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Synthesis of L-2-(2-Carboxy-4-methylenecyclopentyl)glycines (CPGs). Novel Conformationally Restricted Glutamate Analogues

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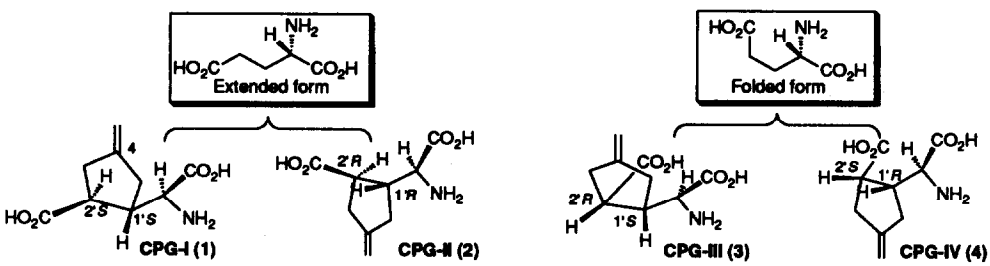
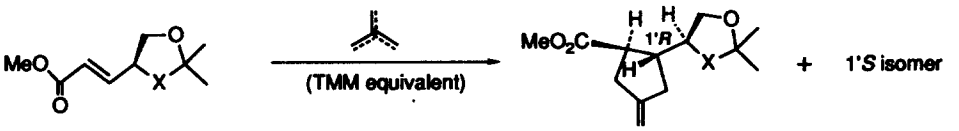
Abstracts: Three diastereomers **1**, **2**, and **4** of a new glutamate analogue incorporating a 5-membered ring were synthesized in a stereocontrolled manner. 1'*R*-Isomers **2** and **4** were constructed from the α,β-unsaturated 2,2,2-trifluoroethyl esters **5b** and **10b** by a [3+2] cycloaddition with a Pd-trimethylenemethane (TMM) complex. The 1'*S* isomer **1** was synthesized by a 1,4-addition of TMM equivalent to the α,β-unsaturated methyl ester **10a**. The folded isomer **4** was characterized electrophysiologically to be a potent agonist of kainate receptors in the mammalian central nervous systems.

Recently, we demonstrated the syntheses and pharmacological profile of L-2-(carboxycyclopropyl)-glycines (CCGs), which restrict the conformation of the excitatory neurotransmitter, L-glutamate, in either an extended or a folded form.[1-3] These analogues can be viewed as useful probes not only for the elucidation of conformational requirements of L-glutamate receptors but also for the neuroscience research. In conjunction with the previous studies, we planned to develop new glutamate agonists, L-2-(2-carboxy-4-methylenecyclo-pentyl)glycines (CPG-I~IV, **1-4**), which were expected to add further informations as to the conformational requirements of glutamate receptors.[1c] In the CPGs, the ring strain and the angle strain that characterize the CCG's structure are minimized, and the exomethylene group allows for further structural modifications. We wish to describe the stereoselective syntheses of (2*S*,1'*S*,2'*S*)-**1** (CPG-I), (2*S*,1'*R*,2'*R*)-**2** (CPG-II), and (2*S*,1'*R*,2'*S*)-**4** (CPG-IV). Preliminary accounts of neuropharmacological actions of synthetic CPGs are briefly disclosed.



Our synthetic plan for these compounds was to construct a 5-membered ring onto the known *E*- and *Z*-α,β-unsaturated esters **5** and **10**. 1,4-Addition or [2+3] cycloaddition of trimethylenemethane (TMM)[4] to the esters **5** and **10** was envisaged to induce stereocontrol, either *S* or *R* configuration, at the C1' (eq 1). Our initial attempt was the synthesis of 1'*R* isomer **2** via a palladium-catalyzed cycloaddition of 2-[(trimethyl-silyl)methyl]-2-propen-1-yl acetate (TMMOAc) to the *E*-ester **5a**.



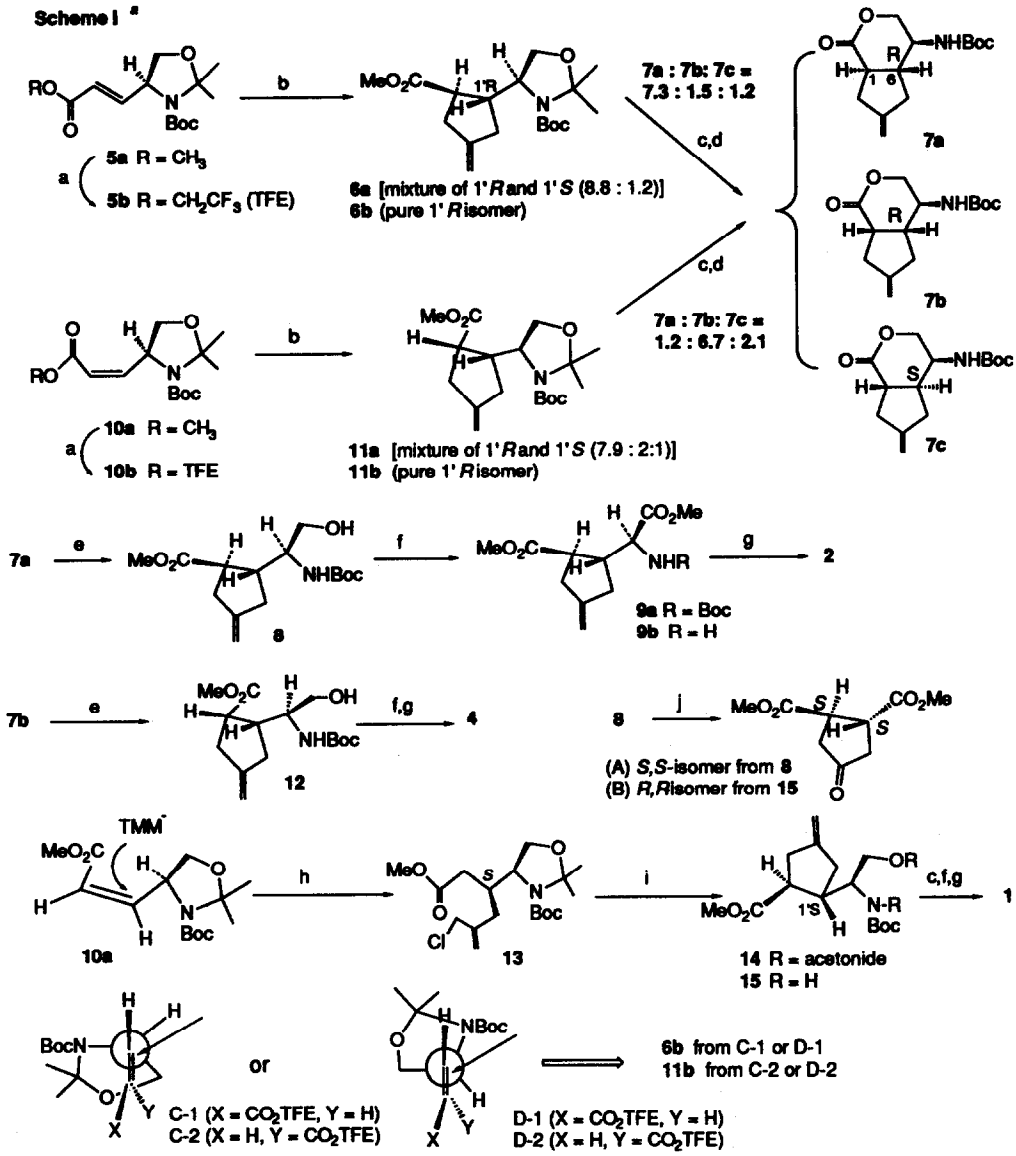
X = NBoc, *E* or *Z*-ester (**5a** or **10a**) ⟶ X = NBoc, 1'*R* : 1'*S* = ? (eq 1)
X = O, *E*-ester ⟶ X = O, 1'*R* : 1'*S* = 7 : 3 (eq 2)

It has been reported that the related ester produces 1'*R*-isomer as the major product (1'*R*/1'*S* = 7 : 3, eq 2).[5] However, the cycloaddition of **5a** was not successful resulting mainly in the recovery of starting **5a** probably due to poor reactivity of the C-C double bond and/or the presence of a sterically bulky group at the allylic position. Our next attempt was the conversion of the methyl ester group to the electronegative 2,2,2-trifluoroethyl (TFE) ester group (**5a**→**5b**) since reactivity of the conjugate ester moiety could be enhanced with the TFE group. The reaction using **5b** underwent smoothly to give a chromatographically inseparable mixture of cycloadducts **6a**, which were composed of the 1'*R* and 1'*S* cycloadducts in 8.8 : 1.2 ratio (79%)[6] and were separated by converting them into a mixture of δ-lactones **7a**-**7c**.[7] Methanolysis of the major isomer **7a** in the presence of a catalytic amount of K_2CO_3 gave the diastereomerically pure alcohol **8**, whose 1'*R*,2'*R* stereochemistry was confirmed by converting it to the diester (A) which was identical in all respects (optical rotation and spectroscopic data) with those of known (A): $[\alpha]_D$ -123° ($CHCl_3$); lit.[8] $[\alpha]_D$-119° ($CHCl_3$). The alcohol **8** was then transformed into the *N*-protected diester **9a**. Removal of the Boc group of **9a** under the acidic conditions (trifluoroacetic acid or 2 *N* HCl) was accompanied by a hydroxylation to the exomethylene group or a migration of the C-C double bond from exo to endo. Therefore, the Boc group was removed using trimethylsilyl trifluoromethanesulfonate (TMSOTf)[9] in the presence of 2,6-lutidine to give **9b**, exclusively, which was then converted to **2**: mp 220 °C (decomp); $[\alpha]_D$ -46.4° (*c* 0.47, 2 *N* HCl).[10]

For the synthesis of the folded-isomer **4** having 1'*R* stereochemistry which mimics the folded glutamate conformation, we examined a Pd-catalyzed cycloaddition of the *Z*-unsaturated ester **10a** with TMMOAc. The cycloaddition to the methyl ester **10a** was not successful, but the reaction with the TFE ester **10b** proceeded smoothly to give an inseparable mixture of cycloadducts **11a**, which were separated by converting them to the δ-lactones **7a**-**7c** in the same manner as above.[7] The major product was **7b** whose 1'*R* configuration was ascertained as follows. After conversion of **7b** to the *N*,*O*-acetonide **11b** by treatment of **12** with 2,2-dimethoxypropane and catalytic CSA, **11b** was subjected to epimerization at C2' using $KN(TMS)_2$ yielding **6b** exclusively which was identical in all respects with the trans-adduct **6b** derived from the *E*-ester **5b**. The alcohol **12** was then converted to CPG-IV (**4**) in the same manner as above: mp 178-182 °C (decomp); $[\alpha]_D$ -19° (*c* 0.42, 2 *N* HCl).[10]

The treatment of the *E*-ester **5a** or the *Z*-ester **10a** with 2-chloromethyl-3-trimethylsilyl-1-propene (TMMCl)/CsF, 18-crown-6 gave a Micheal adduct. In particular, with the *Z*-ester **10a**, only the 1'*S* isomer **13** was obtained (25%, 50% of starting **10a** was recovered), whereas the *E*-ester **5a** gave a 1:1 mixture of the 1'*R* and 1'*S* adducts.[11] The observed stereoselectivity could be explained by the attack of the active TMM species from the sterically less hindered *Si*-face of the relatively rigid conformation of the *Z*-ester **10a** as shown in Scheme I. Intramolecular alkylation of **13** with $LiN(TMS)_2$ gave the single cyclized product **14** whose 1'*S*,2'*R* stereochemistry was confirmed by converting it to the diester (B), which showed an opposite sign of optical rotation with that of reported (A): $[\alpha]_D$ +115° ($CHCl_3$).[8] Finally, the cycloadduct **14** was transformed into L-CPG-I (**1**) in the same manner as above: mp 205 °C (decomp); $[\alpha]_D$ +93° (*c* 0.45, 2 *N* HCl).[10]

Scheme I [a]



[a](a) (1) 0.5 *N* NaOH, MeOH, room temperature, 16 h; (2) 2,2,2-trifluoroethanol, 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (WSC), CH_2Cl_2, 0 °C, 1 h, room temperature, 16 h; **5b**, 75%; **10b**, 75%: (b) (1) 0.05 equiv $Pd(OAc)_2$, 2-[(trimethylsilyl)methyl]-2-propene-1-yl acetate, $(iPrO)_3P$, toluene, 110 °C, 12 h; (2) cat K_2CO_3, MeOH, room temperature, 1 h; **6a**, 81%; **11a**, 55%; (c) CSA, MeOH, room temperature, 24 h; (d) (1) 0.5 *N* NaOH, MeOH, room temperature, 16 h; (2) WSC, CH_2Cl_2, 0 °C, 1 h, room temperature, 16 h; **7a**, 53%; **7b**, 9%; **7c**, 11% (from **6a**); **7a**, 9%; **7b**, 62%; **7c**, 16% (from **11a**); (e) K_2CO_3, MeOH, room temperature, 2 h; **8**, 94%; **12**, 94%; (f) (1) pyridinium dichromate (PDC), DMF, room temperature, 16 h; (2) CH_2N_2; **9a**, 70%; (g) (1) trimethylsilyl trifluoromethanesulfonate (TMSOTf), 2,6-lutidine, room temperature, 16h, then MeOH; (2) 0.5 *N* NaOH, 0 °C, 1 h, room temperature, 16 h; (3) Dowex 50 W x 4 (H^+ form, elution with 1 *N* NH_3); (h) 2-chloromethyl-3-trimethylsilyl-1-propene (TMMCl), 0.3 equiv of CsF, 0.2 equiv 18-crown-6, 40 °C, 16 h, 25% (50% recovery of starting **10a**); (i) $LiN(SiMe_3)_3$, THF, -78 °C, 15 min, 0 °C, 1 h, 74%; (j) (1) TMSOTf, 2,6-lutidine, room temperature, 16h, then MeOH; (2) aqueous $NaIO_4$, SiO_2, CH_2Cl_2, room temperature, 10 min; (3) PDC, DMF, room temperature, 16 h, then CH_2N_2; (4) O_3, MeOH, -78 °C, then $(CH_3)_2S$, 0 °C.

Thus, complementary methods for introducing a substituent with either *S* or *R* configuration into the β-postion of the α,β-unsaturated esters **5** and **10**, were demonstrated which led to the successful syntheses of 3 diastereomers of CPGs (**1**, **2** and **4**), although one of the folded-type CPG-III (**3**) was remained unsynthesized.

Electrophysiological experiments of **1**, **2** and **4** in the new born rat spinal motoneurons suggested that CPG-IV (**4**) was a potent agonist of kainate receptors,[12,13] one of the representative ionotropic glutamate receptor subtypes.[14] Its activity was almost equipotent with kainate and was much more potent than L-glutamate in the C-fibre. The other isomers showed less activity than L-glutamate in the above preparations. It is noteworthy that the activity of the dihydro-derivative of **4** was much less than **4** (~1/50). The exo methylene group of **4** appeared to be esssential to activate kainate receptors as the same way as the C-C double bond of kainic acid is required for its activity.[15]

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References and Notes

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6. The stereoselective formation of the 1'*R* isomer might be attributed to an attack of Pd-TMM complex to the C-C double bond in either Felkin-Anh type (C) or sterically and stereoelectronically more favoured conformer (D), although both C and D give the same product[5] (Scheme I).
7. The 6*R*-cis lactone **7b** by-produced from the *E*-ester **5b**, and the 6*R*-trans-lactone **7a** from **10b** would be partially epimerized products under the lactionization stage.
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10. ^{1}H NMR (270 MHz, D_2O) data for **1**, **2**, and **4**. **1**: δ 4.75 (s, 2 H), 3.70 (d, 1 H, J = 6 Hz), 2.90 (m, 1 H), 2.65 (m, 1 H), 2.55-2.35 (m, 3 H), 2.10 (m, 1 H). **2**: δ 4.85 (br s, 2 H), 3.78 (d, 1 H, J = 6 Hz), 3.00 (m, 1 H), 2.80-2.10 (m, 5 H). **4**: δ 4.95 (br s, 2 H), 3.92 (d, 1 H, J = 9 Hz), 3.30-2.30 (m, 6 H).
11. For a cuprate addition to the related compound of **5a**, where *R* isomer was the exclusive micheal adduct, see: Yoda, H.; Shirai, T.; Katagiri, T.; Takabe, K.; Kimata, K.; Hosoya, K. *Chem. Lett.* **1990**, 2037.
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13. For a recent publication concerning kainate receptors, see: Ishida, M.; Shinozaki, H. *Br. J. Pharmacol.* **1991**, *104*, 873 and references are cited therein. For an example of kainate receptor agonist having non-kainoid skeleton, see: (a) Shimamoto, K.; Ohfune, Y. *Tetrahedron Lett.* **1990**, *31*, 4049. (b) Ishida, M.; Ohfune, Y.; Shimada, Y.; Shimamoto, K.; Shinozaki, H. *Brain Res.* **1991**, *550*, 152.
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