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SYNTHESES OF 3'-SUBSTITUTED-2-(CARBOXYCYCLOPROPYL)GLYCINES VIA INTRAMOLECULAR CYCLOPROPANATION. THE FOLDED FORM OF L-GLUTAMATE ACTIVATES THE NON-NMDA RECEPTOR SUBTYPE

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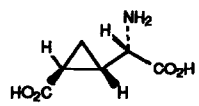
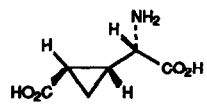
Summary: Four stereoisomers of 3'-methoxymethyl-L-2-(carboxycyclopropyl)glycines, conformationally constrained analogues of L-glutamate, were synthesized in a stereoselective manner from D-serinal derivative. Selective activation of either the NMDA or Non-NMDA receptor by these isomers was observed.

The neurobiological actions of L-glutamic acid (L-Glu) in the mammalian central nervous system have been well documented in view of its excitatory action and its excitotoxic action, and L-Glu is believed to be a neurotransmitter related to memory and early learning.[1] The L-Glu receptor can be classified into the following subtypes: NMDA (N-methyl-D-aspartic acid) and non-NMDA type receptors; the latter is further divided into KA (kainic acid) and QA (quisqualic acid) types.[2] Our recent studies using four stereoisomers of synthetic L-2-(carboxycyclopropyl)glycines (L-CCG-I~IV),[3] which incorporate a conformationally restricted L-Glu moiety in their structures (extended or folded form of L-Glu), have demonstrated that the NMDA receptor is activated by the folded conformer of L-Glu in the rat spinal cord since L-CCG-IV is a potent NMDA-type agonist. However, the conformational role of L-Glu to activate the Non-NMDA receptor remained uncertain: neither the extended nor the folded form of the L-CCG isomers was active as a KA or a QA type agonist.[4,5] On the other hand, L-CCG-III showed novel activity potentiating the L-Glu response, which was putatively explained as uptake inhibition of L-Glu in the synaptic environment.[4] In order to gain further insights into these L-CCG isomers, we designed 3'-substituted analogues of L-CCG-III and IV which can provide information concerning the 3 dimensional circumstances of the receptor where L-Glu adopts a specific conformation. Described herein are the stereoselective syntheses of 3'*R* and 3'*S*-methoxymethyl analogues (*t*-MCG-III **1a** and *c*-MCG-III **1b**, and *t*-MCG-IV **2a** and *c*-MCG-IV **2b**) of both L-CCG-III and IV.[5]


L-CCG-I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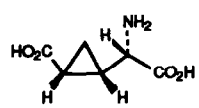
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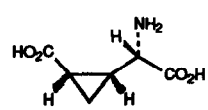
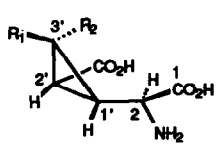
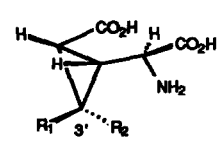

L-CCG-IV


t-MCG-III (1a) R_1=CH_2OMe, R_2=H
c-MCG-III (1b) R_1=H, R_2=CH_2OMe


t-MCG-IV (2a) R_1=CH_2OMe, R_2=H
c-MCG-IV (2b) R_1=H, R_2=CH_2OMe

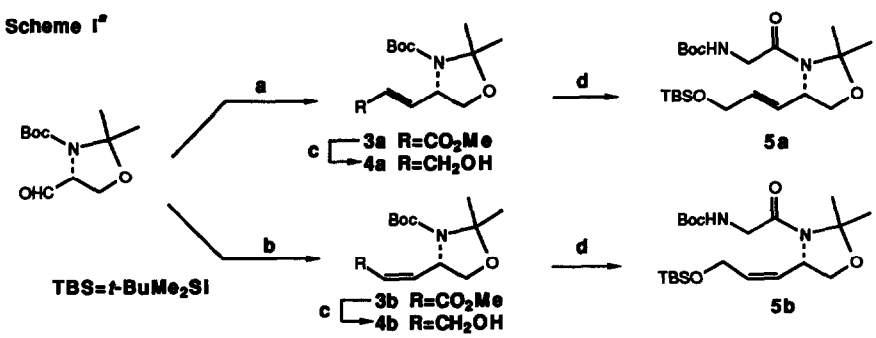
The fact that each receptor subtype is distinguished by the MCG-IV isomers having a different configuration at C-3' is highlighted.

The synthetic plan for the stereoselective introduction of the substituents to the C-3' position is the use of an intramolecular cyclopropanation of the intermediates **5a** and **5b**. (4*R*)-N-Boc-2,2-dimethyl-4-formyl-1,3-oxazolidine[6] was chosen as the starting material, and was converted into the *E* and *Z* unsaturated esters, **3a** and **3b**, using standard procedures, respectively. Although a large amount of saturated alcohol was produced during the reduction of the ester group with $LiAlH_4$ (>80%), iBu_2AlH (>35%), or $iBu_2AlH/BF_3.OEt_2$ (>35%), the use of *ate* complex, $LiAlnBu(iBu)_2H$,[7] provided desired allyl alcohols **4a** and **4b** in excellent yields accompanied by less than 10% of the saturated alcohol. Removal of the protecting groups of **4a** and **4b** under acidic conditions and subsequent coupling with Boc-Gly-OSu followed by protection gave **5a** and **5b**, respectively (Scheme I).

Synthesis of *t*-MCG-III (1a) and *t*-MCG-IV (2a). Prior to cyclopropanation, the Boc group of **5a** was removed chemoselectively by the use of TMSOTf/2,6-lutidine to give the corresponding amine,[8] which upon treatment with $NaNO_2$/citric acid followed by catalytic $Pd(OAc)_2$ gave a mixture of the cyclized products, **6a** (exo-adduct) and **7a** (endo-adduct), in 43% yield (**6a/7a** = 3.3/1). The thermodynamic stability of the transition state structures as depicted in **A** and **B** may reflect the products ratio. Each silyloxymethyl substituent of **6a** and **7a** corresponds to the methoxymethyl group of the target structures, respectively. The silyl group of **6a** was converted to the methyl ether with (1) nBu_4NF and (2) MeI, NaH to give **6b** which upon successive treatments with (1) 60% AcOH, (2) $Ba(OH)_2$, and (3) Boc_2O, furnished glycinol **8**. This was converted into *t*-MCG-III **1a** in two steps, (1) Jones oxidation and (2) TFA. *t*-MCG-IV **2a** was prepared from the endo-isomer **7a** in the same manner as above.

Syntheses of *c*-MCG-III (1b) and *c*-MCG-IV (2b). Intramolecular cycloaddition from the *Z*-isomer **5b** produced the exo-adduct **10a** (61% from **5b**), exclusively. This stereospecificity may be due to a severe steric hindrance in the transition state structure **D** which yields an endo adduct. The

Scheme I[a]

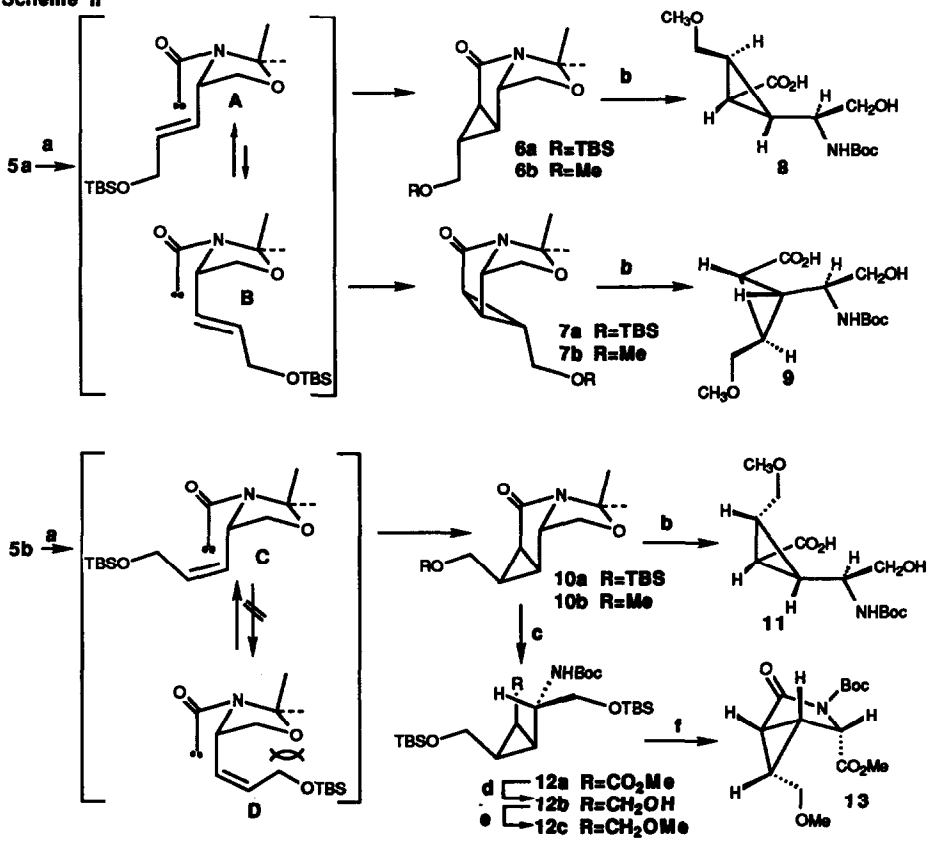


[a](a) Ph_3PCHCO_2Me, benzene, room temperature (95%); (b) $(CF_3CH_2O)_2P(O)CH_2CO_2Me$, NaH, 18-crown-6, -78 °C (85%); (c) iBu_2AlH, *n*BuLi (1/1), toluene, -78 °C, 40 min, 0 °C, 15 min, **4a** (87%) and **4b** (86%); (d) (1) 1 M HCl, MeOH, 0 °C, 16 h; (2) N-*tert*-butoxycarbonylglycine hydroxysuccinimide ester (Boc-Gly-OSu), triethylamine (Et_3N), THF-MeOH (5/1); (3) 2,2-dimethoxypropane-acetone (1/1), *dl*-camphor-10-sulfonic acid (CSA), 60 °C, 2 h, then MeOH, room temperature, 30 min; (4) *tert*-butyldimethylsilyl chloride (TBSCl), imidazole, N,N-dimethylformamide (DMF), room temperature, 3 h, **5a** (63%) and **5b** (71%).

cycloadduct **10a** was converted into *c*-MCG-III **1b** in the same manner as above. Since the amide carbonyl group of **10a** corresponds to the methoxymethyl group of *c*-MCG-IV **2b**, this required initial modification of **10a** to bis-TBS ether **12a** which was carried out in 4 steps: (1) Dowex 50Wx4, MeOH, (2) TBSCl, imidazole, (3) Boc_2O, Et_3N, DMAP, and (4) LiOH, MeOH. The resulting ester group was reduced with iBu_2AlH to give **12b** which upon treatment with $nBuLi/FSO_3Me$ furnished desired methyl ester **12c**. Removal of TBS ether followed by Jones oxidation gave the γ-lactam **13** which was converted into *c*-MCG-IV **2b** in 3 steps: (1) LiOH, MeOH, (2) 1 N NaOH, (3) TFA.[9] Thus, four diastereomeric MCG isomers were prepared in an efficient manner from **5a** and **5b**, respectively.

Among these synthetic analogs, both **1a** and **1b** did not show any potentiating action on the L-Glu

Scheme II[a]



[a](a) (1) Trimethylsilyl trifluoromethanesulfonate (TMSOTf), 2,6-lutidine, CH_2Cl_2, room temperature, 15 min; (2) $NaNO_2$, citric acid, toluene, room temperature, 20 min; (3) 0.05 equiv $Pd(OAc)_2$, toluene, 90 °C, 30 min;**6a** (33%) and **7a** (10%), **10a** (61%); (b) (1) nBu_4NF, THF, 0 °C, 10 min; (2) NaH, MeI, nBu_4NI, room temperature,2 h; **6b** (75%), **7b** (41%), **10b** (77%); (3) 60% AcOH, room temperature, 12 h; (4) $Ba(OH)_2$, EtOH-H_2O (2/1), 80°C,14 h; (5) di-*tert*-butyl dicarbonate (Boc_2O), Et_3N, dioxane, room temperature, 16 h; **8** (73%), **9** (79%), **11** (58%); (c) (1) Dowex 50W x 4, MeOH, room temperature, 14 h; (2) TBSCl, imidazole, DMF, room temperature, 16 h; (3) Boc_2O, Et_3N, 4-dimethylaminopyridine (DMAP), THF, room temperature,16 h, (4) LiOH, MeOH, room temperature, 16 h (45%); (*d*) iBu_2AlH, CH_2Cl_2, -78 °C, 30 min (99%); (*e*) 1 equiv $nBuLi,FSO_3Me$, THF-Et_2O (1/1), -78 °C, 2 h (94%); (f) (1) Dowex 50W x 4, MeOH, room temperature, 18 h; (2) Jones reagent, acetone, 0 °C, 2 h; (3) CH_2N_2, Et_2O (40%).

response unlike L-CCG-III probably because of steric repulsion of the 3'-substituent with the receptor. On the other hand, the depolarizing activity of *t*-MCG-IV **2a** was as potent as that of kainic acid in the rat spinal motoneuron.[10] The depolarizing action induced by **2a** was activation of Non-NMDA type receptor being postulated as the KA type, while that of *c*-MCG-IV **2b** (the activity of this compound was estimated to be ~1/2 of L-CCG-IV) was NMDA type receptor activation.[11,12] These results suggest that (1) activation of the Non-NMDA type receptor requires a folded conformation of L-Glu, (2) the C-3' substituent triggers activation of the Non-NMDA receptors, and (3) the active conformation of the L-Glu at the NMDA receptor may be closely similar to that of **2b** for the reason that the 3'S substituent of MCG-IV constrains the rotation between C1'-C2 bond (large *J* value between 2H and 1'H was observed: J = 11.5 Hz) and that depolarizing activity of **2b** is much greater than that of L-Glu. Thus, these newly designed L-Glu analogues are expected to be useful tools for investigating excitatory amino acid receptors in the mammalian central nervous systems.[13]

References

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4. (a) Shinozaki, H.; Ishida, M.; Shimamoto, K.; Ohfune, Y. *Brain Res.* **1989**,*480*, 355. (b) Shinozaki, H.; Ishida, M.; Shimamoto, K.; Ohfune, Y. *Br. J. Pharmac.* **1989**, *98*, 1213. Depolarizing activity of L-CCG-IV was slightly more potent than kainic aicd and much more potent than L-Glu (>100 times) in the rat spinal cord.
5. The steric repulsion of the space occupied by the cyclopropane ring of CCGs was considered to play a role upon receptor activation, since the depolarizing activity by CCG-IV was more potent than that of L-CCG-III in spite of the fact that both isomers not only have the same folded form but also activate the same NMDA type receptor.[4] Therefore, placement of a substituent at C3' was presumed to show NMDA-like action.
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9. Mp and $[\alpha]_D$ of **1a**, **1b**, **2a**, and **2b**. *t*-MCG-III (**1a**): mp 195-198 °C (decomp); $[\alpha]^{25}_D$ +59.6° (*c* 0.54, H_2O). *c*-MCG-III (**1b**): mp 155.5-156.5 °C; $[\alpha]^{25}_D$ +85.9° (*c* 0.51, H_2O). *t*-MCG-IV (**2a**): mp 185.5-187.0 °C (decomp); $[\alpha]^{25}_D$ +31.5° (*c* 0.47, H_2O). *c*-MCG-IV (**2b**): mp 147-151 °C (decomp); $[\alpha]^{25}_D$ +83.3° (*c* 0.52, H_2O).
10. Details of the neuropharmacological studies will be reported separately.
11. Selective binding of **2a** and **2b** to each receptor was shown by pharmacological studies using several L-Glu antagonists. For NMDA (i) and Non-NMDA (ii) antagonists: (i) Davies, J.; Evans, R. H.; Herrling, P. L.; Jones, A. W.; Olverman, H. J.; Pook, P.; Watkins, J. C. *Brain Res.* **1986**, *382*, 169. (ii) Honore, T.; Davies, S. N.; Drejer, J.; Fletcher, E. J.; Jacobsen, P.; Lodge, D.; Nielsen, F. *Science* **1988**, *241*, 701.
12. 3'*R*-Benzyloxymethyl derivative of *t*-MCG-IV **2a**, synthesized in the same manner as **2a** from **7a**, was found to activate the Non-NMDA receptor. This result supports the idea that the 3'*R* substituent plays a role as a trigger to activate the Non-NMDA receptor.

13. We thank Drs. H. Shinozaki and M. Ishida for the neuropharmacological assay and valuable discussions. We are grateful to Prof. K. Nakanishi, Director, for kind suggestions. This work was supported in part by a grant-in-aid from the Ministry of Education, Science and Culture, Japan.

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