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Enantioselective Synthesis of L-CCG-I†

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Abstract: Introduction of natural menthol as the chiral auxiliary in a γ-Br-α,β-unsaturated ester leads to enantioselective generation of three chiral centers in a single step on reaction with a glycine anion equivalent to provide L-CCG-I in 94% ee.

L-Glutamic acid is known to function as an excitatory neurotransmitter in the mammalian central nervous system and is believed to play an important role in the construction of memory and early learning. Several structural analogues of L-glutamic acid are known to function as important neuropharmacology tools, owing to agonist behavior more specific than that of L-glutamic acid, which not only activates the metabotropic glutamate receptor (m-GluR) but also the ionotropic glutamate receptors.[1,2]

Among the other conformationally constrained analogues of L-glutamic acid, the four isomeric CCG-I−CCG-IV (carboxycyclopropylglycine) (Figure 1) were known to restrict the conformation of L-glutamic acid either in the extended or folded form. These analogues were found to be agonist of either the *N*-methyl-D-aspartic acid (NMDA) or metabotropic glutamate receptor (m-GluR). (2*S*,1′*S*,2′*S*)-2-(Carboxycyclopropyl)glycine (L-CCG-I), which restricts the conformation of L-glutamic acid in the extended form, is a potent and selective agonist of m-GluRs. The neurobiological activity of these compounds has led to several synthetic studies of this class of molecules.[3,4]

In our earlier investigation we found that the course of reaction of a glycine Schiff base with γ-Br-α,β-unsaturated esters in the presence of LiBr/Et_3N can be finely tuned toward either a 1,3-dipolar cycloaddition or a Michael-type reaction by proper choice of the substituent on the glycine Schiff base (Scheme 1).[5]

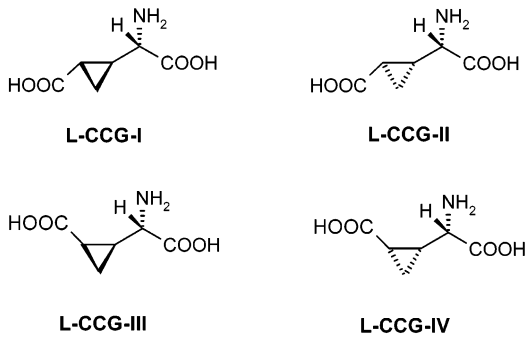

FIGURE 1. L-Isomers of diastereomeric 2-(caboxycyclopropyl)-glycines.

The diastereoselective synthesis of *rac*-CCG-I,[6] where three contiguous stereocenters were generated in a single step, prompted us to undertake the asymmetric synthesis of the molecule using the same strategy. The *l*-menthol-derived ester **2** was used as the chiral electrophile. Reaction of the Schiff base ester **1** with **2** was the key step in the enantioselective synthesis of CCG-I (**5**) which was obtained in 94% ee (Scheme 2).

The single-step cyclopropanation was carried out by dropwise addition of Et_3N (taken in THF) to a mixture of the diphenylimine of ethyl glycinate **1**,[7] menthyl 4-bromocrotonate **2**,[8] and LiBr in THF under an argon atmosphere over a period of 0.5 h at room temperature, after which the mixture was left to stir 16 h at room temperature. After workup and chromatographic purification the product **3** was obtained in 72% yield and 92% diastereomeric ratio as determined by ^{1}H NMR (200 MHz) analysis of the methine (C2) proton. It is pertinent to note that this protocol involves conditions for generation of the cyclopropane milder than those used by Yamaguchi (LDA, −78 °C).[9]

The reaction can be considered as a Michael-induced ring closure (MIRC)[10] of anion (**Y**) to γ-Br-α,β-unsaturated esters to produce the cyclopropane product. The stereochemical outcome can be rationalized by considering participation of the azaallyl anion in the less crowded transition state (Figure 2) to give the erythro adduct in the initial conjugate addition. The formation of *trans*-cyclopropane is in accordance with similar Michael-induced ring closure reaction reported in the literature.[10,11] Thus, this route is complementary to the Yamaguchi synthesis, which yields the threo product.[9] The enolate adopts the *Z*-configuration for the trans-

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(6) Earlier we assigned it as *rac*-CCG-II based on ^{1}H NMR analysis (as there is very minute difference in the ^{1}H NMR spectra of CCG-I and CCG-II) but subsequently found it to be *rac*-CCG-I (ref 5).

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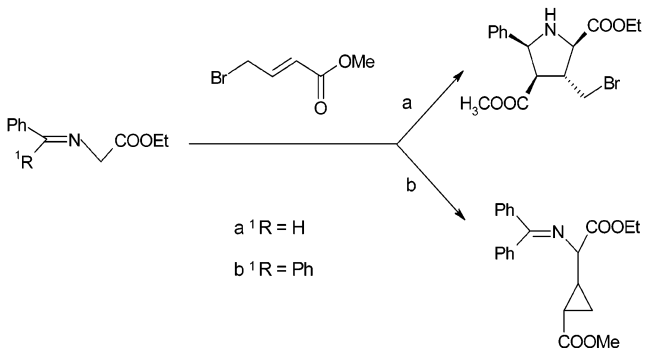
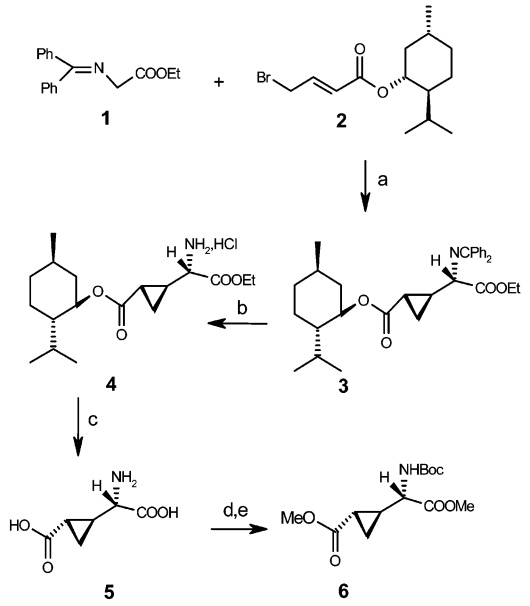
SCHEME 1



SCHEME 2[a]



[a] Reaction conditions: (a) LiBr/Et_3N, THF, rt, 16 h, 72%; (b) 2 N HCl, 0.5 h, 60%; (c) LiOH, MeOH/H_2O (1:1), 6 h, rt, Dowex-50, 98%; (d) Boc_2O, NaOH, *t*-BuOH, rt, 24 h, 50%; (e) CH_2N_2, diethyl ether, 48%.

selective cyclization to promote formation of the *trans*-(2*S*,1′*S*,2′*S*) cyclopropyl derivative.

Treatment of cyclopropane **3** with 2 N HCl afforded the hydrochloride salt **4** in 60% yield as a single stereoisomer. Next, the ester **4** was saponified by treatment with LiOH in MeOH/H_2O. The resulting lithium salt was passed through an ion-exchange resin (DOWEX-50) to give L-CCG-I (**5**). Recrystallization from H_2O/MeOH provided pure L-CCG-I. The optical rotation and the mp of **5** are in excellent agreement with reports in the literature.[3b] The enantioselection of 94% in the final molecule **5** was established by its conversion into the corresponding Boc-protected methyl ester **6** and HPLC analysis. The X-ray crystal structure[12] of ester **6** confirmed the trans orientation of functional groups at C2, C1′, C2′ (Figure 3).

In summary, the three contiguous stereocenters in the constrained glutamic acid analogue L-CCG-I were established in a single step by a Michael-induced ring closure reaction of a chiral, nonracemic electrophile derivative of *l*-menthol with a glycine anion equivalent. The ready availability of *l*-menthol together with the mild reagents and reaction conditions auger well for the application of this strategy to the stereoselective synthesis of this and related products.

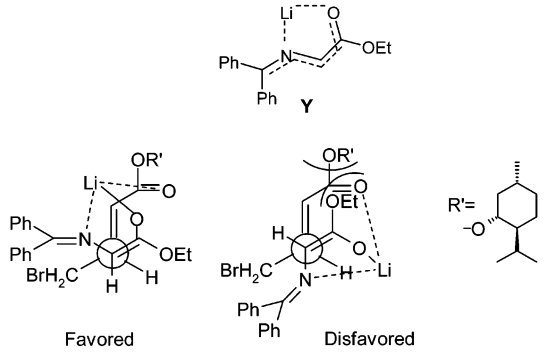


FIGURE 2. Plausible favored and disfavored TSs for initial Michael addition of enolate **Y** to **2**.

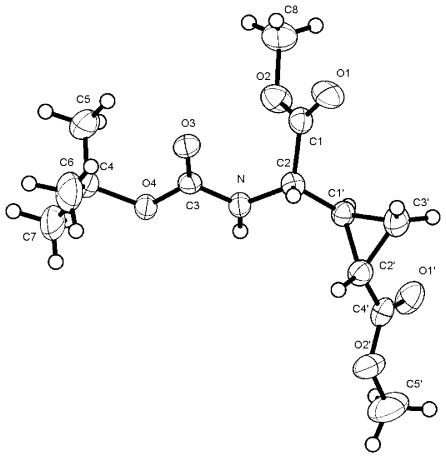


FIGURE 3. ORTEP[13] view of **6**.

Experimental Section

General. All solvents were freshly distilled before use, and dry solvents were distilled under argon from Na/benzophenone. Melting points are uncorrected. Chemical shifts in ^{1}H and ^{13}C NMR are reported relative to residual solvents. Abbreviations for ^{1}H NMR: s = singlet, d = doublet, m = multiplet, br = broad. Progress of the reactions were monitored by TLC using Merck

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(12) Single crystals of the compound (**6**) were obtained from diethyl ether, and a crystal was selected using Leica Polarizing Microscope. X-ray intensity data were collected on a Bruker SMART APEX CCD diffractometer at room temperature. Crystal data: $C_{13}H_{21}NO_6$, M = 287.31, crystal dimensions 1.26 × 0.14 × 0.10 mm^3, crystal system hexagonal, space group *P*65, a = 9.7482(7), c = 28.427(4) Å, V = 2339.4-(4) Å^3, Z = 6, D_c = 1.224 g cm^{-3}, μ (Mo Kα) = 0.097 mm^{-1}, T = 293(2) K, 11720 reflections collected, 2512 unique [$I > 2\sigma(I)$], S = 1.251, R value 0.0556, $wR2$ = 0.1091 (all data R = 0.0627, $wR2$ = 0.1121). All data were corrected for Lorentzian, polarisation, and absorption effects using Bruker's SAINT and SADABS programs. SHELX-97 (Sheldrick, G. M. *SHELX-97*, program for crystal structure solution and refinement; University of Göttingen: Germany, 1997) was used for structure solution and full matrix least squares refinement on *F*2. Hydrogen atoms were included in the refinement as per the riding model.

(13) Johnson, C. K. *ORTEP II, report ORNL-5138*; Oak Ridge National Laboratory: Tennessee, USA, 1976. (Incorporated in SHELX TL package from Bruker-axs).

silica gel 60 F_{254} precoated plates and visualized by flourescence quenching or by charring after treatment with *p*-anisaldehyde. Free amines were detected by ninhydrine charring. The products where purified by column chromatography (SiO_2).

Analytical data of all known compounds were compared with the literature, and new compounds were fully characterized.

trans-**Ethyl-*N*-(diphenylmethylene)-α-(2-carbomenthoxycyclopropyl)-glycinate (3).** To Schiff base **1** (1 g, 3.7 mmol) and menthyl-4-bromocrotonate **2** (1.4 g, 4.6 mmol) in dry THF (25 mL) under argon was added lithium bromide (0.48 g, 5.6 mmol) taken into dry THF (5 mL). To this mixture was added triethylamine (0.471 g, 4.6 mmol) taken into dry THF (10 mL) dropwise over a period of 0.5 h, and the mixture was left to stir for 16 h at room temperature. After completion of the reaction (as per TLC), the reaction mixture was poured into saturated ammonium chloride solution, and the aqueous layer was extracted with 2 × 25 mL of ethyl acetate. The combined organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to give crude cyclopropane **3**. Column chromatography over silica gel (previously neutralized by Et_3N) provided **3** as viscous liquid (1.27 g, 72% and 92% diastereomeric ratio). $[\alpha]_D = -23.2$ ($c = 0.26$, $CHCl_3$). δ_H ($CDCl_3$, 200 MHz): 7.61−7.14 (m, 10H), 4.66 (dt, $J = 10.6$ Hz, $J = 4.4$ Hz, 1H), 4.17 (m, 2H), 3.9 (d, $J = 5.4$ Hz, 1H), 1.87−2.05 (m, 3H), 1.83−1.74 (m, 1H), 1.69 (br s, 1H), 1.63 (br s, 1H), 1.55−1.33 (m, 2H), 1.25 (t, $J = 7.3$ Hz, 3H), 1.17−1.13 (m, 1H), 1.06−1.01(m, 1H), 0.92−0.87 (m, 9H), 0.80−0.69 (m, 3H) ppm. δ_C ($CDCl_3$, 50 MHz): 173.0, 170.9, 170.7, 139.1, 136.0, 130.3, 128.8, 128.4, 127.8, 127.6, 73.7, 64.6, 60.7, 46.9, 40.8, 34.2, 31.2, 26.1, 24.7, 23.3, 21.9, 20.7, 17.1, 16.2, 14.1, 11.5 ppm. IR ($CHCl_3$) $\tilde{\nu}$ (cm^{-1}): 1722; 1446. MS (ESI): *m*/*z* 489.01, 416. Anal. Calcd for $C_{31}H_{39}NO_4$: C 76.041, H 8.028, N 2.860. Found: C 76.09, H 8.10, N 3.03.

(2*S*,1′*S*,2′*S*)-Ethyl α-(2-carbomenthoxycyclopropyl)-glycinate Hydrochloride Salt (4). The cyclopropane **3** (1.27 g, 2.6 mmol) was treated with 2 N HCl (20 mL), and the mixture was allowed to stir at room temperature for 0.5 h. The hydrochloride salt of the free amine precipitated out as a white solid on addition of ethyl acetate, which was filtered and washed several times with ethyl acetate to remove benzophenone. The solid was dried under vaccum to yield **4** (0.63 g, 60%). $[\alpha]_D = +42.8$ ($c = 0.51$, 2-propanol). Mp: 190−193 °C. δ_H (500 MHz, DMSO-d_6): 8.85 (br s, 1H), 4.75 (dt, $J = 10.7$ Hz, $J = 4.4$ Hz, 1H), 4.43−4.35 (m, 2H), 3.82 (d, $J = 9.9$ Hz, 1H), 2.14−2.11 (m, 1H), 2.02 (br d, 1H), 1.85−1.77 (br m, 3H), 1.62−1.56 (m, 1H), 1.54−1.48 (br m, 2H), 1.41 (t, $J = 7.12$ Hz, 3H), 1.38−1.35 (m, 1H), 1.29−1.26 (m, 1H), 1.23−1.17 (m, 2H), 1.15−1.08 (m, 2H), 1.03 (t, $J = 7.2$ Hz, 6H), 0.87 (d, $J = 6.7$ Hz, 3H) ppm. δ_C (125 MHz, DMSO-d_6): 171.7, 168.4, 74.0, 62.1, 54.0, 46.7, 40.7, 33.9, 30.9, 26.1, 23.4, 22.0, 20.9, 20.6, 18.9, 16.6,14.1, 13.2 ppm. IR (KBr) $\tilde{\nu}$ (cm^{-1}): 2902, 1753, 1710, 1591. MS (EI): *m*/*z* 252, 114, 96, 68, 55. Anal. Calcd for $C_{18}H_{32}NO_4Cl$: C 59.738, H 8.904, N 3.870, Cl 9.796. Found: C 59.95, H 8.65, N 3.72, Cl 9.85.

(2*S*,1′*S*,2′*S*)-α-(2-Carboxycyclopropyl)-glycine (5). The amino ester **4** (0.63 g, 1.55 mmol) was treated with LiOH (0.098 g, 4.65 mmol) in 20 mL of methanol/water (1:1) and was allowed to stir for 6 h at room temperature. The methanol was removed on a rotary evaporator, and the aqueous layer was extracted with 3 × 25 mL of ethyl acetate. The aqueous layer was concentrated to 5 mL in a rotary evaporator and loaded onto Dowex 50 × 8 (20-60, H^+ form) ion-exchange resin. The column was eluted first with distilled water (2 × 100 mL) and then with 100 mL of 10% ammonia solution. The eluate was concentrated under reduced pressure, and the crude product was recrystallized from water to furnish colorless crystals of amino acid **5** (0.213 g, 86.5%). $[\alpha]_D = +106$ ($c = 0.50$, H_2O). Mp: 245−250 °C (dec) {lit. $[\alpha]_D = +102$ ($c = 0.50$, H_2O), Mp: 243−247 °C (dec)}. δ_H (500 MHz, D_2O): 3.24 (d, $J = 9.9$ Hz, 1H), 1.74 (ddd, $J = 9.0$ Hz, 5.0 Hz, 4.1 Hz, 1H), 1.66 (dddd, $J = 9.9$ Hz, 9.0 Hz, 6.0 Hz, 4.1 Hz, 1H), 1.30 (ddd, $J = 9.0$ Hz, 6.0 Hz, 5.1 Hz, 1H), 1.2 (ddd, $J = 9.0$ Hz, 5.0 Hz, 5.1 Hz, 1H) ppm. δ_C (125 MHz, D_2O): 179.5, 172.9, 57.6, 21.9, 20.4, 13.1 ppm. IR (KBr) $\tilde{\nu}$ (cm^{-1}): 2923, 1688, 1616, 1586. MS (EI): *m*/*z* 114, 96, 78, 68, 55. Anal. Calcd for $C_6H_9NO_4$: C 45.28, H 5.66, N 8.80. Found: C 44.88, H 5.2, N 8.52.

(2*S*,1′*S*,2′*S*)-Methyl-*N*-Boc-α-(2-carbomethoxycyclopropyl)-glycinate (6). The unrecrystallized amino acid **5** (0.20 g, 1.30 mmol) was taken in NaOH solution (0.060 g in 2 mL of water) and diluted with 1.25 mL of *tert*-butyl alcohol. To the well-stirred reaction mixture was added di-*tert*-butyl dicarbonate (0.292 g, 1 mmol) dropwise, and the mixture was left to stir overnight at room temperature. The reaction mixture was extracted with 2 × 25 mL of hexane, and the organic layer was extracted 3 × 25 mL of saturated bicarbonate solution. The combined aqueous layer was acidified to pH 1−1.5 with 10% $KHSO_4$ and extracted with diethyl ether (4 × 25 mL). The organic layer was washed with 2 × 25 mL of water, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The protected amino acid was used without further purification. The crude compound (0.163 g, 0.6 mmol) was taken in ether (10 mL), cooled, and then treated in portions with diazomethane, generated In situ, until the yellow color persisted, and then concentrated under vaccum. Purification by column chromatography (SiO_2) rendered methyl ester **6** (0.113 g, 48%, 97%ee). $[\alpha]_D = +108.6$ ($c = 0.88$, $CHCl_3$). Mp: 80 °C. δ_H (200 MHz, $CDCl_3$): 5.22 (br d, 1H), 3.96 (br s, 1H), 3.76 (s, 3H), 3.65 (s, 3H), 1.74 (m, 2H), 1.42 (s, 9H), 1.23 (m, 1H), 1.06 (m, 1H) ppm. δ_C (50 MHz, $CDCl_3$): 173.6, 171.6, 80.2, 54.8, 52.5, 51.9, 28.2, 24.1, 17.6, 12.9 ppm. IR ($CHCl_3$) $\tilde{\nu}$ (cm^{-1}): 3440, 1720. MS (ESI): *m*/*z* 286, 188, 128, 156. Anal. Calcd for $C_{13}H_{21}NO_6$: C 54.35, H 7.36, N 4.87. Found: C 53.96, H 7.48, N 4.67. HPLC column CHIRALCEL (OD), mobile phase 10% propan-2-ol in *n*-hexane, flow rate 0.4 mL/min, UV detection 225 nm. t_R: minor isomer 13.5 min, major isomer 14.4 min.

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