A Short and Efficient Synthesis of (2*S*,2′*R*,3′*R*)-2-(2′,3′-Dicarboxylcyclopropyl)glycine (DCG-IV)

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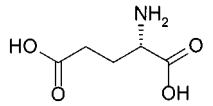
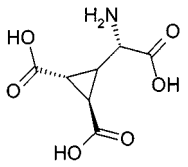
Feist's acid (5) was used in enantiomerically pure form as starting material for the synthesis of (2*S*,2′*R*,3′*R*)-2-(2′,3′-dicarboxylcyclopropyl)-glycine (DCG-IV) (2). This conformationally restricted analog of L-glutamic acid (L-Glu) 1 is a potent group II mGlu receptor agonist.

L-Glutamic acid (L-Glu) **1** is widely recognized as the primary excitatory neurotransmitter in the mammalian central nervous system (CNS).[1] Glutamate receptors have been classified into two major classes, ionotropic glutamate receptors (iGluR) and metabotropic glutamate receptors (mGluRs).[2] The ion channel linked iGluRs are further subdivided into *N*-methyl-D-aspartic acid (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) and kainic acid (KA) receptors according to their responses to exogenous exitatory amino acids (EAAs).[3]

The G-protein coupled mGluRs consist of a family of at least eight receptors, grouped according to primary amino acid sequence homology, agonist pharmacology and signal transduction mechanism.[4] The first group includes mGluR1 and mGluR5, which are negatively coupled to IP3/Ca^{2+} signal transduction by activation of phospholipase C, whereas the members of group II, mGluR2 and mGluR3, as well as those of group III, mGluR4, mGluR6, mGluR7 and mGluR8, are negatively linked to adenylate cyclase.



L-Glu **1**



DCG-IV **2**

Figure 1. Structures of compounds **1** and **2**

The conformationally restricted analog of L-glutamic acid (L-Glu) **1**, (2*S*,2′*R*,3′*R*)-2-(2′,3′-dicarboxylcyclopropyl)-glycine (DCG-IV) **2**,[5] has revealed to be a particularly interesting compound, being a potent group II mGluR agonist (EC_{50} = 0.1 μM) with neuroprotective properties, and also active as an agonist at the NMDA receptor at concentrations above 10 μM.[6]

In order to study the roles of group II mGluRs in vivo large amounts of DCG-IV **2** are required. The synthesis of the compound described in the literature is a multistep procedure not suitable for the preparation of such quantities.[7] The continuing need for DCG-IV **2** motivated us to develop a shorter synthesis of the compound.

Whereas the synthesis described in the literature starts from Garner's aldehyde with the amino acid stereogenic center in place and the cyclopropyl moiety to be built, our strategy was to use the cyclopropyl aldehydes **3a−b** as key intermediates and to construct the amino acid functionality.

To explore our strategy, the racemic aldehyde **3a** was prepared by the addition of dimethylsulfonium-3-carbomethoxallylide to dimethyl fumarate, and treatment of the formed cyclopropyl derivative with osmium tetroxide and sodium metaperiodate according to a protocol described by Nordlander.[8] The key step of the synthesis is a diastereoselective Strecker reaction involving the nucleophilic addition of cyanide to the Schiff base formed by condensation of **3a−b** with (*R*)-α-phenylglycinol to induce preferentially the (*S*)-chirality at the newly formed stereogenic center.[9]

Reaction of **3a** with (*R*)-α-phenylglycinol in methanol at room temperature for 2 hours, followed by treatment with trimethylsilyl cyanide for 16 hours at room temperature, yielded a mixture of the expected four α-amino nitriles **4a−d** as two major (**4a−b**) and two minor (**4c−d**) components in a ratio of 4:1.[10] Extensive column chromatography of the mixture followed by crystallization yielded **4a** (26%) {$[\alpha]_D^{20}$ = −90.4 (*c* = 0.25 in MeOH)} and **4b** (19%) {$[\alpha]_D^{20}$ = −91.6 (*c* = 0.25 in MeOH)}. Compound **4a** was then submitted to oxidative cleavage with lead tetraacetate,[10] acidic hydrolysis (6N HCl) and ion exchange resin chromatography to afford **2** (58%).[11]

The synthesis of the enantiomerically pure aldehyde **3b** was performed starting from (−)-Feist's acid **5**.[12] Bromination of **5** yielded 64% of the dibromo derivative **6** {$[\alpha]_D^{20}$ = + 80.0 (*c* = 0.25 in MeOH)} which was heated in water to give 61% of the lactone **7**. Opening of **7** and esterification was performed by reaction with sulfuric acid in methanol to give the alcohol **8** in 97% yield {$[\alpha]_D^{20}$ = +98.4 (*c* = 0.25 in MeOH)}. This compound was then oxidized with PCC to give the α-bromo aldehyde **9** (69%) {$[\alpha]_D^{20}$ = + 108.0 (*c* = 0.25 in MeOH)}. Treatment of **9** with zinc in acetic acid gave the desired aldehyde **3b** (88%)

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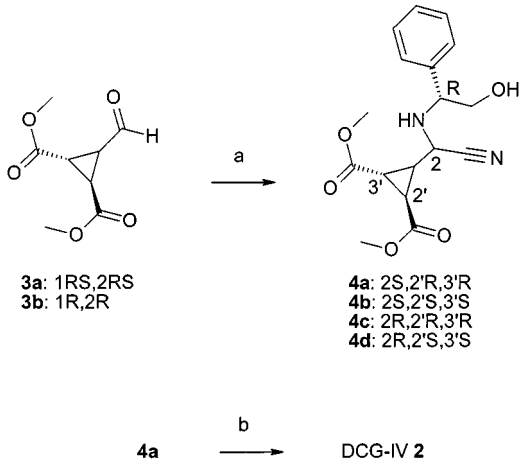
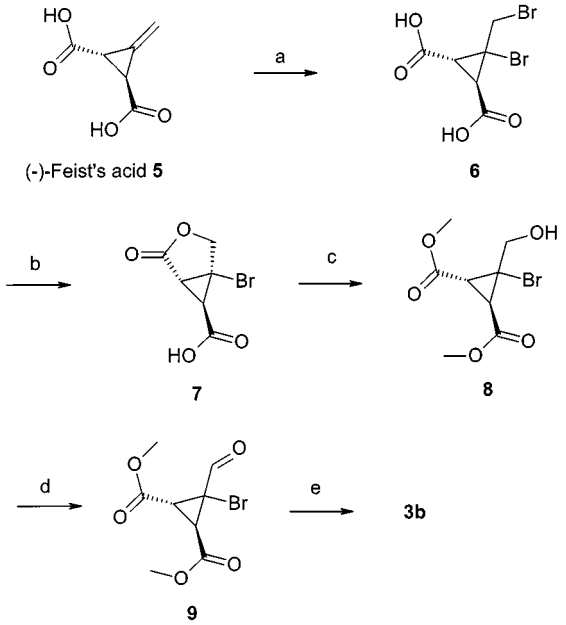


Scheme 1. Synthesis of **2**, (a) 1: (*R*)-α-phenylglycinol, MeOH, RT, 2 h; then TMSCN, RT, 16h, 89% **4a**−**d**; 2: extended CC on silica gel (diethyl ether/hexane 2:1); cryst. from diethyl ether/hexane, 26% **4a** and 19% **4b**; (b) 1: lead tetraacetate, MeOH/dichloromethane 1:1, 0°C, 15 min; 2: 6N HCl, reflux, 16 h

{$[\alpha]_D^{20} = -48.0$ (c = 1 in MeOH)} which was then transformed into **4a** (66%) as described above.



Scheme 2. Synthesis of **3b**, (a) Br_2 in diethyl ether, RT, 16 h, 64%; b) H_2O, reflux, 4 h, 61%; (c) MeOH, conc. sulfuric acid, RT, 2 h, 97%; (d) PCC, CH_2Cl_2, RT, 16 h, 69%; (e) zinc powder, acetic acid, RT, 4 h, 88%

In summary, we have developed a seven step synthesis of DCG-IV **2** starting from (−)-Feist′s acid **5** which makes it possible, for the first time, to prepare sufficient quantities of **2** to study the role of group II mGluRs in vivo. In addition, the α-bromo aldehyde **9** was used to prepare [^{3}H]-DCG-IV,[13] which was used to establish a radioligand binding assay and to study the distribution of group II mGluRs in the brain.

Experimental Section

General: Reagent grade solvents were used without further purification. Evaporation of the solvent was performed with a Büchi rotary evaporator at 30−40° C in vacuo. Silica gel used for column chromatography was Kieselgel-60 (70−230 mesh) supplied by E. Merck AG, Darmstadt. TLC plates coated with silica gel 60 F_{254} (Merck) were used. Melting points were determined with a Büchi 510 apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker AC 250 spectrometer, δ values in ppm relative to internal TMS (J in Hz) are given. Optical rotations were determined with a Perkin−Elmer 241 polarimeter, c in g/100 mL. Mass spectra were recorded with a MS 9 apparatus updated with a Finnigan MAT data system SS 200.

(1*R*,2*R*)-3-Bromomethyl-cyclopropane-1,2-dicarboxylic Acid (6): To a cooled (0°C) and stirred solution of (1*S*,2*S*)-3-methylene-cyclopropane-1,2-dicarboxylic acid **(5)**[12] (4.0 g, 28.2 mmol) in diethyl ether (250 mL) was added bromine (2 mL), and stirring was continued over a period of 16 h at room temperature. Filtration, evaporation of the solvent and crystallization of the crude product from dichloromethane/hexane yielded **6** (5.45 g, 64%) as a pale brown solid. m.p. 233° C (dec.). − $[\alpha]^{20}_D$ = + 80 (c = 0.25 in MeOH). − ^{1}H NMR ([D$_6$]DMSO): δ = 2.58 (d, J = 6.5 Hz, 1 H), 2.63 (d, J = 6.5 Hz, 1 H), 4.07 (d, J = 11 Hz, 1 H), 4.17 (d, J = 11 Hz, 1 H). − MS (FAB) *m/z*: 299, 301, 303 [M−H$^+$].

(1*RS*,5*R*,6*R*)-1-Bromo-4-oxa-bicyclo[3.1.0]hexane-6-carboxylic acid (7): A solution of (1*R*,2*R*)-3-bromomethyl-cyclopropane-1,2-dicarboxylic acid **(6)** (5.4 g, 17.9 mmol) in water (100 mL) was heated to reflux for a period of 4 h. Filtration, evaporation of the solvent and column chromatography of the crude product (dichloromethane/methanol 9:1) gave **7** (2.75 g) as a solid. Further crystallization from dichloromethane/hexane yielded **7** (2.41 g, 61%) as a light yellow solid. m.p. 196−198° C. − $[\alpha]^{20}_D$ = −36 (c = 0.25 in MeOH). − ^{1}H NMR ([D$_6$]DMSO): δ = 2.64 (d, J = 3 Hz, 1 H), 2.93 (d, J = 3 Hz, 1 H), 4.56 (d, J = 10 Hz, 1 H), 4.71 (d, J = 10 Hz, 1 H). − MS (EI) *m/z*: 220, 222 [M$^+$], 202, 204 (48) [M$^+$ −H$_2$O], 123 (100) [M$^+$ −H$_2$O, −Br], 97 (98).

(1*R*,2*R*)-3-Bromo-1,2-dicarbomethoxy-3-hydroxymethyl-cyclopropane (8): To a stirred solution of (1*RS*,5*R*,6*R*)-1-bromo-4-oxa-bicyclo[3.1.0]hexane-6-carboxylic acid (**7**) (2.41 g, 10.9 mmol) in methanol (25 mL) was added sulfuric acid (conc., 2.5 mL) and stirring was continued over a period of 2 h. The reaction mixture was poured into ice/water (100 mL) and extracted with two 100 mL portions of ethyl acetate. The combined organic layers were washed with water (50 mL) and two 50 mL portions of saturated sodium hydrogen carbonate solution, dried ($MgSO_4$) and evaporated to yield **8** (2.85 g, 97%) as a light yellow oil. − $[\alpha]^{20}_D$ = + 98.4 (c = 0.25 in MeOH). − ^{1}H NMR ($CDCl_3$): δ = 2.66 (dd, J = 6, 8 Hz, 1 H), 2.70 (d, J = 6.5 Hz, 1 H), 2.87 (d, J = 6.5 Hz, 1 H), 3.77 (s, 3 H), 3.80 (s, 3 H), 3.99 (dd, J = 8, 12.5 Hz, 1 H), 4.16 (dd, J = 6, 12.5 Hz, 1 H). − MS (EI) *m/z* 267, 269 [M + H$^+$], 249, 251 (3) [M$^+$ −OH], 235, 237 (14) [M$^+$ −OMe], 207, 209 (94), 175, 177 (82), 169 (83), 155 (46), 113 (100), 59 (76).

(1*R*,2*R*)-3-Bromo-1,2-dicarbomethoxy-3-formyl-cyclopropane (9): To a stirred solution of (1*R*, 2*R*)-3-bromo-1,2-dicarbomethoxy-3-hydroxymethyl-cyclopropane (**8**) (2.8 g, 10.5 mmol) in dichloromethane (120 mL) was added pyridinium chlorochromate (3.35 g, 15.7 mmol) and stirring was continued over a period of 16 h. Diethyl ether (120 mL) was added to the reaction mixture, which was then filtered with the aid of a Whatman glass microfibre filter and evaporated. Column chromatography of the crude product (diethyl ether/hexane 1:1) yielded **9** (1.93 g, 69%) as a white solid. m.p. 52°

C. − $[\alpha]^{20}_D$ = + 108 (*c* = 0.25 in MeOH). − ^{1}H NMR ($CDCl_3$): δ = 3.16 (d, *J* = 6.5 Hz, 1 H), 3.27 (d, *J* = 6.5 Hz, 1 H), 3.76 (s, 3 H), 3.83 (s, 3 H), 9.26 (s, 1 H). − MS (EI) *m*/*z*: 265, 267 [M + H^+], 233, 235 (24) [M^+ −OMe], 204, 206 (24), 176, 178 (44), 153 (100), 125 (95), 59 (69).

(1*R*,2*R*)-1,2-Dicarbomethoxy-3-formyl-cyclopropane (3b): A mixture of (1*R*,2*R*)-3-bromo-1,2-dicarbomethoxy-3-formyl-cyclopropane (**9**) (428 mg, 1.6 mmmol), zinc powder (230 mg, 3.5 mmol) and acetic acid (2 mL) was stirred at room temperature over a period of 4 h. Filtration, evaporation and column chromatography yielded **3b** (265 mg, 88%) as a colorless oil. − $[\alpha]^{20}_D$ = −48 (*c* = 1 in MeOH). − ^{1}H NMR ($CDCl_3$): δ = 2.53 (ddd, *J* = 5, 6, 8 Hz, 1 H), 2.71 (dd, *J* = 6, 8 Hz, 1 H), 3.01 (t, *J* = 6 Hz, 1 H), 3.76 (s, 6 H), 9.42 (d, *J* = 5 Hz, 1 H). − MS (FAB) *m*/*e*: 187 [M + H^+].

(2*S*,2′*R*,3′*R*)- and (2*S*,2′*S*,3′*S*)-*N*-[(*R*)-α-Phenylglycinyl]-2-(2′,3′-dicarbo-methoxycyclopropyl)-glycinonitrile (4a and 4b): To a solution of (1*RS*,2*RS*)-1,2-dicarbomethoxy-3-formyl-cyclopropane (**3a**)[8] (3.11 g, 16.7 mmol) in methanol (110 mL) was added (*R*)-a-phenylglycinol (2.29 g, 16.7 mmol), and the resulting solution was stirred at room temperature for 2 h. After cooling to 0° C, TMSCN (4.2 mL, 33.4 mmol) was added, and the resulting mixture was stirred for 16 h at room temperature. Evaporation of the solvent gave a yellow oil, which was then purified as follows:

(1) column chromatography (ethyl acetate/hexane 2:1) yielded 1.32 g (24%) of a colorless oil (main component **4b**), 2.15 g (39%) of a light yellow oil (mixture of **4a−d**) and 1.51 g (27%) of a colorless oil (main component **4a**). − (2) column chromatography (ethyl acetate/hexane 2:1) of the mixture **4a−d** (2.15 g) gave 0.98 g of a colorless oil (main component **4b**) and 1.08 g of a colorless oil (main component **4a**). Further separation of the mixtures was performed by crystallization from diethyl ether/hexane to yield **4a** (1.43 g, 26%) as a light yellow oil and **4b** (1.03 g, 19%) as a white solid. − IR (KBr) $\tilde{\nu}$ = 1070 (OH), 1190 (ester), 1720 (ester), 2227 (CN) cm^{-1}. − MS (FAB) *m*/*z*: 333 (M + H^+).

4a: $[\alpha]^{20}_D$ = −90.4 (*c* = 0.25 in MeOH). − ^{1}H NMR ($CDCl_3$): δ = 1.61 (br, 1 H), 1.89 (br, 1 H), 2.19 (m, 2 H), 2.42 (dd, *J* = 8.5, 9 Hz, 1 H), 3.61 (m, 1 H), 3.64 (s, 3 H), 3.74 (m, 1 H), 3.75 (s, 3 H), 3.80 (dd, *J* = 4, 9 Hz, 1 H), 4.09 (dd, *J* = 4, 8 Hz, 1 H), 7.36 (m, 5 H).

4b: m.p. 111° C. − $[\alpha]^{20}_D$ = −91.6 (*c* = 0.25 in MeOH). − ^{1}H NMR ($CDCl_3$): δ = 1.82 (br, 1 H), 2.24 (ddd, *J* = 6, 7, 9.5 Hz, 1 H), 2.30 (dd, *J* = 6, 9.5 Hz), 2.42 (dd, *J* = 6, 7 Hz), 2.52 (br, 1 H), 3.68 (m, 2 H), 3.65 (s, 3 H), 3.72 (s, 3 H), 3.78 (m, 1 H), 4.04 (dd, *J* = 4, 8 Hz), 7.25 (m, 2 H), 7.32 (m, 3 H).

(2*S*,2′*R*,3′*R*)-*N*-[(*R*)-α-Phenylglycinyl]-2-(2′,3′-dicarbomethoxy-cyclopropyl)-glycinonitrile (4a): To a solution of (1*R*,2*R*)-1,2-dicarbomethoxy-3-formyl-cyclopropane **(3b)** (256 mg, 1.38 mmol) in methanol (15 mL) was added (*R*)-α-phenylglycinol (189 mg, 1.38 mmol), and the resulting solution was stirred at room temperature for 5 h. After cooling to 0° C, TMSCN (0.34 mL, 2.75 mmol) was added, and the resulting mixture was stirred for 16 h at room temperature. Evaporation of the solvent gave a yellow oil, which was then purified by column chromatography (ethyl acetate/hexane 1:1) to yield **4a** (304 mg, 66%) as a colorless oil. − $[\alpha]^{20}_D$ = −89.8 (*c* = 0.25 in MeOH). − ^{1}H NMR ($CDCl_3$): δ = 1.61 (br, 1 H), 1.89 (br, 1 H), 2.19 (m, 2 H), 2.42 (dd, *J* = 8.5, 9 Hz, 1 H), 3.61 (m, 1 H), 3.64 (s, 3 H), 3.74 (m, 1 H), 3.75 (s, 3 H), 3.80 (dd, *J* = 4, 9 Hz, 1 H), 4.08 (dd, *J* = 4, 8 Hz, 1 H), 7.35 (m, 5 H). − MS (FAB) *m*/*z*: 333 (M + H^+).

(2*S*,2′*R*,3′*R*)-2-(2,3-Dicarboxylcyclopropyl)-glycine (DCG-1/4) (2): Lead(IV) acetate (552 mg, 1.42 mmol) was added to a cold (0° C) and stirred solution of (2*S*,2′*R*,3′*R*)-*N*-[(*R*)-α-phenylglycinyl]-2-(2′,3′-dicarbomethoxy-cyclopropyl)-glycinonitrile (**4a**) (375 mg, 1.13 mmol) in anhydrous methanol/dichloromethane 1:1 (10 mL). After 15 min, water (10 mL) was added and the resulting mixture was filtered with the aid of Celite. After evaporation of the solvent, the residue was refluxed in 6 N HCl (30 mL) for 14 h. The reaction mixture was twice washed with dichloromethane (30 mL each) and evaporated to dryness. The residue was submitted to ion exchange resin chromatography (Dowex 50WX4, elution with 2N NH_3) to give **2** (156 mg, 58%) as a white, hygroscopic foam (diammonium salt). m.p. 167−168° C (dec.). − $[\alpha]^{20}_D$ = −57.6 (*c* = 0.25 in H_2O). − ^{1}H NMR (D_2O): δ = 1.93 (ddd, *J* = 6, 9.5, 10 Hz, 1 H), 2.07 (dd, *J* = 5.5, 6 Hz, 1 H), 2.17 (dd, *J* = 5.5, 9.5 Hz, 1 H), 4.03 (d, *J* = 10 Hz, 1H). − MS (FAB) *m*/*z*: 204 (M + H^+).

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