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SYNTHESIS OF L-2-(2,3-DICARBOXYCYCLOPROPYL)GLYCINES. NOVEL CONFORMATIONALLY RESTRICTED GLUTAMATE ANALOGUES.

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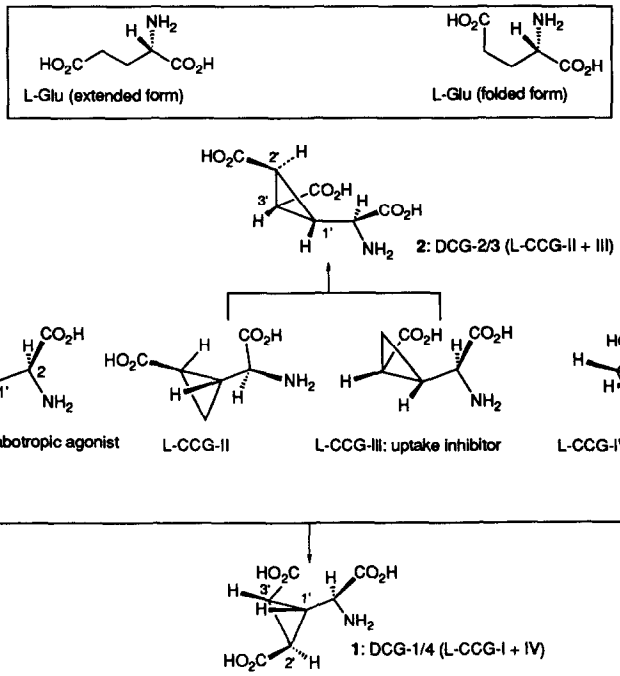
Abstract: New conformationally restricted glutamate agonists **1** and **2** possessing both an extended and a folded conformation of L-glutamate in their structures have been efficiently synthesized in a stereoselective manner. The synthesis of **1** involved a novel α-carbomethoxycyclopropyl anion equilibration.

Excitatory amino acid (EAA) receptors mediate synaptic excitation in the mammalian central nervous system.[1] These receptors have been classified into two major classes, ionotropic glutamate receptors and metabotropic glutamate receptors. The former class is further divided into several subtypes according to their responses to exogeneous EAAs; kainate, N-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA), and L-2-amino-4-phosphonobutyric acid (L-AP4). It is reasonable to assume that each glutamate receptor would be particular about different conformations of L-glulamate, because it is a conformationally flexible molecule. Recently, we reported the syntheses and the pharmacology of L-2-(carboxycyclopropyl)glycines (L-CCG-I~IV), conformationally restricted L-glutamate analogues in which the cyclopropyl group fixes the glutamate chain in either an extended or a folded form.[2-6]

Figure 1



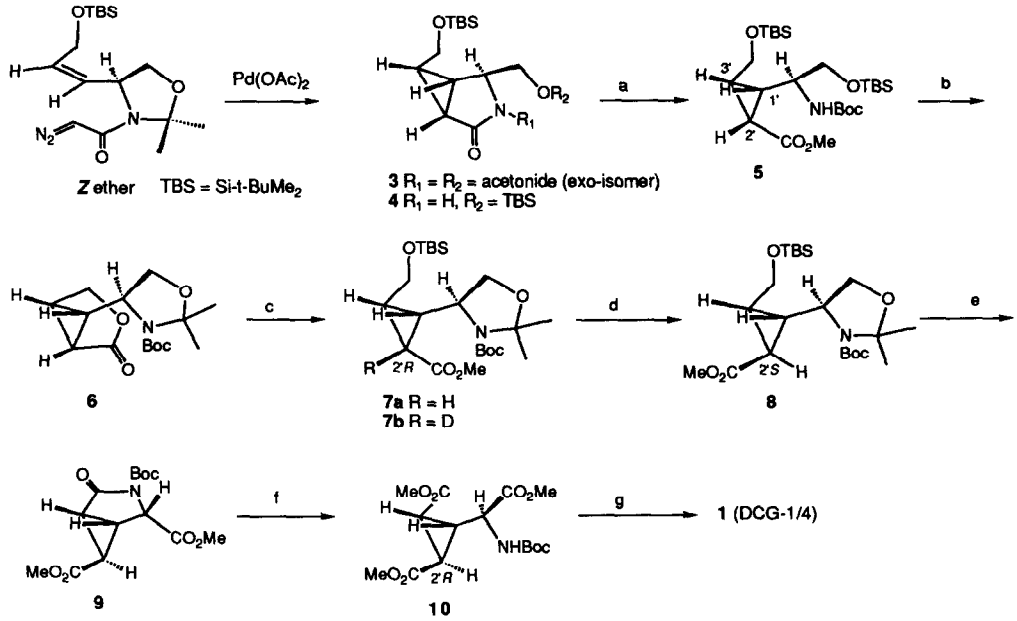
These studies showed that conformation of L-glutamate is one of the most effective factors for activating their receptors; the extended isomer (L-CCG-I) preferentially activated metabotropic glutamate receptors[4] and one of the folded ones (L-CCG-IV) preferentially activated NMDA receptors.[3,6] These experimental results prompted us to design and synthesize new and more effective agonits or antagonists for EAA receptors. In the present paper, we describe two new glutamate analogues which involve novel structural modification of CCGs. They are (2*S*,1'*R*,2'*R*,3'*R*)-**1** (DCG-1/4) and (2*S*,1'*S*,2'*S*,3'*S*)-**2** (DCG-2/3), which are characterized by their structures composed of both an extended and a folded conformer of L-glutamate.

Hybridization of the structures L-CCG-I and IV affords the structure **1**, and the structure of L-CCG-II plus III leads to that of **2** as shown in Figure 1. They have both putative active conformation of L-glutamate in their structures, although their chemical properties are much different from that of L-glutamate because of the presence of tricarboxylate moieties in **1** and **2**.

We started the synthesis of **1** from the cycloadduct **3**, which has been prepared previously by us in a stereoselective fashion from *Z*-unsaturated ether derived from D-serine[5a] (Scheme I). The synthetic route involves a conversion of the C2' ester group of **5** or **7** to the requisite 2'*S* configuration as a key step. Initial attempts using the ester **5** with several bases such as lithium diisopropylamide (LDA) or potassium bis(trimethylsilyl)amide ($KN(TMS)_2$) were unsuccessful and resulted in a complete recovery of the starting material or the formation of γ-lactam **4**, due probably to an anion formation on the amide nitrogen. To avoid this, the amide **5** was converted into its corresponding acetonide derivative **7a** via lactone intermediate **6**. Compound **7a**, upon treatment with $KN(TMS)_2$ in THF followed by acetic acid quench, gave in 84% yield the desired *trans*-isomer **8**, exclusively. We next attempted to incorporate a deuterium atom into C2' of both **7a** and **8**, which would be of importance in view of reaction mechanisms as well as syntheses of radio-isotope labelled derivatives. It has been reported that α-anion in cyclopropanes with electron-withdrawing substituents (CN, ketones, sulfones, etc.) are tetrahedral, and under protic conditions (NaOMe/MeOD) afford the corresponding deuterated products with retention of configuration.[7,8] However, in the case of both **7a** and **8** ($NaOCD_3/CD_3OD$, 60 °C, 5 days) no deuterium atom was incorporated into the strating materials, respectively.[9] This would be due to the lower acidity of the C2'-H of **7a** and **8** compared to that of the other electron-withdrawing substituents.[8] When the reaction of **7a** with $KN(TMS)_2$ was quenched with CD_3CO_2D, deuterium atom was not incorporated into the C2' of the resulting *trans*-isomer **8**. The reaction was found to proceed catalytically even with the use of 0.3 equiv of $KN(TMS)_2$. In aprotic media, an initially formed α-cyclopropyl ester anion might rapidly invert to either a tetrahedral or a planar configuration of the corresponding α-cyclopropyl anion, which is re-protonated by the resulting $HN(TMS)_2$ to give thermodynamically more stable *trans*-isomer **8**. These results suggest, putatively, a formation of planar ester enolate anion, although a lithium tetrahedral α-cyanocyclopropyl anion has been reported.[10]

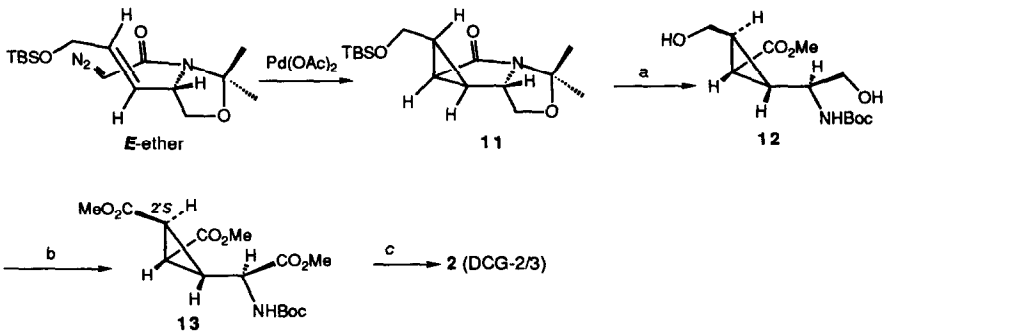
Having the desired *trans*-isomer **8** in hand, this was converted to the γ-lactam **9** using the following sequence of reactions; (1) removal of the acetonide and *tert*-butyldimethylsilyl (TBS) groups with trifluoroacetic acid (TFA) simultaneously, (2) protection of the resulting amino group by the *tert*-butoxycarbonyl group (Boc), (3) Jones oxidation of the primary hydroxyl groups with concomitant γ-lactam formation, and (4) esterification with diazomethane. Treatment of the lactam **9** with a catalytic amount of LiOH in MeOH gave triester **10**. Finally, all the protecting groups were removed with (1) 1*N* NaOH and (2) TFA to give desired **1**: mp 174-176 °C (decomp); $[\alpha]_D$ -20.2° (*c* 0.44, H_2O).[11]

Scheme I.[a] Synthesis of (2*S*,1'*R*,2'*R*,3'*R*)-2-(2,3-dicarboxycyclopropyl)glycine **1**.



[a](a) (1) ref 5a; (b) (1) catalytic CSA, MeOH, room temperature, 5 h; (2) catalytic CSA, 2,2-dimethoxypropane, CH_2Cl_2, reflux, 1.5 h, 81%: (c) 0.5 *N* NaOH, THF/H_2O = 2/1, 0 °C, 16 h; (2) CH_2N_2; (3) TBSCl, imidazole, DMF, 0 °C, 30 min, room temperature, 2 h, 100%: (d) $KN(TMS)_2$ 1 *M* in toluene solution, THF, -78 °C, 30 min, -15 °C, 1.5 h, -78 °C, 10 min, 1.3 equiv of AcOH in THF, 84%: (e) (1) TFA, CH_2Cl_2, 0 °C, 1 h; (2) $(Boc)_2O$, Et_3N, dioxane/H_2O = 1/1, room temperature, 4 h; (3) Jones reagent, 0 °C, 2 h, room temperature, 2 h; (3) CH_2N_2; (f) catalytic LiOH, MeOH, room temperature, 30 min, 66% from **8**: (g) (1) 1 *N* NaOH/THF = 3/5, 0 °C, 2 h, room temperature, 40 h; (2) TFA, CH_2Cl_2, 0 °C, 15 min, room temperature, 45 min; (3) Dowex 50Wx4 (elution with 1 *N* NH_3), ~100% as an ammonium salt.

Scheme II.[a] Synthesis of (2*S*,1'*S*,2'*S*,3'*S*)-2-(2,3-dicarboxycyclopropyl)glycine **2**.



[a](a) (1) 60% AcOH, room temperature, 16 h; (2) $Ba(OH)_2$, EtOH, 80 °C, 16 h; (3) $(Boc)_2O$, Et_3N, room temperature, 6 h; (4) CH_2N_2, 70% from **11**: (b) (1) Jones reagent, 0°C, 1 h, room temperature, 1 h; (2) CH_2N_2, 90%: (c) (1) 1 *N* NaOH, room temperature, 17 h; (2) 3 *N* HCl, room temperature, 16 h; (3) Dowex 50Wx4 (elution with 1 *N* NH_3), ~100% as an ammonium salt.

The synthesis of **2** was carried out in a straightforward manner from the reported cycloadduct **11**, prepared from *E*-unsaturated ether[5a] (Scheme II). Hydrolysis of the lactam ring of **11** with $Ba(OH)_2$/EtOH followed by the protection of the resulting amino acid with the Boc group gave diol **12**, which, upon Jones oxidation and subsequent esterification with diazomethane, gave desired trimethyl ester **13**. This was converted into **2** in the same manner as that of **1**. **2**: Mp 153-157 °C (decomp); $[\alpha]_D$ +74.9° (*c* 0.57, H_2O).[11]

Compound **1** would be expected to be a mixed (non-selective) agonist for both metabotropic and NMDA receptors from its structural features of L-CCG-I and IV.[3,4] Preliminary accounts of electrophysiological experiments in the motoneurone of a new born rat showed that the depolarizing activity of this compound was more potent than that of L-glutamate and less than that of NMDA. The depolarization was due to activation of NMDA receptors and was completely depressed by selective NMDA antagonists, Mg^{2+} and 3-((±)-2-carboxypiperazin-4-yl)-propyl-1-phosphonic acid (CPP). In addition, it was found that this compound significantly depressed the monosynaptic excitation in the new born rat spinal cord in markedly low concentrations without causing postsynaptic depolarization, leading to the expectation of metabotropic effects. The coumpound was about 10 times more potent than L-CCG-I in depressing monosynaptic excitation. (1*S*,3*R*)-1-Aminocyclopentane-1,3-dicarboxylic acid (1*S*,3*R*-ACPD),[12] one of the representative agonists of metabotropic glutamate receptors, and L-AP4[13] also depressed the monosynaptic excitation, but threshold concentration of **1** was significantly lower than that of these compounds. Compound **2** also has similar effects on monosynaptic excitation without causing any postsynaptic depolarization, however its activity was much less than that of **1**. The folded sub-structure of **1** would bind preferentially to NMDA receptors and the extended one to metabotropic glutamate receptors.

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11. ^1H NMR (270 MHz, D_2O) data of **1** and **2.1**: δ1.99 (ddd, 1 H, *J* = 5.9, 9.6, 10.2 Hz), 2.18 (dd, 1 H, *J* = 5.0, 5.9 Hz), 2.32 (dd, 1 H, *J* = 5.0, 9.6 Hz), 3.89 (d, 1 H, *J* =10.2 Hz). **2**: δ 1.98 (ddd, 1 H, *J* = 5.5, 9.0, 10.5 Hz), 2.21 (dd, 1 H, *J* = 5.0, 9.0 Hz), 2.34 (dd, 1 H, *J* = 5.0, 5.5 Hz), 3.93 (d, 1 H, *J* = 10.5 Hz).
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