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Photocycloaddition of α,β-Unsaturated-γ-lactam with Ethylene. Synthesis of Conformationally Restricted Glutamate Analogs, L-2-(2-Carboxycyclobutyl)glycines

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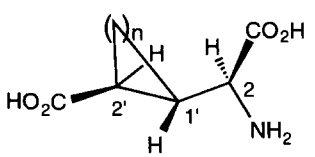
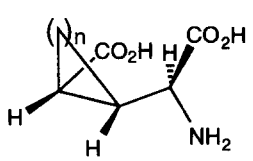
Abstract: Both (2*S*,1'*S*,2'*S*)- and (2*S*,1'*S*,2'*R*)-isomers of 2-(2-carboxycyclobutyl)glycine (CBG-I, **1b**) and (CBG-III, **2b**) are synthesized in a stereoselective manner via a [2+2] photocycloaddition of α,β-unsaturated-γ-lactam **3** with ethylene in acetone. The extended type of isomer **1b** showed a weak activity on group II metabotropic glutamate receptors (mGluR2) of rat brain.

Conformationally restricted glutamate analogs represented by L-2-(2-carboxycyclopropyl)glycines (CCGs) have proven to be potent and selective pharmacological reagents which play a crucial role in investigation of neurobiological functions of glutamate receptors,[1] e.g., CCG-I (**1a**) is a potent agonist of metabotropic glutamate receptors, and CCG-III (**2a**) is a potent inhibitor of glutamate transporters.[2] Relevant to the studies regarding conformational requirements of glutamate receptors, the syntheses of a series of glutamate analogs possessing a carbocyclic ring have been a subject of our current investigation. In this report, we wish to describe the synthesis of the 4-membered ring analogs, (2*S*,1'*S*,2'*S*)- and (2*S*,1'*S*,2'*R*) isomers of 2-(2-carboxycyclobutyl)glycine (**1b** and **2b**), structurally related amino acids to **1a** and **2a**, respectively. Their neuropharmacological profiles are briefly disclosed.



1a CCG-I (n = 1, mGluR2 agonist)
1b CBG-I (n = 2)



2a CCG-III (n = 1, transport inhibitor)
2b CBG-III (n = 2)

The key to the synthesis was a stereoselective construction of the 4-membered ring onto the known γ-lactam **3**,[3] since photocycloaddition of α,β-unsaturated-γ-lactam with an olefin has not been well documented except the Meyers' protocol.[4] Fortunately, this process was accomplished by irradiation (450 W high-pressure

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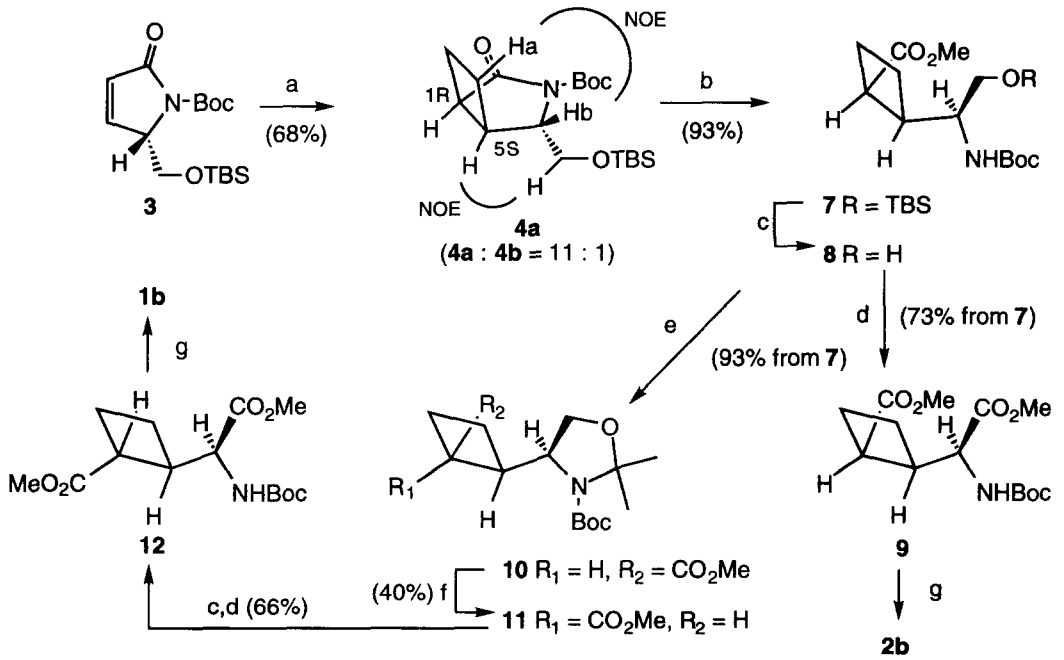
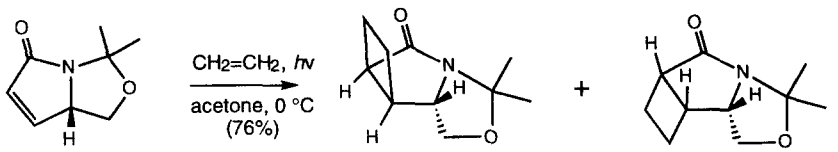
mercury lamp, Pyrex filter) of **3** with ethylene in acetone to give a mixture of cycloadducts in 68% yield (**4a** : 1*S*,5*R*-isomer **4b** = 11 : 1). The structure of the major isomer **4a** was determined to be (1*R*,5*S*)-isomer by its ^{1}H NMR data and extensive NOE experiments.[5] In view of the stereoselectivity, it was of interest to examine the cycloaddition of γ-lactam **5**[6] possessing a fused bicyclo[3.3.0]octane system. The reaction proceeded smoothly under the same reaction conditions as above to give a mixture of cycloadducts **6a** and **6b** albeit with somewhat disappointing stereoselectivity (**6a** : **6b** = 3 : 1).[7,8] These results suggest that the cycloaddition of ethylene occurred from the sterically less hindered β-face. The poor stereoselectivity observed in **5** would be attributed to the presence of a planar amide bond which increased the degree of the attack of ethylene from the sterically more hindered concave face. Photoenolization of the CC-double bond to γ,δ-position is rarely observed in the carbocyclic systems.[9] Contrary to Meyers' example,[4a] both **3** and **5** possess an enolizable proton at the γ-position. Therefore, we examined whether the reaction was accompanied by racemization (i.e., photoenolization) at the γ-position. Thus, the reaction of **3** was quenched after 2 h, and was found to be composed of a mixture of the cycloadducts **4** (48%) and the starting material **3** (31%). The optical rotation value of the recovered **3** [$[\alpha]^{28}_D$ -175.2° (*c* 0.8, $CHCl_3$)] was identical with the starting **3** [$[\alpha]^{25}_D$ -175.6° (*c* 0.9, $CHCl_3$)].[3] In the case of **5**,[6] the major adduct **6a** was converted into **4a** whose $[\alpha]_D$ value was completely identical with the authentic material **4a** derived from **3**.[7] These facts clearly indicated that an unfavorable racemized product was not involved in the cycloadducts.[10]

Scheme 1



[a](a) CH_2=CH_2, *hv*, acetone, 0 °C, 6 h. (b) catalytic amount of LiOH, MeOH, room temperature, 21 h. (c) Dowex 50W x 4 (H^+ form), MeOH, room temperature, 18 h. (d) (1) PDC, DMF, room temperature, 21 h; (2) CH_2N_2, Et_2O, room temperature. (e) catalytic amount of *dl*-camphorsulfonic acid (CSA), 2,2-dimethoxypropane, CH_2Cl_2, reflux, 8 h. (f) 1.3 equiv $KN(SiMe_3)_2$, THF, -78 °C, 30 min, then -5 °C, 5 h. (g) (1) 1 *N* NaOH, THF, room temperature, 20 h; (2) TFA, CH_2Cl_2, 0 °C, 1 h; (3) Dowex 50W x 4 (H^+ form), elution with 1 *N* NH_4OH.

Scheme 2



5 **6a** (**6a** : **6b** = 3 : 1) **6b**

Next, we turned our attention to the syntheses of the target amino acids from the major isomer **4a**. Methanolysis of **4a** underwent smooth lactam-opening to give in 93% yield methyl ester **7** which, upon acidic treatment (Dowex 50W x 4, H^+ form), afforded **8**, a common synthetic intermediate for both **1b** and **2b**. Then, the alcohol **8** was converted into dimethyl ester **9** with (i) pyridinium dichromate (PDC) in DMF and (ii) diazomethane (73% in three steps). Finally, the protecting groups were removed by a routine procedure ((i) 1 *N* NaOH and (ii) trifluoroacetic acid (TFA)) to give in nearly quantitative yield the folded type of a glutamate analog, CBG-III (**2b**): mp 164-165 °C; $[\alpha]^{20}_{D}$ +3.7° (*c* 0.49, H_2O).[11] To synthesize the extended type **1b**, we attempted an inversion of the configuration of the carbomethoxy group starting with **8**. Since the presence of the unprotected amide proton and a hydroxyl group was found to prevent the inversion,[1] the compound **8** was initially protected with an acetonide group to give **10**. The inversion was achieved with $KN(SiMe_3)_2$ in THF to give the desired trans-substituted cyclobutane **11**. This was converted to CBG-I (**1b**) in the same manner as those of **2b**. **1b**: mp 258-263 °C (dec); $[\alpha]^{20}_{D}$ +97.1° (*c* 0.49, H_2O).[11]

Preliminary pharmacological assays of the synthetic glutamate analogs, **1b** and **2b**, were performed using cloned rat mGluR2, expressed on CHO cell. The extended type **1b** inhibited intracellular cAMP production with EC_{50} of 130 μM which was almost 17 times less potent than that of L-glutamate and was much less than that of CCG-I.[1,2b,12] Although further pharmacological and conformational studies are needed, the present result suggests that the puckered conformation of the cyclobutane ring with a greater bond angle than the 3-membered ring places its polar binding functionalities to a little different position in comparison with those of CCG-I, resulting in a pronounced decrease of the activity.[1]

In summary, it was found that the photocycloaddition of the lactams **3** and **5** with ethylene proceeded in a stereoselective manner to give the [2+2] cycloadducts in good yield. The cycloaddition was successfully applied to the synthesis of conformationally constrained glutamate analogs **1b** and **2b**. Studies regarding conformational requirements of glutamate receptors using CCGs, CBGs and other carbocyclic analogs are in progress in our laboratories.

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4. (a) Meyers, A. I.; Fleming, S. A. *J. Am. Chem. Soc.* **1986**, *108*, 306-307. (b) Crimmins, M. T: In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 5; pp 123-150 and references cited therein.
5. **4a**: $[\alpha]^{26}_{D}$ -118.8° (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 0.00 (s, 3 H), 0.01 (s, 3 H), 0.85 (s, 9 H), 1.55 (s, 9 H), 1.95-2.15 (m, 2 H), 2.26 (m, 1 H), 2.47 (m, 1 H), 2.88 (m, 1 H), 3.03 (m, 1 H), 3.59 (dd, 1 H, *J* = 2.0, 10.3 Hz), 3.59 (dd, 1 H, *J* = 3.7, 10.3 Hz), 3.90 (dd, 1 H, *J* = 2.0, 3.7 Hz). Strong NOE was observed between Ha and Hb, indicating the structure of **4a** to be as depicted.
6. Prepared from known (*S*)-5-hydroxymethylpyrrolidin-2-one[a] in 3 steps: (i) 2,2-dimethoxypropane, CSA, (ii) phenylselenenylation, and (iii) oxidative removal of the resulting selenide.(a) Davies, S. G.; Doisneau, G. J.-M.; Prodger, J. C.; Sanganee, H. J. *Tetrahedron Lett.* **1994**, *35*, 2369-2372.
7. The structure of **6a** was determined by converting it into the bicyclic intermediate **4a** by the following sequence of reactions: (i) Dowex 50W x 4 (H^+ form), MeOH, room temperature; (ii) *tert*-butyldimethylsilyl chloride (TBSCl), imidazole, DMF, room temperature; and (iii) di-*tert*-butyl dicarbonate (Boc_2O), Et_3N, 4-dimethylaminopyridine, THF (3 steps, 65%).
8. For related examples, see: (a) carbocyclic bicyclo[3.3.0]octane system; Ohfune, Y.; Shirahama, H.; Matsumoto, T. *Tetrahedron Lett.* **1975**, *16*, 4377-4380 and the exo/endo ratio of the [2+2] cycloadducts was 10 : 1. (b) 2(5*H*)-Furanone derivatives; Alibes, R.; Bourdelande, J. L.; Font, J. T*etrahedron: Asymmetry* **1991**, *2*, 1391-1402 and the ratio of the cycloadducts was 3 : 1.
9. (a) Yang, N, C.; Jorgenson, M. J. *Tetrahedron Lett.* **1964**, 1203-1207. (b) Sammes, P. G. *Tetrahedron* **1976**, *32*, 405-422 and references cited therein.
10. Since the mixture of the cycloadduct **6a** and the starting material **5** was inseparable by TLC in several solvent systems, **6a** was converted into **4a**[7] to compare its optical rotation value with that of **4a** prepared from **3**. The photocycloaddition of **5** produced a mixture of unidentifiable side products (~20%). It could not be ascertained at this stage whether these products were the results of photoenolization.
11. ^1H NMR data of **1b** and **2b** (300 MHz, D_2O). **1b**: δ 1.72-2.08 (m, 4 H), 2.73 (dddd, 1 H, *J* = 9.0, 9.0, 9.0, 9.0 Hz), 3.10 (ddd, 1 H, *J* = 9.0, 9.0, 9.0 Hz), 3.62 (d, 1 H, *J* = 9.0 Hz). **2b**: δ 1.92-2.20 (m, 4 H), 2.86 (m, 1 H), 3.27 (m, 1 H), 3.76 (d, 1 H, *J* = 10.6 Hz).
12. Both CBG-I and III did not inhibit uptake of [^{14}C]glutamate in COS-1 cells expressing human excitatory amino acid transporters (EAAT-1 or -2). In addition, radioligand binding assays using [^{3}H]KA for kainate receptors, [^{3}H]AMPA for AMPA receptors, and [^{3}H]CGS19755 for NMDA receptors in rat brain synaptic membranes revealed that CBGs did not activate ionotropic glutamate receptors. These results suggested that both CBGs were neither an agonist of ionotropic glutamate receptors nor an inhibitor of glutamate transporter, but CBG-I was a weak agonist of mGluR2.