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Efficient synthesis of optically active α-substituted glutamate analogs possessing α-hydroxymethyl and α-alkoxymethyl groups

Masanori Kawasaki, Kosuke Namba, Hidekazu Tsujishima, Tetsuro Shinada and Yasufumi Ohfune*

Graduate School of Science, Osaka City University, Sugimoto, Osaka 558-8585, Japan

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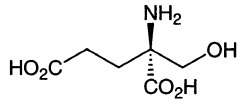
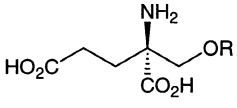
Abstract—Highly enantioselective synthesis of (2*R*)-α-(hydroxymethyl)glutamate (**1**), a selective agonist of mGluR2 and 3, was achieved in short steps using an asymmetric version of the Strecker synthesis. This was converted into its α-methoxymethyl- and α-benzyloxymethyl derivatives **2** and **3**, possible ligands as tools to investigate glutamate receptors, via protection of the sterically hindered amino group by means of phase transfer catalyst. © 2003 Elsevier Science Ltd. All rights reserved.

L-Glutamic acid functions at many synapses in mammalian central nervous systems as an excitatory neurotransmitter and is implicated in the construction of memory and learning as well as in the pathogenesis of neuron damage to cause various neuronal diseases.[1] Glutamate receptors have been classified into two types: ionotropic (iGluRs) and metabotropic (mGluRs) types. The mGluRs are coupled to intracellular second-messenger systems and are sub-divided into the following three groups by the sequence similarity of the protein, transduction mechanisms, and pharmacological profile to agonists and antagonists: group I (mGluR1 and 5), group II (mGluR2 and 3), and Group III (mGluR4 and 6∼8).[2] It has been reported that group I receptors activate PLC resulting in stimulation of PI hydrolysis and inhibition of different types of K^+ ion channels which enhance neuronal toxicity and accelerate neuronal cell death, while the other groups reduce cAMP accumulation resulting in neuroprotecting effect and are closely linked to construction of memory and learning.[2] Several types of agonists and antagonists for the group II receptors have been developed.[3] Representative agonists are L-CCG-I,[4] DCG-IV,[5] and LY-354740[6] whose structures fix the conformation of glutamate to an extended form (*anti–anti* conformation).[5,7] On the other hand, α-substituted CCG-I has shown to exhibit antagonistic action to this group.[3] Recent efforts for the synthesis of α-substituted glutamate analogs have revealed that (2*R*)-α-(hydroxymethyl)glutamate (**1**) acts as a selective agonist of the group II receptors.[8,9] Among these analogs, our attention was focused on the α-hydroxymethyl derivative **1** which is not only a useful ligand for glutamate receptors but also can be viewed as a synthetic precursor common to various types of ether-linked derivatives which enable the preparation of an isotope-labelled or resin-bounded glutamate analog. Described herein are a five-step synthesis of optically active **1** and its conversion to α-(methoxymethyl)- and α-(benzyloxymethyl)-glutamate (**2**) and (**3**) as representative examples of the α-(alkoxymethyl)glutamate analogs.



(2*R*)-α-(hydroxymethyl)glutamic acid (**1**)



2 R = Me
3 R = CH_2Ph

The key to the synthesis is enantioselective construction of the quarternary carbon center of (2*R*)-**1**. Our plan is the use of an asymmetric version of the Strecker synthesis which has proven to be an efficient method for the synthesis of optically active β-hydroxy α,α-disubstituted α-amino acid from the corresponding α-acyloxy ketone (Eq. (1)).[10] According to this method, the stereochemistry of the α-amino nitrile intermediate is controlled by the configuration of the acyloxy amino chiral center,

Keywords: α-substituted glutamate analogs; mGluRs agonist; asymmetric Strecker synthesis; sterically hindered amine; protection; etherification.

* Corresponding author. Fax: 81-6-6605-3153; e-mail: ohfune@sci.osaka-cu.ac.jp

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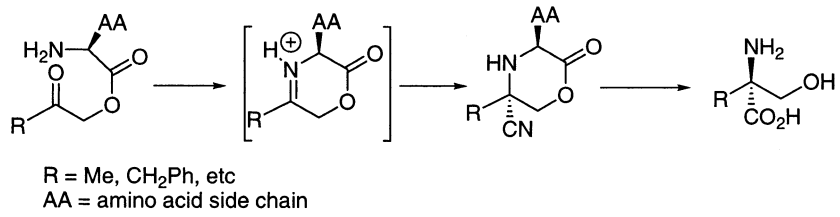


R = Me, CH_2Ph, etc
AA = amino acid side chain

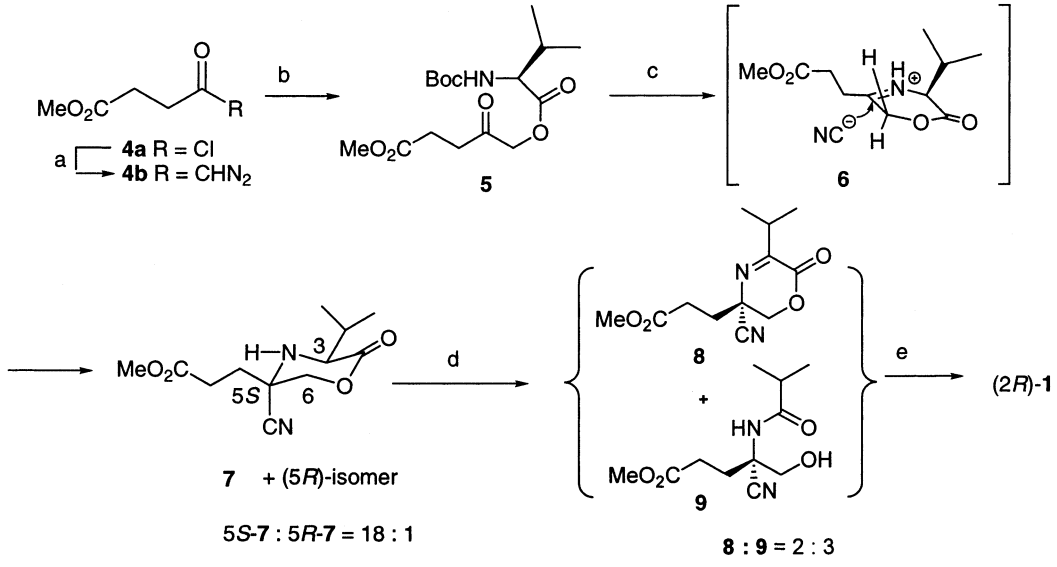
(1)

i.e. the relative configuration of the nitrile group is usually *anti* to that of the amino acid side chain. Accordingly, the use of L-amino acid as the acyloxy group would give rise to the desired (2*R*)-enantiomer **1**.

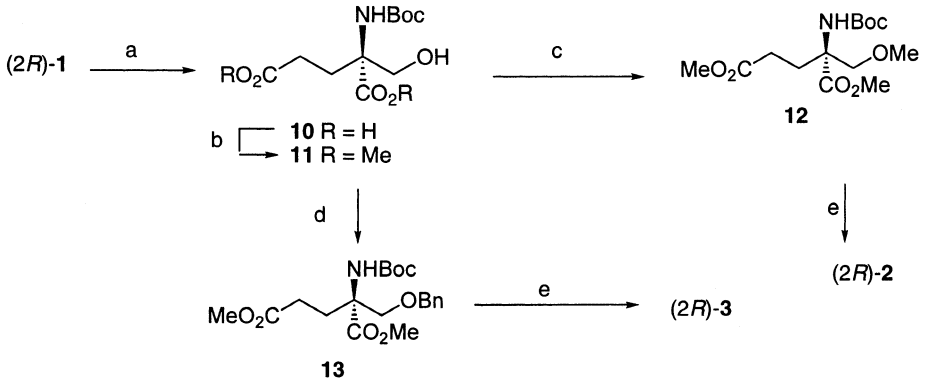
The Strecker precursor **5**, possessing L-valine as the acyloxy group, was prepared from methyl 3-(chlorocarbonyl)propanoate in two steps (Scheme 1): (1) addition of diazomethane and (2) insertion of the resulting diazoketone **4b** to Boc-L-valine using a catalytic amount of $Cu(acac)_2$.[11] After removal of the Boc group with trifluoroacetic acid, the resulting amine–TFA salt was treated with powdered NaCN in 2-PrOH to give crude α-amino nitrile **7** which was composed of a mixture of (5*S*)- and (5*R*)-isomers (18:1) by ^1H NMR spectral analysis.[12] Upon purification using short-pass column chromatography on SiO_2, the minor isomer was completely removed from the mixture to give in 64% yield the pure (5*S*)-**7**.[13] The stereochemical outcome of the reaction was examined by the use of 2-PrOD as the solvent or $Na^{13}CN$. These experiments in combination with the ^1H and ^{13}C NMR data of **7** indicated that (1) no racemization was encountered during the reaction since no D atom was incorporated into the C3 position of **7**, (2) the reaction accompanied certain imine–enamine equilibrium (incorporation of 70% D atom at C6), and (3) the configuration of the product at C5 was assigned to be *S* by the ^1H and ^{13}C NMR data which were consistent with those of the related compounds, in particular, $^3J_{C-H}$ values were 2.1 and 8.9 Hz indicating axial orientation of the nitrile group.[10]

Removal of the chirality transferring group leading to **1** requires oxidation of α-amino nitrile **7** to α-imino nitrile **8** followed by acidic hydrolysis. The classical method was an initial chlorination with *t*-BuOCl and subsequent dechlorination with triethylamine. This method gave **8** in 78% yield. On the other hand, the use of ozone as the oxidant gave a mixture of **8** and α-amide nitrile **9** in 94% yield as previously reported.[14] The mixture was subjected to acidic hydrolysis to give **1** in 98% yield. The sign of the optical rotation and ^1H NMR data of synthetic **1** were identical with those of the reported data.[15]

We turned our attention to introduce an alkyl group onto the α-hydroxymethyl group of **1** where troublesome γ-lactam or δ-lactone formation would compete. Protection of the amino group with a Boc group was



Scheme 1. *Reagents and conditions*: (a) CH_2N_2, 0°C, 5 min, 90%; (b) Boc-L-valine, 0.1 equiv. $Cu(acac)_2$, toluene, rt, 1.5 h, 40%; (c) (i) TFA, CH_2Cl_2, 0°C to rt, 2 h; (ii) 2 equiv. NaCN, 2-PrOH, rt, 18 h, 64%; (d) O_3, AcOEt, −78°C, 30 min, 94%; (e) conc. HCl, 100°C, 15 h, 98%.



Scheme 2. *Reagents and conditions*: (a) Boc_2O, 5.0 equiv. *n*-Bu_4NOH, CH_3CN–H_2O (10:1), rt, 72 h, then, Dowex 50W×4; (b) CH_2N_2, 0°C, 5 min, 57% (two steps); (c) 4.0 equiv. MeOTf, 4.4 equiv. DBMP, CH_2Cl_2, rt, 20 h, 65%; (d) 1.5 equiv. BTCA, 0.2 equiv. TMSOTf, CH_2Cl_2, 0°C, 3.5 h, 38%; (e) (i) 1N NaOH, THF, rt; (ii) TFA, CH_2Cl_2, rt, 89% for **2** and 93% for **3**.

examined first. Under the usual reaction conditions using Boc_2O in the presence of a tertiary amine or NaOH as the base, only 5–27% of the desired *N*-Boc derivative **10** was obtained due probably to steric reasons (Scheme 2). The use of a phase transfer catalyst (tetramethylammonium hydroxide in CH_3CN) commonly used for the protection of a sterically hindered amine[16] formed a white suspension and gave in only 5% yield the protected product due probably to poor solubility of **1** in the solvent. We chose tetrabutylammonium hydroxide as a hydrophobic base to increase solubility of **1**, but the solution, again, formed a white suspension. Finally, it was found that addition of a small amount of H_2O ($CH_3CN/H_2O = 10:1$) formed a homogeneous solution. Using this reaction system, the desired protected compound **11** was obtained after diazomethane treatment in 57% yield. It is noted that hazardous contamination of the ammonium salt in the reaction mixture was easily removed by means of Dowex 50W×4 (H^+ form) prior to CH_2N_2 treatment.[17]

Next, we examined the introduction of a methyl or a benzyl group onto the α-hydroxymethyl group. A combination of MeI or benzyl bromide with NaH, *t*-BuOK, LDA, or LHMDS was not successful and gave δ-lactone as the major product. Since a weak base would prevent undesired δ-lactone formation, a combination of 2,6-di-*tert*-butyl-4-methylpyridine (DBMP)[18] and MeOTf was examined next. The reaction proceeded smoothly to give in 65% yield the desired methyl ether **12**. In the case of the benzyl ether, a combination of benzyltrichloroacetoimidate (BTCA) and TMSOTf[19] was found to be an effective method to give benzyl ether **13**. Hydrolysis of the protected **12** and **13** with 1N NaOH followed by TFA afforded **2** (89%) and **3** (93%), respectively.[20]

In summary, (2*R*)-α-(hydroxymethyl)glutamate (**1**), an agonist of group II mGluRs, was synthesized in short steps in a highly enantioselective manner. Its conversion into two types of α-alkoxymethyl-substituted glutamate analogs **2** and **3** accompanied a useful method for protection of the sterically hindered amine and the introduction of an alkyl group onto the hydroxymethyl group. These results would enable the preparation of useful tools to investigate glutamate receptors. Neuropharmacological characterization of **2** and **3**, and preparation of the resin-connected glutamate through a hydroxymethyl linker are in progress in our laboratories.

Acknowledgements

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12. L-Valine was a superior acyloxy group to other amino acids in the present substrate. The use of L-phenylalanine gave a 10:1 mixture of (5*S*)- and (5*R*)-α-amino nitrile in 60% yield.
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20. Compound **2**: amorphous powder; $[\alpha]_D^{23}$ +27.0 (*c* 1.68, MeOH); ^{1}H NMR (400 MHz, D_2O): δ 3.76 (d, $J=10.5$ Hz, 1 H), 3.56 (d, $J=10.5$ Hz, 1 H), 3.36 (s, 3 H), 2.28–2.24 (m, 2 H), 1.93–2.05 (m, 2 H); ^{13}C NMR (100 MHz, D_2O): δ 179.9, 174.4, 75.4, 65.3, 59.9, 31.4, 29.2. Compound **3**: amorphous powder; $[\alpha]_D^{24}$ −55.0 (*c* 0.70, MeOH); ^{1}H NMR (300 MHz, D_2O): δ 7.20–7.40 (m, 5 H), 4.47 (s, 2 H), 3.72 (d, $J=10.5$ Hz, 1 H), 3.52 (d, $J=10.5$ Hz, 1 H), 2.05–2.25 (m, 2 H), 1.84 (t, $J=7.3$ Hz, 2 H); ^{13}C NMR (75 MHz, D_2O): δ 181.4, 174.6, 162.1, 138.2, 129.2, 74.1, 72.9, 65.5, 32.4, 29.6.