INTRAMOLECULAR [2+2] PHOTOCYCLOADDITION OF FUMARAMIC ACID ESTER DERIVATIVES. SYNTHESES OF 2-(2,3-DICARBOXY-CYCLOBUTYL)GLYCINES

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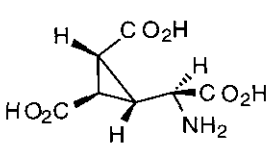
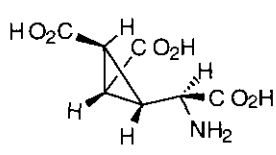
Abstract - Two isomers of new glutamate analogs, (2*S*,1'*R*,2'*S*,3'*S*)- and (2*S*,1'*R*,2'*R*,3'*S*)-2-(2,3-dicarboxycyclobutyl)glycines (**1a**) and (**1b**), are synthesized from the novel 3-azabicyclo[3.1.1]heptan-2-one intermediates (**5a**) and (**5b**), respectively, *via* an intramolecular photocycloaddition of α,β-unsaturated amide ester (**3**).

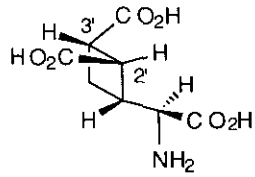
Conformationally restricted analogs of L-glutamate have played an important role not only as potent and subtype-selective activators of glutamate receptors, but also as a useful probe for investigating conformational requirements of glutamate receptors.[1] Among these ligands, (2*S*,2'*R*,3'*R*)-2-(2,3-dicarboxycyclopropyl)glycine (DCG-IV, a potent agonist) and its (2*S*,2'*S*,3'*S*)-isomer (DCG-III, a weak agonist) have been known as excellent ligands for group II metabotropic glutamate receptors (mGluR2 and 4) which are negatively coupled through adenylate cyclase to an inhibition of c-AMP.[2] In fact, in recent years a number of physiological studies regarding the group II receptors using DCGs have been reported.[3] These results led us to develop a related amino acid structurally similar to DCGs.[4] In this communication, we wish to describe the synthesis of a novel DCG-III analog, (2*S*,1'*R*,2'*S*,3'*S*)-2-(2,3-dicarboxycyclobutyl)glycine (**1a**), and its (2*S*,1'*R*,2'*R*,3'*S*)-isomer (**1b**).



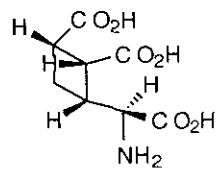
DCG-IV
(potent mGluR2 agonist)



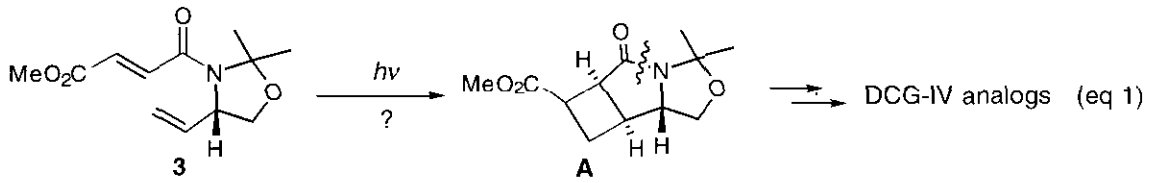
DCG-III
(weak mGluR2 agonist)



1a

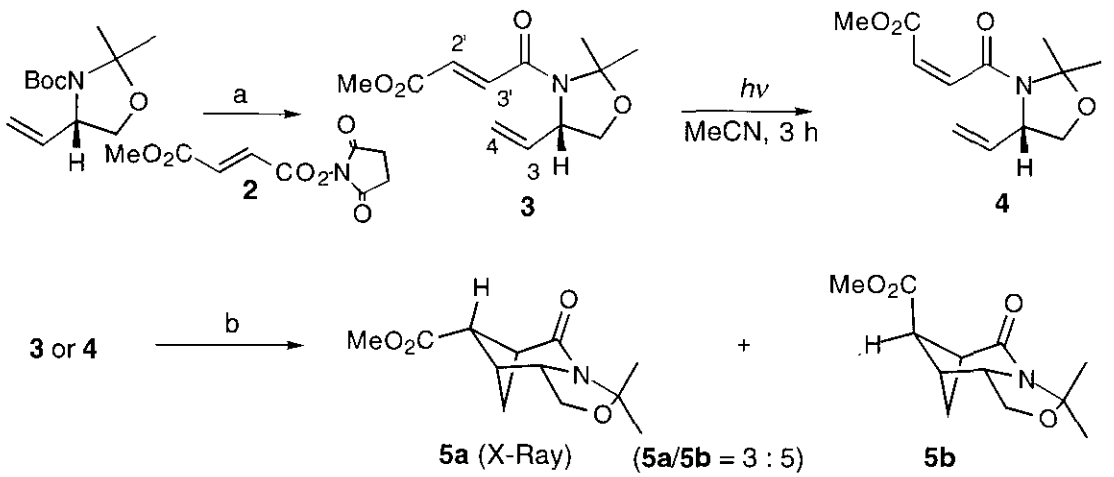


1b



Initially, we assumed that an intramolecular photocycloaddition of the fumaramic acid ester (**3**), possessing a vinylglycinol moiety, would undergo [2+2] photocycloaddition to give a key bicyclo[3.2.0]heptane ring system **A** which would enable construction of DCG-IV analogs with a 4-membered ring where the requisite two carboxyl groups are placed (eq 1). Thus, the synthesis began with condensation of the optically active 2-amino-3-butenol derivative[5] with fumaramic acid activated ester (**2**), prepared by DCC coupling of *N*-hydroxysuccinimide (HOSu) with a fumaric acid monomethyl ester. The coupling gave a polar amide alcohol which was immediately protected with an acetonide group to give the *N,O*-acetonide (**3**) (77%). Photo-irradiation (450-W high-pressure mercury lamp, Pyrex filter) of a solution of **3** in acetonitrile for 3 h only resulted in exclusive isomerization of its *E*-double bond to the corresponding *Z*-isomer (**4**) (96%). In contrast, an addition of acetone to the solution as a photo-sensitizer as well as a co-solvent was found to be quite effective for the cycloaddition. When a solution of acetonitrile and acetone (4:1) was employed, the reaction completed within 8 h to give a mixture of cycloadducts in 90% yield. The mixture was composed of mainly two products (less polar isomer (**5a**) and more polar isomer (**5b**), **5a/5b** = 3:5) which were separated by silica gel column chromatography (28% for **5a** and 45% for **5b**).[6] ^{1}H NMR (750 and 500 MHz) studies of both isomers suggested that their structures were not the expected bicyclo[3.2.0]heptane **A**, but both cycloadducts possessed a novel 3-azabicyclo[3.1.1]heptane ring system.[6] Finally, the structure of the less polar isomer was unambiguously determined as **5a** by X-Ray crystallographic analysis (Scheme 1).[7] The structure of the more polar isomer was assigned to **5b** based on ^{1}H NMR correlation studies with that of **5a** (*vide infra*).

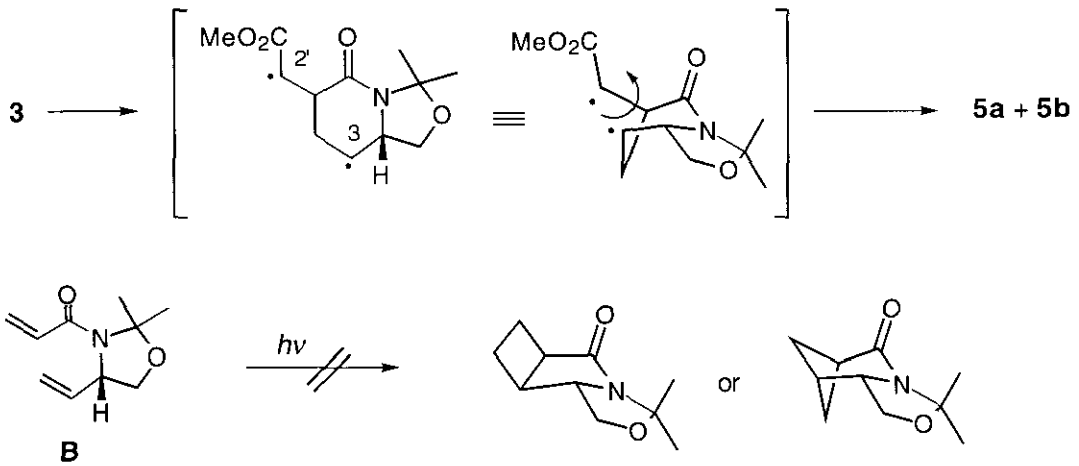
Scheme 1[a]



[a](a) (1) HCl, MeOH, 0 °C to rt, 12 h; (2) Et_3N then **2**, rt, 1 h; (3) 2,2-dimethoxypropane, cat. TsOH, benzene, reflux, 1 h (77%); (b) *hv*, acetonitrile/acetone = 4:1, 0 °C, 8 h.

It is of interest to note that the photo-irradiation of the *Z*-isomer (**4**) also gave the same mixture of the cycloadducts and that the double bond isomerization from *E* to *Z* completed within 3 h even in the absence of acetone (the isomerization rate was faster than the cycloaddition).[8] These results suggest that the reaction proceeded in a stepwise manner as shown in Scheme 2, which involved an initial isomerization of the *E* double bond to the *Z* isomer and subsequent carbon-carbon bond formation between the C4 and C3' positions to generate a biradical species where the C2'-C3' bond can freely rotate, resulting in scrambling of the ester stereochemistry in the cycloadducts.[8,9] To add a further example of the present unusual mode of the [2+2] photocycloaddition, we examined the reaction of the related amide **B**.[10] However, the reaction was quite slow and neither the cycloadducts such as the previously reported bicyclo[3.2.0]heptane[11] nor the 3-azabicyclo[3.1.1]heptan-2-one was detected in the reaction mixture. This may be due to the poor depolarizing nature of the acrylamide system.

Scheme 2

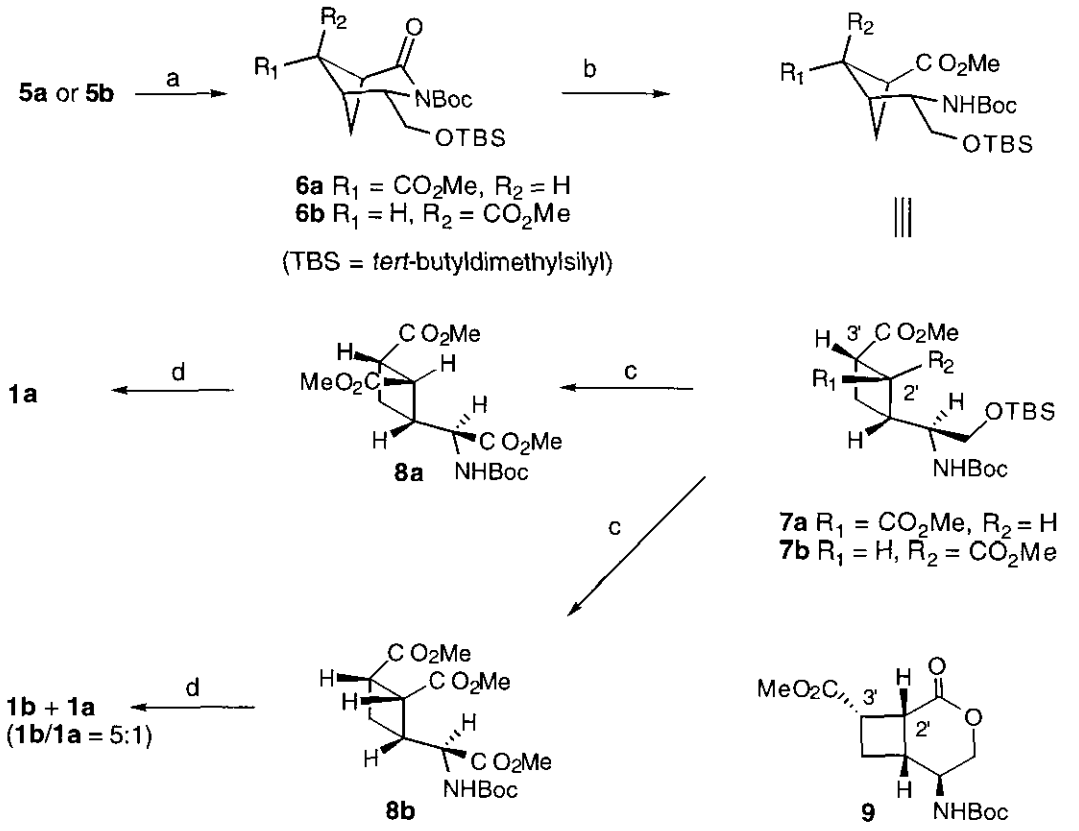


Despite the fact that the cycloadducts (**5a**) and (**5b**) were the unexpected products, a simple cleavage of the amide bond of **5a** would give the 4-membered ring compounds convertible to DCG-III. Thus, the less polar isomer (**5a**) was subjected to acid hydrolysis (Dowex 50W x 4, H^+ form). Filtration of the reaction mixture followed by concentration of the filtrate *in vacuo* gave a polar amide alcohol, which was immediately reprotected to give **6a**. Methanolysis of **6a** in the presence of a catalytic amount of LiOH gave dimethyl ester (**7a**) in excellent yield. This was converted into the triester (**8a**) by the following sequence of reactions: (i) removal of the *tert*-butyldimethylsilyl (TBS) group with Dowex 50W x 4 (H^+ form), (ii) oxidation of the resulting hydroxy group with PDC, and (iii) esterification with diazomethane. Finally, removal of the protecting groups with (i) 1 *N* NaOH and (ii) trifluoroacetic acid afforded **1a**.[12] Preliminary neuropharmacological assays of **1a**, structurally analogous to DCG-III, were performed using cloned rat mGluR2 expressed on CHO cell. However, synthetic **1a** did not activate mGluR2 even at 1 mM concentration.[13]

The more polar isomer (**5b**) was converted into the all-*cis* (**1b**) in an almost similar manner with that of **1a**. During these transformations, further proofs for the structure of **5b** were obtained (*vide supra*): (i)

removal of the TBS group of **7b** followed by oxidation of the resulting alcohol by-produced lactonized product **9** in which the C2' ester group was condensed with the hydroxy group, and (ii) partial isomerization of the C2 ester group occurred when the triester (**8b**) was subjected to the alkaline hydrolysis to give a mixture of the all-*cis* triacid (**1b**) and an isomerized product whose structure was found to be identical with the structure of **1a** by the ^{1}H NMR comparison of the mixture with that of **1a** (**1a/1b** = 1:5). Since an unexpected isomerization occurred during the final synthetic operation, **1b** was obtained as a mixture with **1a** which could not be removed from the mixture even by chromatographic methods.[14]

Scheme 3[a]



[a](a) (1) Dowex 50W x 4, MeOH, rt; (2) TBSCl, Et_3N, DMAP, CH_2Cl_2, rt; (3) Boc_2O, Et_3N, DMAP, THF, rt (68%); (b) cat. LiOH, MeOH, rt (98%); (c) (1) Dowex 50W x 4, MeOH, rt; (2) PDC, DMF, rt; (3) CH_2N_2, Et_2O, rt (75%); (d) (1) 1 *N* NaOH, THF; (2) TFA, CH_2Cl_2; (3) Dowex 50W x 4, 1 *N* NH_3.

In summary, intramolecular photocycloaddition of the fumaramide derivative (**3**) afforded a mixture of 3-azabicyclo[3.1.1]heptan-2-ones (**5a**) and (**5b**). These isomers were converted to the novel glutamate analogs (**1a**) and (**1b**), respectively. Since synthetic **1a** showed a pronounced decrease of its activity to mGluR2 compared with a weak mGluR2 agonist DCG-III, we are currently working on the synthesis of other 4-membered ring analogs which resemble the potent mGluR2 agonist, DCG-IV, in their structure.

ACKNOWLEDGEMENT

We thank Dr. N. Hamanaka, Minase Research Institute of Ono Pharmaceutical Co. Ltd., for his measurement of X-Ray of **5a**, Dr. H. Naoki and Ms. Y. Kan for their measurement of ^{1}H NMR (750 and 500 MHz) of **5a** and **5b**, and Professor S. Nakanishi for his gift of cloned mGluRs. This work was supported by a Grant-in-Aid from the Ministry of Education, Science, Sports and Culture, Japan.

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6. **5a**: mp 107.5-108.5 °C; R_f = 0.68 (hexane/ethyl acetate = 1:2); $[\alpha]^{22}_D$ +84.6° (*c* 2.01, $CHCl_3$); ^{1}H NMR (750 MHz, C_6D_6): δ 1.06 (d, 1 H, *J* = 9.6 Hz), 1.18 (ddd, 1 H, *J* = 9.6, 5.4, 5.4 Hz), 1.61 (s, 3 H), 1.71 (s, 3 H), 2.14 (ddd, 1 H, *J* = 5.4, 5.4, 5.4 Hz), 2.61 (dd, 1 H, *J* = 5.4, 5.4 Hz), 2.78 (ddd, 1 H, *J* = 5.4, 5.4, 5.4 Hz), 2.87 (dd, 1 H, *J* = 10.5, 8.2 Hz), 3.21 (dd, 1 H, *J* = 10.5, 5.3 Hz), 3.29 (s, 3 H), 3.34 (dd, 1 H, *J* = 8.2, 5.3 Hz). **5b**: Oil; R_f = 0.39 (hexane/ethyl acetate = 1:2); $[\alpha]^{16}_D$ +6.0° (*c* 1.10, $CHCl_3$); ^{1}H NMR (500 MHz, C_6D_6): δ 0.89 (d, 1 H, *J* = 9.6 Hz), 1.18 (ddd, 1 H, *J* = 9.6, 5.4, 5.4 Hz), 1.60 (s, 3 H), 1.75 (s, 3 H), 2.14 (dddd, 1 H, *J* = 5.4, 5.4, 5.4, 1.4 Hz), 2.61 (dd, 1 H, *J* = 5.4, 5.4 Hz), 2.78 (ddd, 1 H, *J* = 5.4, 5.4, 5.4 Hz), 2.90 (dd, 1 H, *J* = 10.5, 7.9 Hz), 3.26 (s, 3 H), 3.36 (dd, 1 H, *J* = 7.9, 5.2 Hz), 3.86 (ddd, 1 H, *J* = 10.5, 5.2, 1.4 Hz).
7. X-Ray crystallographic data of **5a**: Cell; a = 5.504, b = 11.087, c = 9.630, α = 90.00, β = 92.00, γ = 90.00. SPACEG: $P2_1$. Z: 2. Density: 1.353. MU: 8.464. R-factors: R = 0.055, Rw = 0.061. Goodness of fit = 7.960.
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9. For related examples, see: (a) F. T. Bond, H. L. Jones, and L. Scerbo, *Tetrahedron Lett.,* 1965, 4685. (b) F. T. Bond, C. Y. Ho, and O. McConnell, *J. Org. Chem.*, 1976, **41**, 1416. (c) M. C. Pirrung, *Tetrahedron Lett.*, 1980, **21**, 4577. (d) P. Hughes, M. Martin, and J. Clardy, *Tetrahedron Lett.*, 1980, **21**, 4579.
10. The acrylamide **B** was prepared from **2** by the following sequence of reactions: (1) removal of the protecting groups (HCl, MeOH), (2) condensation with EtCOSu (Et_3N), (3) protection of the resulting amide alcohol with an acetonide (2,2-dimethoxypropane, TsOH, benzene, reflux (3 steps, 86%)), and (4) selenenylation and deselenenylation of the resulting propionamide ((i) LDA, THF, -78 °C, then PhSeCl; (ii) H_2O_2, 0 °C (2 steps, 46%)).
11. H. Tsujishima, K. Nakatani, K. Shimamoto, Y. Shigeri, N. Yumoto, and Y. Ohfune, *Tetrahedron Lett.*, 1998, **39**, 1193.
12. **1a**: Amorphous powder: $[\alpha]^{16}_{D}$ +46.4° (*c* 1.00, H_2O); ^1H NMR (300 MHz, D_2O): δ 1.82 (ddd, 1 H, *J* = 10.6, 9.8, 9.8 Hz), 2.12 (ddd, 1 H, *J* = 10.6, 8.4, 8.4 Hz), 2.66 (dddd, 1 H, *J* = 9.8, 9.8, 8.4, 6.4 Hz), 2.87 (ddd, 1 H, *J* = 9.8, 9.8, 8.4 Hz), 2.98 (dd, 1 H, *J* = 9.8, 9.8 Hz), 3.64 (d, 1 H, *J* = 6.4 Hz).
13. Radioligand binding assays of synthetic **1a** 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 **1a** did not activate ionotropic glutamate receptors. These results suggested that **1a** was not an agonist of ionotropic glutamate receptors.
14. **1b**: ^1H NMR (300 MHz, D_2O): δ 2.02-2.24 (m, 2 H), 2.88 (dddd, 1 H, *J* = 9.3, 9.3, 9.3, 4.8 Hz), 3.11 (ddd, 1 H, *J* = 9.3, 9.3, 9.3 Hz), 3.42 (br t, 1 H, *J* = 9.3 Hz), 3.75 (d, 1 H, *J* = 4.8 Hz).

Received, 7th May, 1998