



## First Enantioselective Synthesis of (-)-(Z)-2,3-Methano-L-glutamic Acid

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**Abstract.** (-)-(Z)-2,3-Methano-L-glutamic acid, a potential mGluR agonist, has been synthesized for the first time in 40% overall yield from a homochiral amino pentenoate as an easily available precursor. A conveniently protected (-)-(Z)-cycloaspartic acid derivative was the key intermediate, homologation of the carboxylic acid having been accomplished via the Arndt-Eistert procedure.

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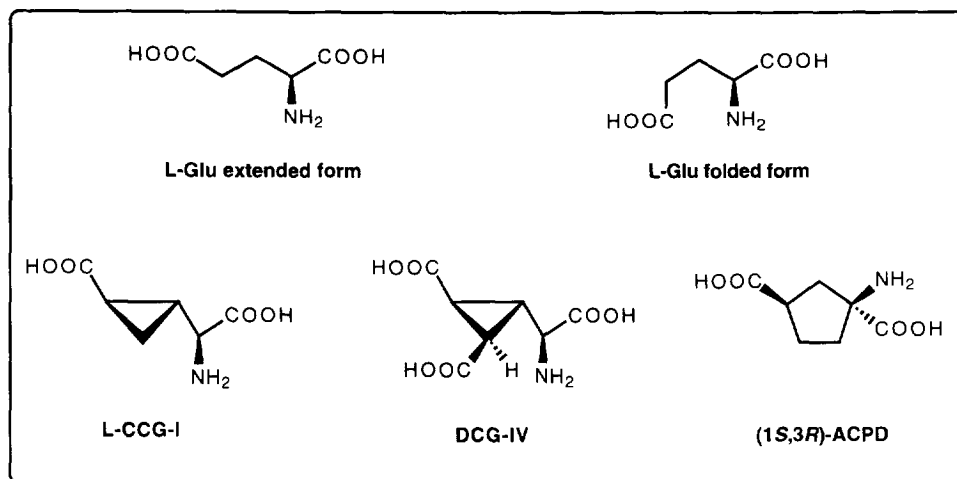
### INTRODUCTION

L-Glutamate is the major excitatory neurotransmitter in the mammalian central nervous system. Among the glutamate receptors, the metabotropic glutamate receptors (mGluRs) are so called because the initial result of their activation is a stimulation of second messenger transduction systems, especially of phospholipase C, rather than a change of ionic conductance as in the case of the ionotropic receptors.<sup>1,2</sup> The existence of mGluRs was first postulated in 1985 and, although a lot of work has been done in this last decade, the precise localization and the structural features of their transmitter recognition sites are not yet known and the search of new structures with activity as mGluR agonists or antagonists is a very active field.

While L-Glu not only activates mGluRs but also the ionotropic glutamate receptors, several structural derivatives of L-Glu act as more specific agonists.<sup>2</sup> Since certain conformations of this acyclic neurotransmitter molecule seem to exclusively or preferentially recognize and bind to the various types of glutamate receptors, the synthesis of conformationally constrained analogs, such as those represented below, has been stimulated in order to ascertain which are the active conformations that enable the interaction with G-proteins.

With this purpose, several syntheses of all enantio- and diastereoisomers of 3,4-methanoglutamic acid have been developed.<sup>3,4</sup> Nevertheless, the syntheses described for optically pure 2,3-methano derivatives are scarce. Burgess *et al* have recently published the asymmetric synthesis of the stereoisomers of protected 2,3-methanoglutamine<sup>5</sup> but, to the best of our knowledge, only the preparation of racemic (Z)-2,3-methanoglutamic acid has been reported.<sup>6-8</sup>

We present herein the first enantioselective synthesis of (-)-(Z)-2,3-methano-L-glutamic acid, **1**, employing a very simple and concise methodology. In connection to our research project on the synthesis of enantiopure cyclopropane amino acids we have prepared diol **7** (Scheme 1) through highly diastereoselective cyclopropanation<sup>9</sup> of the homochiral dehydro amino pentenoate **8** (Scheme 2) obtained, in turn, through Wittig-Horner condensation of a suitable phosphonate and D-glyceraldehyde acetonide as a source of chirality.<sup>10,11</sup> Diol **7** is a very versatile precursor to prepare compounds such as acid **4**,<sup>12</sup> the vinyl derivative **5**<sup>9</sup>, or aldehyde **6**<sup>12</sup> (Scheme 1) which are useful intermediates in the synthesis of several 2,3-cyclopropane amino acids.<sup>11</sup>



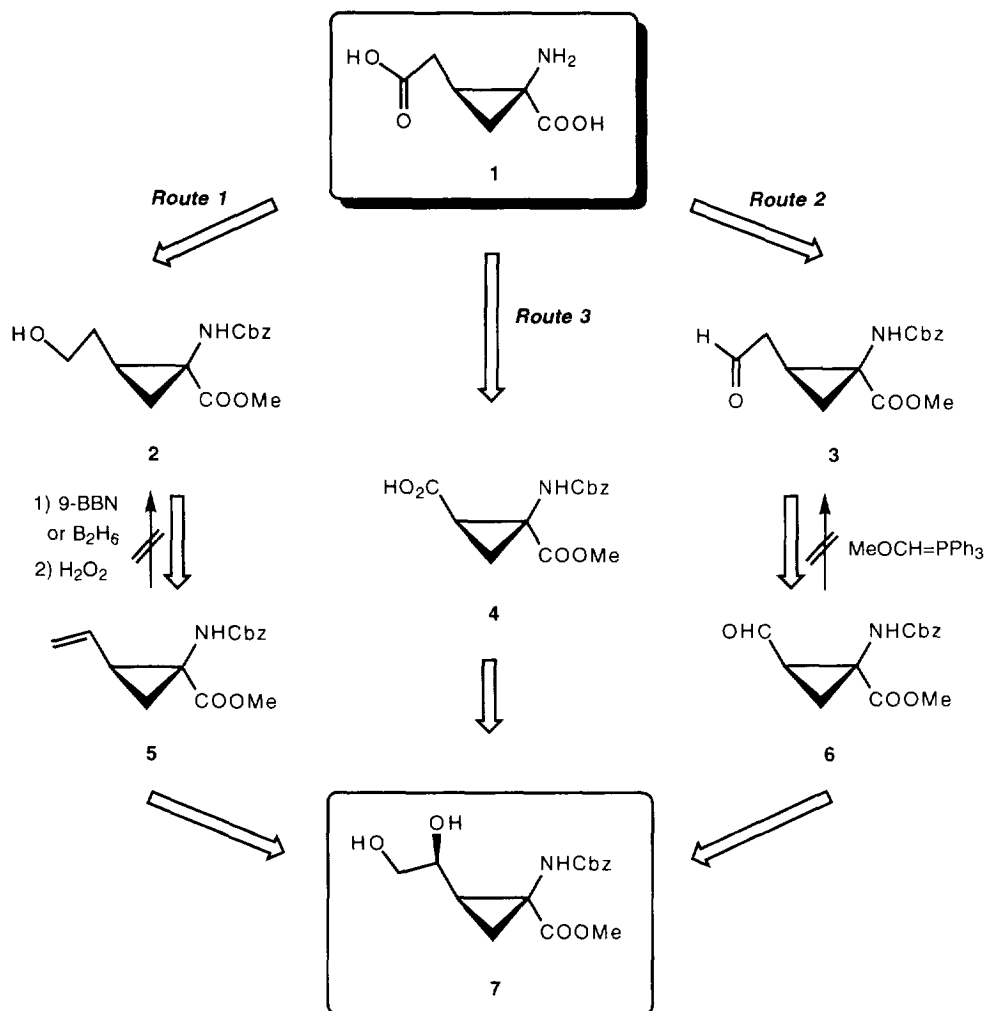
## RESULTS AND DISCUSSION

From the inspection of molecule **1** we envisaged the retrosynthetic routes depicted in Scheme 1, all three starting from diol **7**. The first route involves, as a key step, regioselective hydroboration and subsequent oxidation of olefin **5** to furnish alcohol **2**. Nevertheless, treatment of **5** with 9-BBN or diborane did not afford the expected organoborane. Hydroboration followed by oxidation is a well established method to obtain primary alcohols from monosubstituted olefins, but conjugation between the double bond and the cyclopropane ring gives an especial reactivity to the vinyl group in **5**. This feature was also noticeable when **5** was submitted to catalytic hydrogenation conditions, remaining unaltered under hydrogenation at atmospheric pressure in the presence of 10% palladium on charcoal and methanol as a solvent.<sup>12</sup>

Next we tried the second synthetic route in which homologation of the formyl side-chain in compound **6** would be accomplished through a Wittig condensation. In earlier work carried out in our laboratory, aldehyde **6** had been made to react with a convenient phosphonate leading to the corresponding condensation product in 53% yield.<sup>11</sup> On the other hand, the reactions of aldehydes with (methoxymethyl)-triphenylphosphorane have been reported to occur with good yields, related to the syntheses of steroids<sup>13</sup> and prostaglandin analogs.<sup>14</sup> In our case, however, treatment of **6** with this phosphorane in several conditions did not provide neither the corresponding enol ether nor the equivalent aldehyde.

All these results demonstrate, also in these cyclopropane systems, the peculiar reactivity of the chemical functions directly linked to a cyclopropane ring, often cannot be compared with functional groups located at normal aliphatic positions.<sup>15</sup>

In contrast with these results, the third synthetic route allowed homologation of the carboxylic acid **4** via the Arndt-Eistert procedure. In earlier publications we described the efficient synthesis of conveniently protected (*Z*)-cyclo-aspartic acid **4** by oxidation of diol **7** with catalytic ruthenium dioxide in the presence of sodium periodate.<sup>11,12</sup> Product **4** was reacted with thionyl chloride in toluene at 60 °C to afford the new acid chloride **9** as a yellowish solid in 94% yield (Scheme 2). Without further purification, compound **9** was submitted to treatment with a freshly distilled ether solution of diazomethane at 0°C giving the corresponding diazo ketone **10** which was not isolated. Wolff rearrangement leading to methyl ester **11**



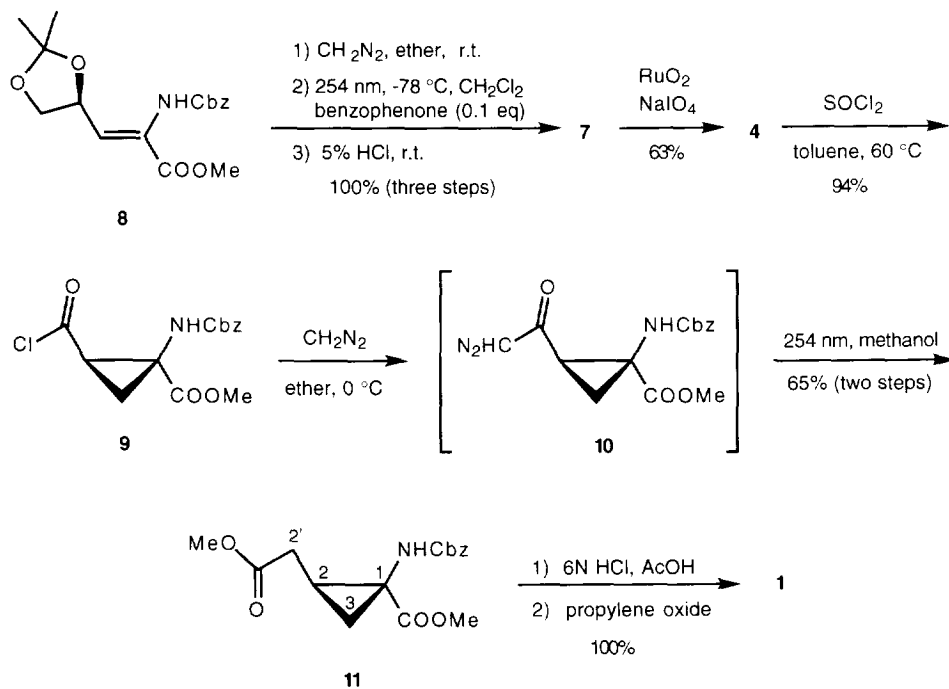
Scheme 1

was accomplished by photolysis of **10** as a methanol solution contained in a Pyrex reactor by irradiation with a 125 W medium-pressure mercury-lamp, at room temperature for 4.5 hours. Thus diester **11** was obtained, in 65% yield for the two steps, as an oil  $[\alpha]_D + 8.6$  (c 0.70, chloroform). Finally, hydrolysis with 6N HCl and some drops of glacial acetic acid, at 90 °C for 6 hours, followed by treatment with propylene oxide at 35 °C and elution through a C<sub>18</sub>-reverse phase cartridge allowed the quantitative obtention of free amino acid **1** in 40% overall yield from aminopentenoate **8**. Compound **1** is a solid, m.p. 167-169 °C (from ethanol-water),  $[\alpha]_D -10.0$  (c 0.40, water).

The advantages of this synthetic approach, in addition to its efficiency and simplicity, lie on the fact that photochemical decomposition of diazo ketones can be performed in the presence of water, ammonia, or several kinds of alcohols<sup>16</sup> that would lead, in our case, to different functional derivatives of (Z)-2,3-

methanoglutamic acid as suitable moieties to be incorporated in peptide or protein mimics for biological studies.

Therefore, the synthesis of these compounds and their (*E*)-diastereoisomers is under active investigation in our laboratory.



Scheme 2

## EXPERIMENTAL SECTION

Flash column chromatography was carried out on silica gel (240–400 mesh). Melting points were determined on a hot stage and are uncorrected. Electron-impact mass spectra were recorded at 70 eV. Chemical shifts in NMR spectra are given in ppm relative to internal TMS ( $\delta$  scale).

**Methyl (1*S*,2*R*)-1-[*N*-(benzyloxycarbonyl)amino]-2-chlorocarbonylcyclopropanecarboxylate, 9.** Thionyl chloride (30  $\mu\text{L}$ , 0.42 mmol) was added to a stirred solution of acid 4 (76 mg, 0.7 mmol) in anhydrous toluene (3 mL) and the mixture was stirred at  $60\text{ }^\circ\text{C}$  for 24 h. The solvent was removed at reduced pressure and the residue was chromatographed (2:1 ethyl acetate-hexane) to afford chloride 9 (60 mg, 94% yield) as a yellowish solid that was identified by its spectral data and used in the subsequent transformations without further purification. IR (KBr) 3339 (br), 1780, 1732 (br)  $\text{cm}^{-1}$ ; MS, *m/e* (%) 311 (M, 1), 216 (9), 190 (3), 172 (10), 92 (8), 91 (100), 65 (8), 55 (5); 250 MHz  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) 1.81–1.91 (complex absorption, 2 H,  $\text{H}_{3\text{a}}$ ,  $\text{H}_{3\text{b}}$ ), 3.22 (t,  $J_{2,3\text{a}} = J_{2,3\text{b}} = 7.7\text{ Hz}$ , 1 H,  $\text{H}_2$ ), 3.68 (s, 3 H,  $\text{OCH}_3$ ), 5.06 (s, coalescent AB system, 2 H,

$\text{CH}_2\text{Ph}$ , 6.03 (br s, 1 H, *N-H*), 7.27 (br s, 5 H,  $\text{C}_6\text{H}_5$ ); 62.5 MHz  $^{13}\text{C}$ -NMR ( $\text{CDCl}_3$ ) 23.89 (*C-3*), 38.41 (*C-2*), 43.24 (*C-1*), 53.32 ( $\text{OCH}_3$ ), 67.27 ( $\text{CH}_2\text{Ph}$ ), 127.94 (2  $\text{C}_o$ ), 128.11 ( $\text{C}_p$ ), 128.38 (2  $\text{C}_m$ ), 135.76 ( $\text{C}_{ipso}$ ), 155.94 ( $\text{HNC=O}$ ), 168.97 ( $\text{C=O}$ ), 169.41 ( $\text{C=O}$ ).

**Methyl (1S,2R)-(+)-1-[N-(benzyloxycarbonyl)amino]-2-methoxycarbonylmethylcyclopropanecarboxylate, 11.** A solution of acid chloride **9** (190 mg, 0.61 mmol) in ether (7 mL) was added slowly with stirring to an ice-cooled and freshly distilled solution of excess diazomethane in ether. The reaction was monitored by IR spectroscopy that allowed to observe the disappearance of the signal at  $1780\text{ cm}^{-1}$  ( $\text{CIC=O}$ ) and the appearance of a new signal at  $2107\text{ cm}^{-1}$  corresponding to the diazoketone. After stirring at  $0^\circ\text{C}$  for 1 h, solvent was removed at reduced pressure and the residue was poured into 25 mL of anhydrous methanol. The solution was introduced into a Pyrex reactor under argon atmosphere and stirred at room temperature whilst irradiated with a 125 W medium-pressure mercury-lamp for 4.5 h. Decomposition of the diazoketone was also monitored by IR. The solvent was evaporated and the residue was chromatographed (2:1 ethyl acetate-hexane) to afford diester **11** (110 mg, 63% yield) as a colorless oil.  $[\alpha]_D + 8.6$  (c 0.70,  $\text{CHCl}_3$ ); IR (film) 3353 (br), 1743, 1701,  $1652\text{ cm}^{-1}$ ; MS, *m/e* (%) 321 (M, 1), 230 (2), 186 (23), 154 (15), 92 (9), 91 (100), 65 (9), 59 (10). 250 MHz  $^1\text{H}$ -NMR (acetone  $\text{d}_6$ ) 1.08 (m, 1 H,  $\text{H}_{3a}$ ), 1.82 (m, 1 H,  $\text{H}_{3b}$ ), 1.95 (m, 1 H,  $\text{H}_2$ ), 2.34 (dd,  $J_{2a',2b'} = 16.2\text{ Hz}$ ,  $J_{2a',2} = 8.9\text{ Hz}$ , 1 H,  $\text{H}_{2a'}$ ), 2.62 (dd,  $J_{2b',2a'} = 16.2\text{ Hz}$ ,  $J_{2b',2} = 5.8\text{ Hz}$ , 1 H,  $\text{H}_{2b'}$ ), 3.67 (s, 6 H, 2 x  $\text{OCH}_3$ ), 5.10 (d, AB system,  $J_{gem} = 12.4\text{ Hz}$ , 1 H,  $\text{CH}_2\text{Ph}$ ), 5.17 (d, AB system,  $J_{gem} = 12.4\text{ Hz}$ , 1 H,  $\text{CH}_2\text{Ph}$ ), 5.60 (br s, 1 H, *N-H*), 7.33 (complex absorption, 5 H,  $\text{C}_6\text{H}_5$ ); 62.5 Hz  $^{13}\text{C}$ -NMR ( $\text{CDCl}_3$ ) 22.46 (*C-3*), 23.76 (*C-2*), 33.12 (*C-2'*), 37.70 (*C-1*), 51.68 ( $\text{CH}_3\text{O}$ ), 52.30 ( $\text{CH}_3\text{O}$ ), 66.69 ( $\text{CH}_2\text{Ph}$ ), 127.64 (2  $\text{C}_o$ ), 127.85 ( $\text{C}_p$ ), 128.21 (2  $\text{C}_m$ ), 136.05 ( $\text{C}_{ipso}$ ), 156.86 ( $\text{HNC=O}$ ), 172.44 ( $\text{MeOC=O}$ ), 172.64 ( $\text{MeOC=O}$ ). Anal. Calcd. for  $\text{C}_{15}\text{H}_{19}\text{O}_6\text{N}$ : C, 57.32; H, 5.16; N, 4.78. Found: C, 57.31; H, 5.26; N, 4.84.

**(-)-(Z)-2,3-methano-L-glutamic acid, 1.** A mixture of compound **11** (100 mg, 0.31 mmol), 6N HCl (2.5 mL) and three drops of glacial acetic acid was stirred at  $90^\circ\text{C}$  for 6 h. Then it was evaporated to dryness under vacuo and the obtained yellowish solid was poured into absolute ethanol (3 mL) and propylene oxide (1.5 mL) was added. The mixture was stirred at  $35^\circ\text{C}$  for 10 min. Then solvent and excess reagent were removed at reduced pressure to give a solid which was poured into bidistilled water (2 mL) and eluted through a  $\text{C}_{18}$ -reverse phase cartridge to furnish quantitatively (-)-(Z)-2,3-methano-L-glutamic acid, **1** (47 mg). Crystals, m.p.  $167\text{--}169^\circ\text{C}$  (from water-ethanol);  $[\alpha]_D -10.0$  (c 0.40, water); IR (KBr)  $3600\text{--}2200$  (br), 1725,  $1722\text{ cm}^{-1}$ ; MS, *m/e* (%) 141 (57), 113 (84), 96 (68), 68 (78), 54 (48), 41 (100); 250 MHz  $^1\text{H}$ -NMR ( $\text{D}_2\text{O}$ ) 1.00 (t,  $J_{3a,3b} = J_{3a,2} = 7.1\text{ Hz}$ , 1 H,  $\text{H}_{3a}$ ), 1.45 (dd,  $J_{3b,2} = 9.8\text{ Hz}$ ,  $J_{3b,3a} = 7.1\text{ Hz}$ , 1 H,  $\text{H}_{3b}$ ), 1.81 (m, 1 H,  $\text{H}_2$ ), 2.40 (dd,  $J_{2a',2b'} = 17.5\text{ Hz}$ ,  $J_{2a',2} = 7.7\text{ Hz}$ , 1 H,  $\text{H}_{2a'}$ ), 2.52 (dd,  $J_{2b',2a'} = 17.5\text{ Hz}$ ,  $J_{2b',2} = 7.5\text{ Hz}$ , 1 H,  $\text{H}_{2b'}$ ); 62.5 MHz  $^{13}\text{C}$ -NMR ( $\text{D}_2\text{O}$ -methanol  $\text{d}_4$ ) 18.72 (*C-3*), 21.33 (*C-2*), 33.16 (*C-2'*), 39.39 (*C-1*), 174.38 ( $\text{C=O}$ ), 176.41 ( $\text{C=O}$ ). Anal. Calcd. for  $\text{C}_6\text{H}_7\text{O}_4\text{N}$ : C, 45.28; H, 5.70; N, 8.80. Found: C, 45.32; H, 5.86; N, 8.98.

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