Synthesis of (*S*)-α-Cyclopropyl-4-phosphonophenylglycine

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Since it was discovered that some phenylglycine analogues could selectively modulate the activity of metabotropic glutamate receptors (mGluRs),[1] many efforts have been directed to the development of more selective agonists or antagonists based on the phenylglycine skeleton.[2] By varying the substituents on either the α-position or aromatic ring, several subtype-selective antagonists **1a**−**h** (Figure 1) were reported.[3−9] Among these antagonists, CPPG (α-cyclopropyl-4-phosphonophenylglycine **1d**), an analogue of phenylglycine with a 4-phosphono group and a α-cyclopropyl group, was found to be a most potent and selective antagonist for group III mGluRs. Recently this compound has been widely used in probing the neurotransmission mechanism and physiological functions of mGluRs.[10] Because only *S*-isomers of this class of analogues showed selective antagonist activity,[2] an efficient synthetic route for preparing enantiopure CPPG is highly required in order to check if it displayed similar stereoselective recognition to mGluRs. Herein, we report the first asymmetric synthesis of (*S*)-CPPG.

Our synthesis started from (*R*)-4-benzoxyphenylglycine **2**, which was prepared using (*R*)-4-hydroxyphenylglycine as the starting material (Scheme 1).[11] After the amino group was protected with methyl chloroformate, the carbamate generated was reacted with benzaldehyde dimethyl acetal in ether in the presence of boron trifluoride etherate to produce *trans*-oxazolidinone **3**.[12] The pure product was obtained in 73% overall yield after recrystallization, and its stereochemistry was confirmed by its NOESY spectra. With the oxazolidinone **3** in hand, we planned to introduce a dicarbon functional group at the α-position of amino acid moiety using the self-regeneration of stereocenter strategy.[13] Initially, reaction of lithium enolate of **3** with ethylene oxide was attempted.[14] Under several literature conditions such as direct coupling or using trifluoride etherate as an additive, we did not detect any coupling product. This problem might result from the lower reactivity of the present enolate compared with those reported in the literature.[14] By using a more reactive electrophile, we obtained the alkylation product **4** successively. It was found that only one diastereomer formed in this step as shown by either

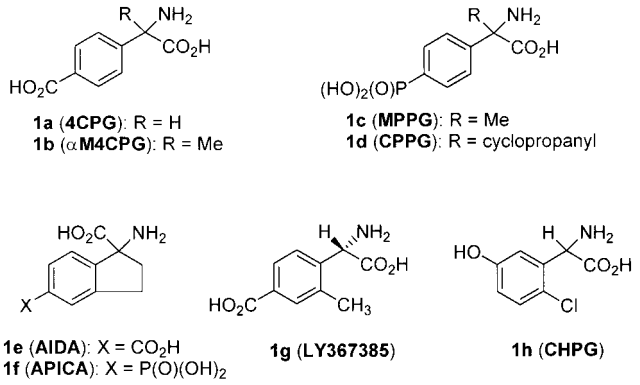
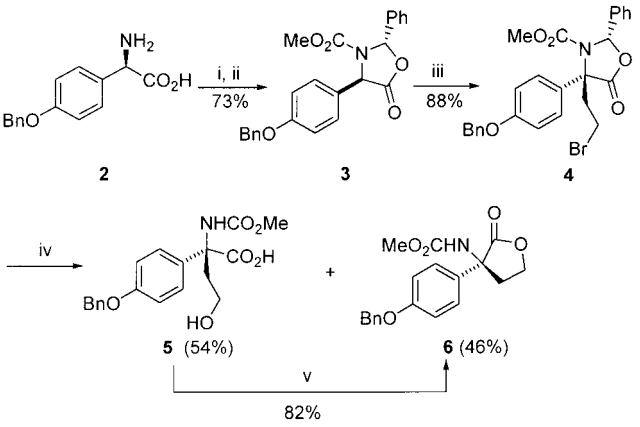


Figure 1. Structures of phenylglycine-type antagonists of metabotropic glutamate receptors.

Scheme 1[a]



[a] Reagents and conditions: i. ClCOOMe/$NaHCO_3$; ii. $PhCH(OMe)_2$, $BF_3{\cdot}Et_2O$; iii. NaHMDS then $BrCH_2CH_2OTf$; iv. LiOH, H_2O, THF; v. MeOH/HCl.

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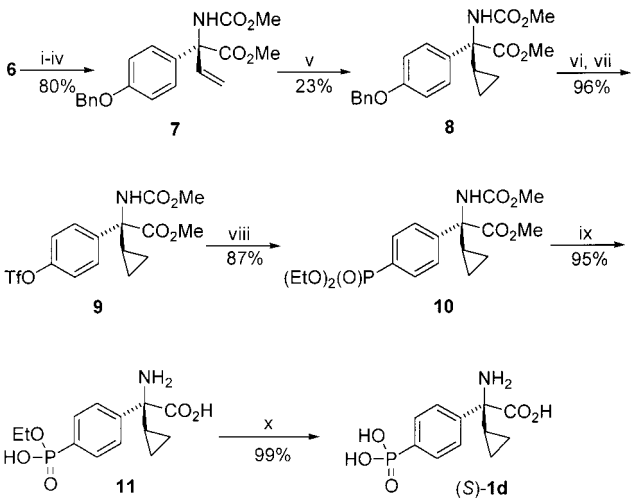
Scheme 2[a]



[a] Reagents and conditions: i. $(PhSe)_2$, $NaBH_4$; ii. CH_2N_2; iii. O_3; iv. CCl_4, reflux; v. CH_2N_2, $Pd(acac)_2$; vi. Pd/C, H_2; vii. Tf_2O, Et_3N; viii. $Pd(Ph_3P)_4$, $HP(O)(OEt)_2$, Et_3N; ix. 2 N NaOH, reflux, then Dowex-50W; x. 2 N HCl, 80 °C, then Dowex-50W.

HPLC (DIKMA C_{18}, 4.6 × 150 mm, 1/1−1/0 MeCN/H_2O as eluent) or ^{1}H NMR. Treatment of the bromide **4** with aqueous lithium hydroxide in THF provided the desired lactone **6** in 54% yield, together with a byproduct **5** in 46% yield, which was converted into the lactone **6** by refluxing in methanolic hydrochloride. Next, lactone cleavage of **6** with benzeneselenolate anion followed by oxidation/pyrolysis produced the olefin **7** in 80% overall yield (Scheme 2).[15] Cyclopropanation of **7** with diazomethane under the action of various catalysts such as $Pd(OAc)_2$, $Pd(acac)_2$, CuI, $Cu(acac)_2$, and $PdCl_2$ was tried.[16] In most cases the reaction occurred with low conversion. The highest conversion (23%) was observed when $Pd(acac)_2$ was used as catalyst. In this case 85% yield was reached based on the recovery of the starting material. The reason for this low conversion is unclear, but one possible explanation is the steric hindrance of olefin **7**. It was notable that under Simmons−Smith condition[17] less 10% conversion was observed. By careful column chromatography, the pure cyclopropanation product **8** was isolated, which was deprotected by Pd/C-catalyzed hydrogenation and then transformed into triflate **9** with Tf_2O. Finally, coupling of the triflate **9** with diethyl phosphite catalyzed by $Pd(Ph_3P)_4$ afforded phosphonate **10**.[11a] The deprotection of **10** was found to be another challenging step in this synthesis. Under higher reaction temperatures (>100 °C), hydrolysis of **10** with aqueous hydrochloride provided the ring-opened products, while under lower reaction temperature it gave incomplete deprotection products. After some experimentation, we found that this problem could be solved by stepwise hydrolysis. Accordingly, refluxing the phosphonate **10** in 2 N NaOH for 2 days afforded amino acid **11** as a single product, which was further hydrolyzed in 2 N HCl at 80 °C for 3 days, providing crude **1** as the hydrochloride salt. Upon purification by a Dowex-50W column, the pure (*S*)-CPPG was obtained in 99% yield.

In conclusion, we developed a stereospecific route to synthesize (*S*)-CPPG. The biological evaluation of this compound and amino acid **11** is in progress.

Experimental Section

(2*R*,4*R*)-2-Phenyl-4-((4-phenylmethoxy)phenyl)-5-oxo-3-oxazolidininecarboxylic Acid, Methyl Ester 3. To a suspension solution of (*R*)-4-benzoxyphenylglycine (25 g, 97.3 mmol), $NaHCO_3$ (16.3 g, 194.6 mmol) in 150 mL of water, and 25 mL of chloroform was added methyl chloroformate (15.0 mL, 194.6 mmol) in a dropwise manner. After the solution was stirred for another 24 h, 1 N HCl was added to adjust pH = 4. The mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated to yield a crude solid, which was dissolved in 150 mL of dry ether. To this stirring solution were added benzaldehyde dimethyl acetal (14.8 mL, 107.0 mmol) and boron trifluoride etherate (50.9 mL, 414.5 mmol) by syringe. After it was stirred for 72 h, the reaction mixture was filtered. The filter cake was washed with ether to give 28.6 g (73%) of **3** as a white solid. Mp: 229−231 °C (ethyl acetate); $[\alpha]^{24}_D$ −165 (*c* 1.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41−7.27 (m, 12H), 7.00 (d, J = 8.7 Hz, 2H), 6.69 (s, 1H), 5.36 (s, 1H), 5.05 (s, 2H), 3.43 (s, 3H); MS *m*/*z* 403 (M^+); HRMS found *m*/*z* 403.1420 (M^+); $C_{24}H_{21}NO_5$ requires 403.1421.

(2*R*,4*S*)-2-Phenyl-4-(2-bromoethyl)-4-((4-phenylmethoxy)-phenyl)-5-oxo-3-oxazolidininecarboxylic Acid, Methyl Ester 4. A solution of **3** (5.0 g, 12.4 mmol) in 350 mL of anhydrous THF was cooled to −78 °C. To this solution was added NaHMDS (1 M in THF, 14.9 mL, 14.9 mmol) at −78 °C under argon atmosphere. After the stirring was continued for 30 min, $BrCH_2$-CH_2OTf (4.14 g, 16.1 mmol) was added by syringe. The reaction mixture was stirred for another 45 min at the same temperature, and then 50 mL of saturated aqueous NH_4Cl was added to quench the reaction. The mixture was extracted with ethyl acetate, and the organic layer was washed with brine and dried over $MgSO_4$. After the solvent was evaporated, the residual oil was purified by flash chromatography (silica gel, 2/1 petroleum ether/ethyl acetate as eluent) to afford 5.6 g (88%) of **4** as a colorless oil. $[\alpha]^{20}_D$ +44 (*c* 1.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43−7.27 (m, 12H), 6.95 (d, J = 8.4 Hz, 2H), 6.61 (s, 1H), 5.06 (s, 2H), 3.70 (s, 3H), 3.40 (m, 2H), 3.05 (m, 1H), 2.38 (m, 1H); MS *m*/*z* 509 (M^+, ^{79}Br); HRMS found *m*/*z* 509.0838 (M^+, ^{79}Br); $C_{26}H_{24}BrNO_5$ requires 509.0833.

(*S*)-α-(2-Hydroxyethyl)-α-((methylcarboxy)amino)-4-(phenylmethoxy)benzeneacetic Acid 5 and (*S*)-2-Oxo-3-(4-phenylmethoxy)phenyl-3-(methoxycarbonyl)aminotetrahydrofuran 6. A mixture of **4** (5.6 g, 10.9 mmol) and LiOH (1.0 g, 19.4 mmol) in 50 mL of THF and 10 mL of H_2O was stirred at room temperature until the starting material was consumed. The mixture was added 1 N HCl to adjust pH = 5 before it was extracted with ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The residual oil was purified by flash chromatography (silica gel, 2/1 petroleum ether/ethyl acetate as eluent) to afford 2.0 g (54%) of **6** as a white solid, together with 1.8 g (46%) of alcohol **5**.

To a solution of **5** (1.8 g, 5 mmol) in 20 mL of methanol was introduced gaseous hydrogen chloride until the starting material was consumed. The mixture was evaporated, and the residual oil was purified by flash chromatography (silica gel, 2/1 petroleum ether/ethyl acetate as eluent) to provide 1.4 g (82%) of **6**.

5: $[\alpha]^{16}_D$ +55 (*c* 1.4, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45−7.31 (m, 7H), 6.95 (d, J = 8.1 Hz, 2H), 5.60 (br s, 1H), 5.02 (s, 2H), 3.65 (s, 3H), 3.41−2.53 (m, 4H); MS (ESI) *m*/*z* 382 ($M^+ + Na^+$).

6: Mp: 103−105 °C (ethyl acetate/hexane); $[\alpha]^{20}_D$ +50 (*c* 0.43, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47−7.31 (m, 7H), 7.00 (d, J = 8.1 Hz, 2H), 5.53 (s, 1H), 5.08 (s, 2H), 4.50 (t, J = 9.0 Hz, 1H), 4.10 (dt, J = 9.1, 5.7 Hz, 1H), 3.66 (s, 3H), 3.11 (dd, J = 13.0, 9.4 Hz, 1H), 2.95 (dd, J = 13.0, 5.6 Hz, 1H); MS *m*/*z* 341 (M^+); HRMS found *m*/*z* 341.1263 (M^+); $C_{19}H_{19}NO_5$ requires 341.1260.

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(*S*)-α-Vinyl-α-(methoxycarbonyl)amino-4-phenylmethoxybenzeneacetic Methyl Ester 7. A 250 mL two-neck flask containing sodium borohydride (1.2 g, 31.7 mmol) was fitted with a no. 17 needle as gas outlet and purged with argon over a period of 1 h. Solutions of diphenyl diselenide (4.9 g, 15.6 mmol) in dry DMF (100 mL) and compound **6** (8.9 g, 26 mmol) in dry DMF (100 mL) were prepared and cooled to −78 °C. Each frozen solution was subjected to 20 cycles of argon purging followed by evacuating to 0.1 Torr. Finally each solution was allowed to thaw to room temperature under vacuum and then placed under argon atmosphere. The diphenyl diselenide solution was rapidly transferred to the solid $NaBH_4$ via cannula and stirred to produce a clear faint yellow solution. To this solution was added in an identical manner the solution of compound **6** in DMF. The reaction mixture was then heated at 110 °C for 30 min. The reaction mixture was cooled to 0 °C, and methanol was added to destroy the borane formed in the reaction. After the solvent was removed on a rotary evaporator, the residue was adjusted to pH = 2.5 and extracted with ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated to give a crude acid, which was put into a 100 mL flask, and then diazomethane ether solution (about 1 M) was added. After the acid was consumed monitored by TLC, the reaction was quenched with acetic acid. The solvent was evaporated in vacuo, and the crude oil was purified by flash chromatography (silica gel, 4/1 petroleum ether/ethyl acetate as eluent) to give the corresponding ester.

After the purified ester was dissolved in 150 mL of CH_2Cl_2, ozone was bubbled into the solution at −78 °C until a light blue color persisted. To this mixture was added 1-hexene to give a colorless solution. The cold solution was then added dropwise to refluxing CCl_4, and the refluxing was continued for 30 min. The mixture was concentrated in vacuo, and the residual oil was purified by flash chromatography (silica gel, 4/1 petroleum ether/ethyl acetate as eluent) to provide 7.4 g (80%) of **7** as a colorless oil. $[\alpha]^{16}_D$ +18 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40−7.30 (m, 7H), 6.90 (d, J = 6.9 Hz, 2H), 6.55 (dd, J = 17.3, 10.5 Hz, 1H), 5.97 (s, 1H), 5.39 (d, J = 10.5 Hz, 1H), 5.31 (d, J = 17.3 Hz, 1H), 5.01 (s, 2H), 3.71 (s, 3H), 3.59 (s, 3H); MS *m*/*z* 355 (M^+); HRMS found *m*/*z* 355.1411 (M^+); $C_{20}H_{21}NO_5$ requires 355.1416.

(*S*)-α-Cyclopropyl-α-(methoxycarbonyl)amino-4-(phenylmethoxy)benzeneacetic Methyl Ester 8. An excess of ethereal diazomethane was added slowly to a solution of compound **7** (7.4 g, 20.8 mmol) and $Pd(acac)_2$ (300 mg, 0.98 mmol) in 50 mL of ether. After the solution was stirred for 10 h at room temperature, the excess diazomethane was removed using a stream of nitrogen. The mixture was evaporated, and the residual oil was purified by flash chromatography (silica gel, 4/1 petroleum ether/ethyl acetate as eluent) to afford 5.4 g (73%) of starting material and 1.77 g (23%) of **8**. $[\alpha]^{16}_D$ +16 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45−7.34 (m, 7H), 6.93 (d, J = 8.8 Hz, 2H), 5.97 (s, 1H), 5.01 (s, 2H), 3.70 (s, 3H), 3.59 (s, 3H), 1.93 (m, 1H), 0.62 (m, 2H), 0.48 (m, 2H); MS *m*/*z* 369 (M^+); HRMS found *m*/*z* 369.1578 (M^+); $C_{21}H_{23}NO_5$ requires 369.1572.

(*S*)-α-Cyclopropyl-α-(methoxycarbonyl)amino-4-((trifluoromethyl)sulfonyloxy)benzeneacetic Methyl Ester 9. To solution of **8** (3.2 g, 8.6 mmol) in 50 mL of methanol was added Pd/C (10%, 320 mg). The suspension solution was stirred for 3 h under H_2 atmosphere at ambient temperature before it was filtered. The filtrate was evaporated to yield a crude oil, which was dissolved in 50 mL of methylene chloride. To this stirring solution was added triethylamine (2.3 mL, 17 mmol) and a solution of Tf_2O (1.6 mL, 11.3 mmol) in 10 mL of methylene chloride at −30 °C, respectively. After the reaction mixture was stirred for another 2 h, it was concentrated, and the residual oil was purified by flash chromatography (silica gel, 3/1 petroleum ether/ethyl acetate as eluent) to provide 3.4 g (96%) of **9** as a pale yellow oil. $[\alpha]^{16}_D$ +10 (*c* 0.77, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, J = 8.1 Hz, 2H), 7.23 (d, J = 8.1 Hz, 2H), 6.09 (s, 1H), 3.70 (s, 3H), 3.56 (s, 3H), 1.89 (m, 1H), 0.68 (m, 2H), 0.52 (m, 2H); MS *m*/*z* 411 (M^+); HRMS found *m*/*z* 411.0600 (M^+); $C_{15}H_{16}F_3NO_7S$ requires 411.0597.

(*S*)-α-Cyclopropyl-α-(methoxycarbonyl)amino-4-(diethylphosphono)benzeneacetic Methyl Ester 10. To a solution of **9** (3.0 g, 7.2 mmol) in 30 mL of Et_3N were added diethyl phosphite (1.8 mL, 10.8 mmol) and $Pd(PPh_3)_4$ (800 mg, 0.72 mmol) under argon. After the resultant mixture was refluxed for 3 h, the cooled solution was concentrated, and the residue was partitioned between 5 mL of water and 50 mL of ethyl acetate. The organic layer was dried over $MgSO_4$ and concentrated. The residual oil was purified by flash chromatography (silica gel, 1/1 petroleum ether/ethyl acetate as eluent) to afford 2.5 g (87%) of **10** as a pale yellow oil. $[\alpha]^{16}_D$ +16 (*c* 0.55, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (dd, J = 12.8, 8.2 Hz, 2H), 7.66 (dd, J = 8.1, 2.3 Hz, 2H), 6.10 (s, 1H), 4.13 (m, 4H), 3.68 (s, 3H), 3.55 (s, 3H), 1.91 (m, 1H), 1.26 (t, J = 6.3 Hz, 6H), 0.69 (m, 2H), 0.48 (m, 2H); MS *m*/*z* 399 (M^+); HRMS found *m*/*z* 399.1447 (M^+); $C_{18}H_{26}NO_7P$ requires 399.1443.

(*S*)-α-Cyclopropyl-4-(ethylphosphono)phenylglycine 11. A mixture of **10** (1.0 g, 2.5 mmol) in 10 mL of 2 N NaOH was heated at reflux for 2 days. The cooled solution was concentrated in vacuo to dryness, and the residue was extracted by ethanol. The unsolved solid was filtered off, and the filtrate was concentrated. The residue was purified by Dowex-50W using water as eluent to provide 740 mg (99%) of **11** as a white solid. Mp: 246 °C (dec); $[\alpha]^{27}_D$ +10 (*c* 1.05, H_2O); ^{1}H NMR (300 MHz, D_2O) δ 7.79−7.66 (m, 4H), 3.81 (m, 2H), 1.51 (m, 1H), 1.17 (t, J = 7.5 Hz, 3H), 0.84 (d, J = 8.3 Hz, 2H), 0.71 (m, 1H), 0.48 (m, 1H); ^{31}P NMR (121 MHz, D_2O) δ 15.32; ^{13}C NMR (75 MHz, D_2O) δ 178.86, 141.74, 136.60 (d, J = 135.0 Hz), 134.23 (d, J = 7.5 Hz), 129.57 (d, J = 10.6 Hz), 69.69, 64.25 (d, J = 3.9 Hz), 18.40, 18.00, 5.3; MS (ESI) *m*/*z* 300 ($M^+ + H^+$).

(*S*)-α-Cyclopropyl-4-phosphonophenylglycine 1d. A solution of **11** (600 mg, 2.0 mmol) in 10 mL of 2 N HCl was heated to 80 °C for 3 days. The cooled solution was concentrated, and the residue was purified by Dowex-50W using water as eluent to provide 540 mg (99%) of **1d** as a white solid. Mp: 243 °C (dec); $[\alpha]^{27}_D$ +17 (*c* 1.05, 10% NaOH/H_2O); ^{1}H NMR (300 MHz, D_2O) δ 7.82 (dd, J = 12.5, 8.0 Hz, 2H), 7.71 (dd, J = 7.6, 1.5 Hz, 2H), 1.70 (m, 1H), 0.89 (d, J = 8.2 Hz, 2H), 0.75 (dd, J = 10.3, 5.7 Hz, 1H), 0.53 (dd, J = 10.0, 5.6 Hz, 1H); ^{31}P NMR (121 MHz, D_2O) δ 11.91; ^{13}C NMR (75 MHz, D_2O) δ 185.38, 148.68, 141.88 (d, J = 125.4 Hz), 132.80 (d, J = 6.8 Hz), 128.78 (d, J = 9.6 Hz), 66.73, 20.76, 3.85, 2.81; MS (ESI) *m*/*z* 272 ($M^+ + H^+$).

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Supporting Information Available: ^{1}H NMR spectra of compounds **3** and **6**−**10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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