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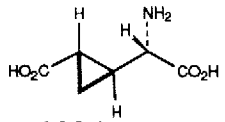
NEW ROUTES TO THE SYNTHESES OF CIS-α-(CARBOXYCYCLOPROPYL)GLYCINES FROM L-GLUTAMIC ACID. CONFORMATIONALLY RESTRICTED ANALOGUES OF THE EXCITATORY NEUROTRANSMITTER L-GLUTAMIC ACID

Keiko Shimamoto and Yasufumi Ohfune*
Suntory Institute for Bioorganic Research, Shimamoto-cho, Mishima-gun, Osaka 618, Japan

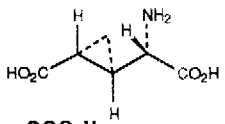
Summary: Potent neuroactive amino acids, (2S,3S,4R) and (2S,3R,4S) isomers of α-(carboxycyclopropyl)glycines (CCG-III and CCG-IV), were synthesized from L-glutamic acid via a palladium(II) catalyzed cyclopropanation of the α,β-unsaturated pyrrolidone and γ-amino-δ-lactone derivatives, respectively.

Recently, the neurobiological actions of L-glutamic acid (L-Glu) are of much interest because of its neurotransmitter action in the mammalian central nervous system and its excitotoxic action which is related to various acute and chronic brain damage.[1] In our previous papers,[2] we described the syntheses of four diastereomers of L-α-(carboxycyclopropyl)glycines (CCG-I~CCG-IV), conformationally restricted analogues of L-Glu, and the structure-activity relationship of these diastereomers in isolated rat spinal cord, suggesting that a specific conformation of L-Glu was required for receptor activation. Furthermore, it was found that the (2S,3R,4S)-isomer (CCG-IV) preferentially activated one of the L-Glu receptor subtypes (N-methyl-D-aspartic acid (NMDA) subtype receptor)[3] more markedly than established agonists. In addition, CCG-III markedly potentiated L-Glu response possibly by an inhibition of L-Glu uptake from the environment of the synapse.[4] Thus, these CCGs are useful tools for the investigation of the mechanism underlying the glutamate function as well as the design of effective therapeutic drugs of various neuronal diseases. In the present paper, we focus on the practical syntheses of these useful amino acids, in particular CCG-III and IV, since the purpose of the previous method was to synthesize all CCG-isomers based on the non-stereoselective method.

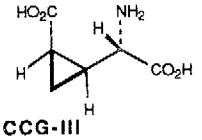
Our approach to these amino acids is a palladium (II) catalyzed cyclopropanation of the α,β-unsaturated lactone **4** and of the lactam **8**. Although 5-hydroxy-4-aminopentanoic acid **2** is a plausible synthetic intermediate for these synthons, the previous synthetic route from L-Glu required multi-step transformations via pyrroglutamic acid.[5] For this problem, we examined an active ester/reduction procedure from commercially available L-glutamic acid half ester **1**. Thus treatment of **1** with HOSu/DCC followed by $NaBH_4$/THF-EtOH yielded the desired alcohol **2** [83%, mp 40.5-41.5 °C, $[\alpha]_D$ -13.2° (*c* 1.0, $CHCl_3$)]. This was subjected to a lactonization with CSA/benzene to give δ-lactone **3** [92%, mp 104-104.5 °C, $[\alpha]_D$ -37.4° (*c* 1.09, $CHCl_3$)] which was converted into its α,β-unsaturated **4** using the Saegusa method[6] [68%, mp 128-129 °C, $[\alpha]_D$ +113° (*c* 1.07, $CHCl_3$)]. For the other diastereomer, treatment of the silyl ether **6**



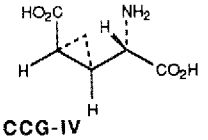
CCG-I



CCG-II

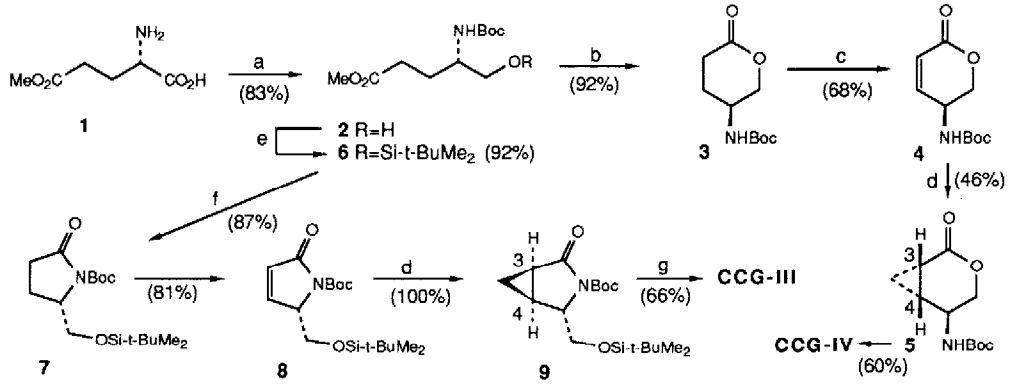


CCG-III



CCG-IV

with NaH provided the pyrrolidone in which the Boc group was cleaved under the reaction conditions. This group was reintroduced with Boc_2O to give **7** [87% from **3**, oil, $[\alpha]_D$ -62.2° (*c* 1.23, $CHCl_3$)]. Unsaturated **8** was prepared using the reported method.[7] Cyclopropanation of **4** and **8** was carried out with CH_2N_2 in the presence of catalytic $Pd(OAc)_2$. From δ-lactone **4**, the (3S,4R)-isomer **5** was produced as the major product (6/1, 46%). This was converted into CCG-IV using reported procedure.[2a] Pyrrolidone **8** gave predominantly (3R,4S)-**9** (9/1, 100%). Conversion of **9** into CCG-III was carried out by the following sequence of reactions: (1) removal of the silyl group, (2) cleavage of the amide bond by methanolysis, (3) oxidation of the primary hydroxyl group, (4) removal of the protecting groups.[2a] Overall yield of CCG-III from **1** was 36% and CCG-IV,14%. Thus, CCG-III and IV were synthesized via unsaturated **8** and **4**, respectively, versatile chiral synthons prepared from L-Glu. Further synthetic and neuropharmacological studies of excitatory amino acid analogues are currently in progress.[8]



(a) (1) Di-*tert*-butyl dicarbonate (Boc_2O), $NaHCO_3$, dioxane/H_2O (1/1); (2) N-hydroxysuccinimide (HOSu), 1,3-dicyclohexylcarbodiimide (DCC), AcOEt; (3) $NaBH_4$, tetrahydrofuran (THF)/EtOH (3/1), 0 °C, 15 min: (b) *dl*-10-camphorsulfonic acid (CSA), benzene, 80 °C, 3 h: (c) (1) 2.2 equiv of Me_3SiCl, 2.2 equiv of $LiN(SiMe_3)_2$, -78 °C, 15 min; (2) 1.2 equiv of $Pd(OAc)_2$, CH_3CN, 20 °C, 45 min. (d) CH_2N_2, catalytic $Pd(OAc)_2$, ether: (e) *t*-$BuMe_2SiCl$, imidazole, DMF: (f) (1) 1 equiv of NaH, ether,16 h; (2) Boc_2O, Et_3N, 4-dimethylaminopyridine (DMAP), THF, 4 h: (g) (1) CSA, MeOH; (2) LiOH, MeOH,14 h; (3) Jones reagent, acetone, 0 °C, 2 h and 20 °C, 2 h; (4) 0.5 N NaOH, 0 °C, 3 h; (5) CF_3CO_2H, CH_2Cl_2, 30 min. **5**→ CCG-IV and **7**→**8**: see, ref 2a and 7.

References and Footnotes

1. For a review, see: H. Shinozaki, *Progress in Neuropharmacol.* **1988**, *30*, 399.
2. (a) K. Yamanoi, Y. Ohfune, K. Watanabe, P. N. Li, and H. Takeuchi, *Tetrahedron Lett.* **1988**, *29*, 1181. (b) H. Shinozaki, M. Ishida, K. Shimamoto, and Y. Ohfune, *Brain Res*, **1989**, *480*, 399.
3. It is suggested that L-glutamate receptors in the mammalian central nervous system are classified into three subtypes according to their different physiological functions by the exogenous amino acids; viz, kainic acid (KA), quisqualic acid (QA), and N-methyl-D-aspartic acid (NMDA) subtypes. J. Davies and J. C. Watkins, *J. Physiol*, **1979**, *297*, 621.
4. Details will be described separately. It is suggested that potentiation of the response to L-Glu closely mimics the neuronal plasticity which are expected to be responsible for the cellular mechanisms of learning and memory in the mammalian brain, see: G. L. Collingridge and T. V. P. Bliss, *Trend in Neuroscience*, **1987**,*10*, 288.
5. R. B. Silverman and M. A. Levy, *J. Org. Chem.* **1980**,*45*, 815.
6. Y. Ito, T. Hirao, and T. Saegusa, *J. Org. Chem.* **1978**,*43*, 1011.
7. Y. Ohfune and M. Tomita, *J. Am. Chem. Soc*, **1982**, *104*, 3511.

8. We thank Dr. H. Shinozaki for his helpful comments and discussions from the physiological point of view in this study. We thank Professor K. Nakanishi, director, for discussions. This work was supported in part by a grant-in-aid from the Ministry of Education, Science and Culture, Japan.

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