*** in 91 and 95% yields, respectively (Scheme 10).

In summary, we have successfully synthesized six enantiopure novel homokainoids, **1**, *ent*-**1**, **2a**, **2b**, **3-**α, and **3-*β***, from

Garner's aldehydes, featuring the highly diastereoselective conjugate addition of alkenylcuprates to acrylate **5** and the Rh-catalyzed CHC of homoallylic *N*-*t*-Boc-amines **7**, **7a**, and **17**. For the introduction of a 5-phenyl group, we also used 5-bromo-5,6-didehydropiperidine **13** and Suzuki coupling besides the CHC of **7a**. The 5-methyl group was introduced through Vilsmeier reaction of 5,6-didehydropiperidine **8**, giving the corresponding aldehyde **14**, followed by reduction. The hydrogenation of **8a** and **8b** proceeded with complete diastereoselectivity to give only a single diastereomer in both cases. The introduction of a 4-methyl group was carried out through CHC of homomethacryl amine **21** to give **22**, followed by separation of two diastereomers and subsequent transformations. Further studies on the applications of CHC reactions as well as the biological evaluation of those homokainoids are actively underway.

Experimental Section

General Materials and Methods. See Supporting Information.

Synthesis of (2*S*,3*R*)-1-*t*-Butoxycarbonyl-2-acetoxymethyl-3-methoxycarbonylmethyl-5,6-didehydropiperidine (8) through Cyclohydrocarbonylation. In a 5 mL round-bottomed flask, Rh(acac)$(CO)_2$ (1.9 mg, 7.3 μmol, 0.25 mol %) and BIPHEPHOS (11.6 mg, 0.0148 mmol, 0.5 mol %) were dissolved in toluene (1 mL) under nitrogen. The resulting catalyst solution was degassed by the freeze−thaw procedure at least three times. Methyl (3*S*,4*S*)-5-acetyloxy-4-*t*-butoxycarbonylamino-3-ethenylpentanoate (**7**) (938 mg, 2.95 mmol) was placed in a 100 mL flask. The catalyst solution was transferred to the reaction flask containing **7** by a pipette, and then the total volume was adjusted to 50 mL. The reaction flask was placed in a 300 mL stainless steel autoclave. The autoclave was pressurized with CO (2 atm) followed by H_2 (2 atm). The reaction mixture was stirred at 75 °C for 20−24 h. The reaction was monitored by TLC using EtOAc/*n*-hexane (1:3) as eluant (R_f: 0.58 for the starting material and 0.74 for enecarbamate **8**). Upon completion of the reaction, the reaction mixture was concentrated under reduced pressure to give the residue. The residue was purified by flash chromatography on silica gel, using EtOAc/*n*-hexane as eluant to give the title product **8** (961 mg, 99% yield) as a colorless oil: $[\alpha]^{20}_D$ −40.4° (*c* 1.98, $CHCl_3$) [for its enantiomer (*ent*-**8**) from L-serine: $[\alpha]^{20}_D$ +38.0° (*c* 2.05, $CHCl_3$)]; IR (dry film) ν_{max} (cm^{-1}): 2976, 1740, 1706, 1651, 1367, 1232, 1170, 862; ^{1}H NMR (400 MHz, 70 °C, C_6D_6, δ): 1.39 (s, 9H, $(CH_3)_3C$-O-), 1.52−1.63 (m, 1H, H-4), 1.71 (s, 3H, CH_3CO-), 1.98−2.05 (m, 1H, H-4), 2.07−2.18 (m, 2H at C-8), 2.37 (brs, 1H, H-3), 3.35 (s, 3H, $-CO_2CH_3$), 3.88−4.14 (m, 2H, H-7), 4.33−4.68 (m, 2H, H-2 and H-5), 6.60−7.12 (br, 1H, H-6); ^{13}C NMR (100 MHz, 70 °C, C_6D_6, δ): 20.8 (CH_3CO-), 23.6 (C-4), 28.6 ($(CH_3)_3C$-), 28.9 (C-3), 37.5 (C-8), 51.4 −($-CO_2CH_3$), 53.4 (C-2), 63.3 (C-7), 81.1 ($(CH_3)_3C$-O-), 102.3 (C-5), 124.6 (C-6), 153.0 (O-*C*O−N-), 170.3 (CH_3CO-), 172.6 (C-9). HRMS-FAB (*m*/*z*): $[M + H]^+$ calcd for $C_{16}H_{25}NO_6 \cdot H^+$, 328.1761; found, 328.1766 (Δ: 1.5 ppm).

(2*S*,3*R*)-3-Hydroxycarbonylmethylpipecolinic Acid (1). A solution of the dimethyl ester **10** (394 mg, 1.25 mmol) in hydrochloric acid solution (6 N, 35 mL) was stirred under reflux for 1 h and then concentrated under reduced pressure to give the residue. Reflux of the crude product in EtOH (15 mL) and propylene oxide (3 mL) gave a white precipitate. Filtration followed by washing with cold ether afforded the title product **1** as a white solid (167 mg, 83% yield): mp 164−169 °C; $[\alpha]_D^{20}$ +17.9° (*c* 0.84, H_2O) [for its enatiomer (*ent*-**1**) from L-serine: $[\alpha]_D^{20}$ −16.2° (*c* 1.42, H_2O)]; IR (KBr disc) ν_{max} (cm^{-1}): 3100 to ∼2500 −(-COOH), 1712, 1612, 1396, 1364, 1318; ^{1}H NMR (400 MHz, 25 °C, D_2O, δ): 1.45 (dq, *J* = 3.6, 12.4 Hz, 1H, axial H-4), 1.77 (tq, *J* = 4.4, 13.2 Hz, 1H, axial H-5), 1.89−2.05 (m, 2H, equatorial H-4 and H-5), 2.18−2.28 (m, 1H, H-3), 2.43 (dd, *J* = 16.4, 7.6 Hz, 1H, H-8), 2.73 (dd, *J* = 16.4, 5.2 Hz, 1H, H-8), 3.01 (dt, *J* = 3.6, 12.8 Hz, 1H, axial H-6), 3.42 (d, *J* = 10.4 Hz, 2H, H-2 and equatorial H-6); ^{13}C NMR (100 MHz, 25 °C, D_2O, δ): 21.5 (C-4), 28.3 (C-5), 33.9 (C-3), 37.6 (C-8), 43.4 (C-6), 63.3 (C-2), 173.1 (C-7), 176.3 (C-9). HRMS-FAB (*m*/*z*): $[M + H]^+$ calcd for $C_8H_{13}NO_4 \cdot H^+$, 188.0924; found, 188.0921 (Δ: 1.6 ppm).

(2*S*,3*R*)-1-*t*-Butoxycarbonyl-2-acetoxymethyl-3-methoxycarbonylmethyl-5-phenyl-5,6-didehydropiperidine (8a). Cyclohydrocarbonylation Route. To a toluene solution (1 mL) of Rh(acac)$(CO)_2$ (1.3 mg, 5.1 μmol, 2 mol %) was added freshly distilled triphenylphosphite (5.5 μL, 0.021 mmol, 8 mol %) under nitrogen. The resulting catalyst solution was degassed by the freeze−thaw procedure at least three times. Methyl (3*S*,4*S*)-5-acetyloxy-4-*t*-butoxycarbonylamino-3-[2-(*E*)-phenylethenyl]pentanoate (**7a**) (101 mg, 0.258 mmol) was placed in a 25 mL flask. The catalyst solution was transferred to the reaction flask containing **7a** by a pipette, and then the total volume was adjusted to 5.2 mL. The reaction flask was placed in a 300 mL stainless steel autoclave. The autoclave was pressurized with CO (60 atm) followed by H_2 (60 atm). The reaction mixture was stirred at 75 °C for 3 days. The reaction was monitored by TLC using EtOAc/*n*-hexane as the eluant. Upon completion of the reaction, the reaction mixture was concentrated under reduced pressure to give the residue. The residue was purified by flash chromatography on silica gel, using EtOAc/*n*-hexane as the eluant to give the product **8a** (104 mg, 96% yield) as a colorless oil: $[\alpha]^{20}_D$ −66.2° (*c* 1.54, $CHCl_3$); IR (dry film) ν_{max} (cm^{-1}): 3022, 2976, 1742, 1704, 1644, 1391, 1369, 1250, 1163; ^{1}H NMR (400 MHz, 70 °C, C_6D_6, δ): 1.43 (s, 9H, $(CH_3)_3C$-O-), 1.73 (s, 3H, CH_3CO-), 2.09−2.25 (m, 3H, equatorial H-4, 2H at C-8), 2.42 (dd, *J* = 13.2, 5.6, 1H, axial H-4), 2.51−2.61 (m, 1H, H-3), 3.35 (s, 3H, $-CO_2CH_3$), 4.05 (brs, 2H at C-7), 4.54 (brs, 1H, H-2), 7.02−7.25 (m, 5H, $-C_6H_5$), 7.52 (brs, 1H, H-6); ^{13}C NMR (100 MHz, 70 °C, C_6D_6, δ): 20.7 (CH_3CO-), 26.4 (C-4), 28.6 ($(CH_3)_3C$-), 29.3 (C-3), 37.4 (C-8), 51.4 −($-CO_2CH_3$), 53.2 (C-2), 63.7 (C-7), 81.5 ($(CH_3)_3C$-O-), 114.2 (C-5), 122.0 (C-6), 125.3 (C_6H_5), 126.9 (C_6H_5), 129.1 (C_6H_5), 140.8 (ipso at C_6H_5), 153.2 (O-*C*O−-N-), 170.2 (CH_3CO-), 172.5 (C-9). HRMS-FAB (*m*/*z*): HRMS-FAB (*m*/*z*): $[M + H]^+$ calcd for $C_{22}H_{29}NO_6 \cdot H^+$, 404.2075; found, 404.2062 (Δ: 3.2 ppm).

Cross-Coupling Route. In a 25 mL flask with a magnetic stirring bar under nitrogen, to a DMF solution (4.5 mL) of bromide **13** (151 mg, 0.372 mmol, 1.0 equiv) was added Tl_2CO_3 (345 mg, 0.736 mmol, 2.0 equiv), phenylboronic acid (68 mg, 0.558 mmol, 1.5 equiv), and Pd(dppf)Cl_2 (10.0 mg, 0.012 mmol, 3.3 mol %). The resulting mixture was stirred at 85 °C for 4 days. The reaction was monitored by LC-MS. When the reaction was complete, the reaction mixture was partitioned with water (20 mL) and ether (30 mL). The aqueous layer was extracted with ether (15 mL × 2). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, and then concentrated under reduced pressure to give the crude product. Purification of the crude product **8a** by flash chromatography on silica gel using EtOAc/*n*-hexane as eluant afforded the product **8a** as a colorless oil (98 mg, 65% yield). All of the NMR data were identical to those of the product from the cyclohydrocarbonylation route.

(2*S*,3*R*,5*S*)-5-Phenyl-3-hydroxycarbonylmethylpipecolinic Acid (2a). The same procedure for the synthesis of **1** was employed to yield **2a** from **10a** as a white solid (77 mg, 94% yield): mp 171−176 °C; $[\alpha]^{20}_D$ +34.3° (*c* 0.35, H_2O); IR (KBr disc) ν_{max} (cm^{-1}): 3400−2500 −(-COOH), 1724, 1629, 1496, 1400, 756, 700; ^{1}H NMR (500 MHz, 25 °C, D_2O, δ): 1.56 (q, *J* = 12.0 Hz, 1H, axial H-4), 1.87−1.97 (m, 1H, equatorial H-4), 2.21−2.32 (m, 1H, H-3), 2.32 (dd, *J* = 16.0, 7.5 Hz, 1H, H-8), 2.67 (dd, *J* = 16.0, 4.5 Hz, 1H, H-8), 2.99 (t, *J* = 12.5 Hz, 1H, axial H-6), 3.00−3.08 (m, 1H, H-5), 3.33−3.38 (m, 1H, equatorial H-6), 3.37 (d, *J* = 11.5 Hz, 1H, H-2), 7.18−7.32 (m, 5H, C_6H_5-); ^{13}C NMR (100 MHz, 25 °C, D_2O, δ): 34.2 (C-3), 36.0 (C-4), 37.5 (C-8), 39.0 (C-5), 47.8 (C-6), 63.0 (C-2), 127.3 (ortho at C_6H_5), 127.9 (para at C_6H_5), 129.2 (meta at C_6H_5), 140.5 (ipso at C_6H_5), 172.9 (C-7), 176.0 (C-9).

HRMS-FAB (*m*/*z*): $[M + H]^+$ calcd for $C_{14}H_{17}NO_4 \cdot H^+$, 264.1236; found, 264.1238 (Δ: 0.9 ppm).

(2*S*,3*R*,5*R*)-5-Methyl-3-hydroxycarbonylmethylpipecolinic Acid (2b). The same procedure for the synthesis of **1** was employed to yield **2b** from **10b** as a white solid (133 mg, 91% yield): mp 168−174 °C; $[\alpha]^{20}_D$ +19.1° (*c* 1.41, H_2O); IR (KBr disc) ν_{max} (cm^{-1}): 3500−2500 −(-COOH), 1721, 1628, 1461, 1395; ^1H NMR (500 MHz, 25 °C, D_2O, δ): 0.98 (d, *J* = 6.5 Hz, 3H, -C*H*$_3$ at C-5), 1.16 (quartet, *J* = 13.0 Hz, 1H, axial H-4), 1.92−2.06 (m, 2H, equatorial H-4 and H-5), 2.18−2.28 (m, 1H, H-3), 2.40 (dd, *J* = 16.0, 8.0 Hz, 1H, H-8), 2.66 (t, *J* = 12.0 Hz, 1H, axial H-6), 2.74 (dd, *J* = 16.0, 5.0 Hz, 1H, H-8), 3.33−3.38 (m, 1H, equatorial H-6), 3.34 (d, *J* = 11.5 Hz, 1H, H-2); ^{13}C NMR (125 MHz, 25 °C, D_2O, δ): 20.1 (*C*H$_3$ at C-5), 30.6 (C-5), 36.5 (C-3), 39.6 (C-4), 40.2 (C-8), 51.5 (C-6), 65.6 (C-2), 175.6 (C-7), 178.9 (C-9). HRMS-FAB (*m*/*z*): $[M + H]^+$ calcd for $C_9H_{15}NO_4 \cdot H^+$, 202.1079; found, 202.1069 (Δ: 4.9 ppm).

(1*S*,6*S*)-2-Aza-2-*t*-butoxycarbonyl-5-methyl-8-oxo-9-oxabicyclo-[4.4.0]dec-3-ene (22-α, 22-β). In a 5 mL round-bottomed flask, $Rh(acac)(CO)_2$ (13.0 mg, 0.05 mmol, 5 mol %) and BIPHEPHOS (79.0 mg, 0.10 mmol, 10 mol %) were dissolved in toluene (2 mL) under nitrogen. The resulting catalyst solution was degassed by the freeze−thaw procedure at least three times. (4*S*,5*S*)-5-*t*-Butoxycarbonylamino-4-(1-methylethenyl)tetrahydropyran-2-one (**22**) (255 mg, 1.00 mmol) was placed in a 50 mL flask. The catalyst solution was transferred to the reaction flask containing **22** by a pipette, and then the total volume was adjusted to 50 mL. The reaction flask was placed in a 300 mL stainless steel autoclave. The autoclave was pressurized with CO (60 atm) followed by H_2 (60 atm). The reaction mixture was stirred at 75 °C for 48 h. The reaction mixture was concentrated under reduced pressure to give a residue. Purification of the residue by flash chromatography on silica gel, using EtOAc/*n*-hexane as the eluant, afforded the product as white solid: R_f 0.66 for **22-β** (122 mg, 46%) and R_f 0.62 for **22-α** (116 mg, 44%).

(1*S*,5*S*,6*S*)-2-Aza-2-*t*-butoxycarbonyl-5-methyl-8-oxo-9-oxabicyclo[4.4.0]dec-3-ene (22-β). mp 129−131 °C; $[\alpha]^{20}_D$ −361.6° (*c* 0.73, $CHCl_3$); IR (KBr disc) ν_{max} (cm^{-1}): 2973, 2932, 1736, 1711, 1654, 1360, 1167, 1129, 1078, 958; ^1H NMR (500 MHz, 25 °C, $CDCl_3$, δ): 1.01 (d, *J* = 7.0 Hz, 3H, C*H*$_3$ at C-5), 1.48 (s, 9H, (C*H*$_3$)$_3$C-O-), 1.74 (dddd, *J* = 12.5, 11.0, 11.0, 5.0 Hz, 1H, H-6), 1.96 (dqd, *J* = 10.0, 7.5, 2.5 Hz, 1H, H-5), 2.22 (dd, *J* = 18.0, 13.0 Hz, 1H, axial H-7), 2.98 (dd, *J* = 18.0, 5.0 Hz, 1H, equatorial H-7), 3.64 (ddd, *J* = 11.5, 10.0, 4.5 Hz, 1H, H-1), 3.93 (t, *J* = 10.0 Hz, 1H, axial H-10), 4.70 (dd, *J* = 8.0, 1.5 Hz, 1H, H-4), 5.32 (dd, *J* = 11.0, 4.5 Hz, 1H, equatorial H-10), 6.64 (dd, *J* = 8.5, 2.5 Hz, 1H, H-3); ^{13}C NMR (100 MHz, 25 °C, $CDCl_3$, δ): 18.0 (*C*H$_3$ at C-5), 28.4 ((*C*H$_3$)$_3$C-), 31.5 (C-5), 34.8 (C-7), 41.6 (C-6), 53.1 (C-1), 72.2 (C-10), 82.4 ((CH$_3$)$_3$*C*-O-), 112.3 (C-4), 126.0 (C-3), 153.0 (O-*C*O−-N-), 169.3 (C-8); HRMS-FAB (*m*/*z*): $[M + H]^+$ calcd for $C_{14}H_{21}NO_4 \cdot H^+$, 268.1549; found, 268.1549 (Δ: 0.1 ppm).

(1*S*,5*R*,6*S*)-2-Aza-2-*t*-butoxycarbonyl-5-methyl-8-oxo-9-oxabicyclo[4.4.0]dec-3-ene (22-α). $[\alpha]^{20}_D$ −190° (*c* 0.2, $CHCl_3$); IR (dry film) ν_{max} (cm^{-1}): 2970, 1746, 1705, 1656, 1356, 1167, 1128, 1078, 958; ^1H NMR (500 MHz, 25 °C, $CDCl_3$, δ): 0.90 (d, *J* = 7.5 Hz, 3H, C*H*$_3$ at C-5), 1.46 (s, 9H, (C*H*$_3$)$_3$C−-O-), 2.15 (quintet doublet, *J* = 7.0, 4.0 Hz, 1H, H-5), 2.23 (dddd, *J* = 13.5, 12.0, 4.5, 4.5 Hz, 1H, H-6), 2.40 (dd, *J* = 17.5, 13.5 Hz, 1H, axial H-7), 2.59 (dd, *J* = 17.5, 4.5 Hz, 1H, equatorial H-7), 3.73 (ddd, *J* = 11.5, 10.0, 5.5 Hz, 1H, H-1), 3.94 (t, *J* = 10.0 Hz, 1H, axial H-10), 5.09 (t, *J* = 7.5 Hz, 1H, H-4), 5.30 (brs, 1H, equatorial H-10), 6.63 (d, *J* = 8.0 Hz, 1H, H-3); ^{13}C NMR (100 MHz, 25 °C, $CDCl_3$, δ): 14.6 (*C*H$_3$ at C-5), 28.3 (C-5), 28.4 ((*C*H$_3$)$_3$C-), 33.8 (C-7), 37.2 (C-6), 48.6 (C-1), 72.5 (C-10), 82.3 ((CH$_3$)$_3$*C*-O-), 111.9 (C-4), 125.4 (C-3), 152.9 (O-*C*O−-N-), 169.8 (C-8); HRMS-FAB (*m*/*z*): $[M + H]^+$ calcd for $C_{14}H_{21}NO_4 \cdot H^+$, 268.1549; found, 268.1547 (Δ: 0.7 ppm).

(2*S*,3*S*,4*R*)-4-Methyl-3-hydroxycarbonylmethylpipecolinic Acid (3-β). The same procedure for the synthesis of **1** was employed to yield **3-β** from **22-β** as a white solid (62 mg, 0.308 mmol, 95% yield): mp 152−158 °C; $[\alpha]^{20}_D$ −10.0° (*c* 0.1, H_2O); IR (KBr disc) ν_{max} (cm^{-1}): 3500−2400 −(-COOH), 1721, 1621, 1397, 1203, 1135, 1046, 934; ^1H NMR (500 MHz, 25 °C, D_2O, δ): 1.04 (d, *J* = 6.5 Hz, 3H, C*H*$_3$ at C-4), 1.54 (qd, *J* = 12.0, 4.0 Hz, 1H, axial H-5), 1.73 (tq, *J* = 7.0, 11.0 Hz, 1H, H-4), 1.91 (tt, *J* = 11.0, 5.0 Hz, 1H, H-3), 1.94−1.97 (m, 1H, equatorial H-5), 2.67 (dd, *J* = 17.0, 4.0 Hz, 1H, H-8), 2.76 (dd, *J* = 17.0, 5.5 Hz, 1H, H-8), 3.07 (td, *J* = 13.0, 3.0 Hz, 1H, axial H-6), 3.43 (ddd, *J* = 13.0, 4.0, 2.0 Hz, 1H, equatorial H-6), 3.59 (d, *J* = 11.0 Hz, 1H, H-2); ^{13}C NMR (100 MHz, 25 °C, D_2O, δ): 18.5 (*C*H$_3$ at C-4), 30.2 (C-5), 33.1 (C-4), 34.1 (C-8), 39.9 (C-3), 43.1 (C-6), 62.9 (C-2), 173.1 (C-7), 176.4 (C-9). HRMS-FAB (*m*/*z*): $[M + H]^+$ calcd for $C_9H_{15}NO_4 \cdot H^+$, 202.1079; found, 202.1070 (Δ: 4.6 ppm).

(2*S*,3*S*,4*S*)-4-Methyl-3-hydroxycarbonylmethylpipecolinic Acid (3-α). The same procedure for the synthesis of **1** was employed to yield **3-α** from **22-α** as a white solid (30 mg, 91% yield): mp 160−165 °C; $[\alpha]^{20}_D$ +11.3° (*c* 2.40, H_2O); IR (KBr disc) ν_{max} (cm^{-1}): 3500−2400 −(-COOH), 1721, 1627, 1397, 1236, 1102, 1048; ^1H NMR (500 MHz, 25 °C, D_2O, δ): 1.03 (d, *J* = 7.5 Hz, 3H, Me at C-4), 1.69−1.74 (m, 1H, H-5), 1.92−1.97 (m, 1H, H-5), 2.12 (brs, 1H, H-3), 2.52 (dd, *J* = 19.0, 10.0 Hz, 1H, H-8), 2.58−2.65 (m, 2H, H-3 and H-8), 3.22−3.33 (m, 2H at C-6), 3.72 (d, *J* = 8.0 Hz, 1H, H-2); ^{13}C NMR (100 MHz, 25 °C, D_2O, δ): 13.1 (*C*H$_3$ at C-4), 27.3 (C-5), 28.7 (C-4), 33.9 (C-8), 36.3 (C-3), 39.5 (C-6), 58.7 (C-2), 173.0 (C-7), 176.4 (C-9); HRMS-FAB (*m*/*z*): $[M + H]^+$ calcd for $C_9H_{15}NO_4 \cdot H^+$, 202.1079; found, 202.1081 (Δ: 0.9 ppm).

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Supporting Information Available: Characterization data for 5−7, 7a, 9, 9a, 9b, 10, 10a, 10b, 13, 14, 17, 18, 21-α, 21-β, and **22** as well as ^1H and ^{13}C NMR spectra of **1**, **2a**, **2b**, **3-α**, **3-β**, **4**, **4a**, **4b**, **5**, **5a**, **5b**, **6**, **6b**, **7**, **7b**, **8**, **13**, **14**, **16**, **17**, **18-α/β**, **19-α/β**, **20-α/β**, **20-α**, **20-β**, **21**, **22-α**, and **22-β**. This material is available free of charge via the Internet at http://pubs.acs.org.

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