Stereoselective synthesis of (*S*)-MPPG, (*S*)-MTPG and (*S*)-(+)-αM4CPG from (*R*)-4-hydroxyphenylglycine

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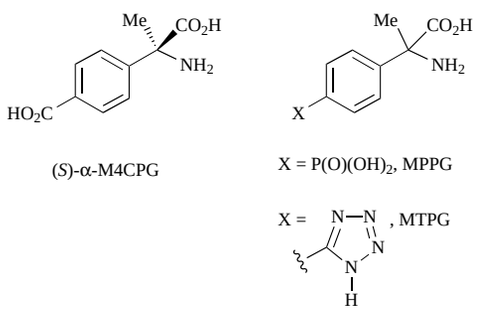
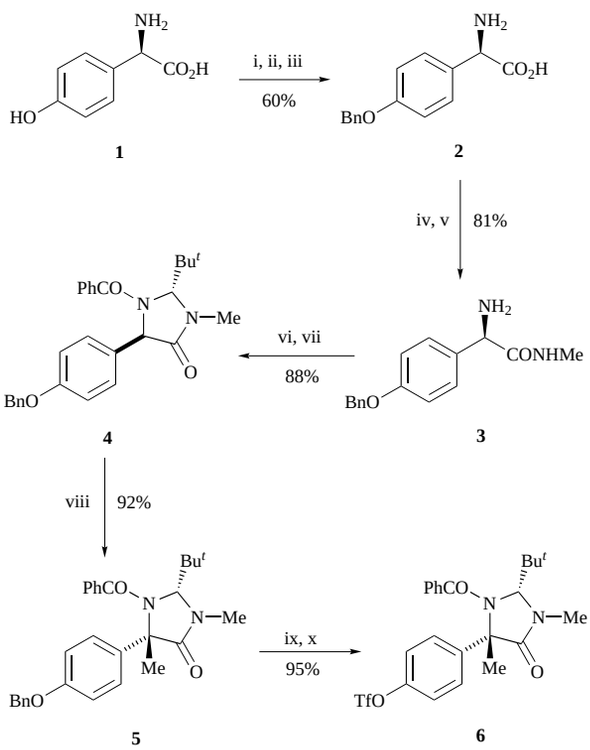
(*R*)-4-Hydroxyphenylglycine was protected with a benzyl group and a methyl group was introduced at the α position by using the self-regeneration-of-stereocentre method. After the 4-hydroxy group had been converted into the corresponding trifluoromethanesulfonate (triflate), three palladium-catalyzed reactions were employed to furnish (*S*)-α-methyl-4-phosphonophenylglycine [(*S*)-MPPG], (*S*)-α-methyl-4-(tetrazol-5-yl)phenylglycine [(*S*)-MTPG] and (*S*)-4-carboxyphenyl-α-methylglycine [(*S*)-αM4CPG], a class of new and selective antagonists of metabotropic glutamate receptors.

The metabotropic glutamate receptor (mGluR) family consists at least eight distinct subtypes termed mGluR1 to mGluR8. Based on their sequence homology, transduction mechanism, and agonist selectivity, these subtypes have been classified into three subgroups.[1] Group I includes mGluR1 and mGluR5, which are coupled to phospholipase C (PLC) and show very similar agonist selectivity for quisqualate. In contrast, group II, which contains mGluR2 and mGluR3, and group III, including mGluR4, mGluR6, mGluR7, mGluR8 negatively couple to adenylate cyclase and, thereby, depress elevations in cyclic adenosine monophosphate (cAMP) levels. However, group II and group III can be distinguished by their marked agonist-selectivity. The former group effectively interact with (2*S*,1′*S*,2′*S*)-2-(2-carboxycyclopropyl)glycine (L-CCG-I) and (1*S*,3*R*)-1-aminocyclopentane-1,3-dicarboxylic acid [(1*S*,3*R*)-ACPD], whereas the latter potently interact with (*S*)-2-amino-4-phosphonobutyric acid (L-AP4).[1] In order better to characterize the different synaptic functions for different subtypes, antagonists, in particular those with subtype selectivity for metabotropic glutamate receptors, are very much required. Owing to Watkins' pioneering work, a number of phenylglycine derivatives have been identified as selective antagonists for mGluRs.[2] Among them, (*S*)-α-methyl-4-carboxyphenylglycine [(*S*)-αM4CPG], was described as an antagonist of group I and group II mGluRs,[3] while α-methyl-4-phosphonophenylglycine (MPPG) and α-methyl-4-(tetrazol-5-yl)phenylglycine (MTPG) were identified as potent antagonists for group II and group III mGluRs with different selectivities.[4] In the past three years, these compounds have found very immediate applications in investigations of the functions of mGluRs in synaptic activity.[1,5] In a preliminary communication,[6] we reported the first asymmetric synthesis of (*S*)-αM4CPG and the configurational assignment of this compound. Although no report about the activity of optical isomers of either MPPG or MTPG has appeared, it is obvious that *S*-isomers for both compounds should be active isomers. Recently, we found that our synthetic protocol for (*S*)-αM4CPG was also suitable for asymmetric synthesis of (*S*)-MPPG and (*S*)-MTPG. Herein, we detail our results.



Structures of (*S*)-α-M4CPG, MPPG and MTPG



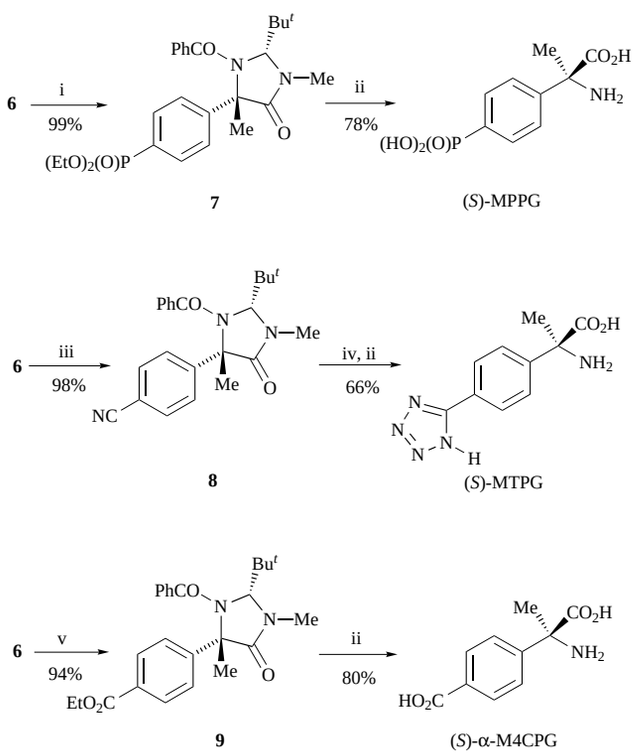
Scheme 1 Synthesis of key intermediate **6**. *Reagents*: i, NaOH, then $CuSO_4$; ii, NaOH, then BnBr; iii, HCl; iv, MeOH, HCl; v, $MeNH_2$; vi, ^tBuCHO, then HCl, MeOH; vii, PhCOCl, Et_3N; viii, LDA, then MeI; ix, Pd/C, H_2; x, Tf_2O, 2,6-lutidine, DMAP.

Results and discussion

As outlined in Scheme 1, we started our total synthesis from commercially available (*R*)-4-hydroxyphenylglycine **1**. To avoid problems from the hydroxy group in the following steps, we needed a suitable protecting group. We found that a method similar to that used for the protection of tyrosine[7] could be successfully extended to this case. Thus, (*R*)-4-hydroxyphenylglycine was treated with one mole equivalent of NaOH and the resulting salt was mixed with $CuSO_4$ to form an amino acid–copper complex. This complex was treated with another

mole equivalent of NaOH, followed by reaction with benzyl bromide, and then the product was triturated with 1 M HCl to release the free benzyl-protected (*R*)-4-hydroxyphenylglycine **2**. This operation could be carried out in one pot and gave compound **2** in ~60% overall yield. We then used Seebach's self-regeneration-of-stereocentre strategy[8] to introduce a methyl group at the α position of this amino acid. Therefore, compound **2** was converted into the corresponding methyl ester and this was treated with methylamine to obtain amide **3** in 81% yield. Amide **3** was allowed to react with *tert*-valeraldehyde, and then the imine product was treated with methanol saturated with gaseous HCl followed by the reaction with benzoyl chloride to afford **4** in ~88% overall yield. The *trans*-isomer is the major product and only a small amount of *cis*-isomer was separated by silica gel chromatography. After treatment of *trans*-isomer with lithium diisopropylamide (LDA), the resulting anion was trapped with methyl iodide to produce compound **5**. The configuration of the new stereogenic centre should be *S*, and ^{1}H NMR spectroscopy showed that only one isomer was formed. It is worth noting that the present methodology should permit the preparation of a wide variety of analogous compounds, some of which have been previously reported,[9] just by employing different electrophiles. After removal of the benzyl protecting group of compound **5** by Pd/C-catalyzed hydrogenation, the resulting free hydroxy group was converted into the triflate **6** by reaction with trifluoromethanesulfonic anhydride (Tf_2O).[10]

With the key intermediate **6** in hand, we could use three Pd-catalyzed reactions to generate our desired functional groups. Thus, as shown in Scheme 2, treatment of triflate **6** with diethyl



Scheme 2 Pd-catalyzed route to (*S*)-MPPG, (*S*)-MTPG and (*S*)-α-M4CPG. *Reagents*: i, $(Ph_3P)_4Pd$, $HP(O)(OEt)_2$, Et_3N; ii, 6 M HCl, then propylene oxide, or ion-exchange chromatography; iii, $(Ph_3P)_4Pd$, TMSCN, Et_3N; iv, Bu_3SnN_3; v, $Pd(OAc)_2$, DPPP, CO, EtOH.

hydrogen phosphite under catalysis by tetrakis(triphenylphosphine)palladium[11] afforded the diethyl arylphosphonate **7**. After heating of a solution of compound **7** in 6 M HCl at 150 °C, all the protecting groups were removed and the resulting hydrochloride salt of the amino acid was treated with propylene oxide to release the free (*S*)-MPPG. Next, palladium-catalyzed cyanation[12] of triflate **6** by using trimethylsilyl cyanide (TMSCN) as cyanide source produced the corresponding nitrile, which was elaborated to the tetrazole **8** by heating of a solution of the nitrile with 2 mol equiv. of azidotri-*n*-butylstannane in the absence of solvent.[13] The tetrazole **8** was deprotected with 6 M HCl to afford (*S*)-MTPG after ion-exchange chromatography (Dowex 50-X-8). Finally, we could obtain ester **9** by employing a palladium-catalyzed carbonylation,[14] and the ester was hydrolyzed with 6 M HCl, followed by treatment with propylene oxide to afford (*S*)-αM4CPG.

To conclude, we have developed a general and asymmetric route to (*S*)-MPPG, (*S*)-MTPG and (*S*)-αM4CPG. The syntheses of other phenylglycine derivatives by using this method, together with their biological evaluation, are underway in this group and will be reported in due course.

Experimental

General procedures

Mps were measured on a capillary melting point apparatus and are uncorrected. IR spectra were measured on a Shimadzu 440 spectrometer. ^{1}H NMR spectra were recorded with $SiMe_4$ as an internal standard in a Bruker AM-300 spectrometer. *J*-Values are given in Hz. MS spectra were determined on a Finnigan 4201 spectrometer or a VG Quattro MS/MS spectrometer. Optical rotations were obtained on a Perkin-Elmer 241 Autopol polarimeter, with $[a]_D$-values, given in units of 10^{-1} deg cm^2 g^{-1}. CH_2Cl_2 was distilled from CaH_2, and tetrahydrofuran (THF) was distilled from a deep blue ketyl prior to use. All other solvents were reagent-grade quality and were used as received. Na_2SO_4 was used as the drying agent in all work-up procedures. All reactions were run in flame-dried glassware under nitrogen atmosphere unless stated otherwise. Light petroleum refers to the fraction distilled between 60–90 °C.

(*R*)-4-Benzyloxyphenylglycine 2

25 g (0.15 mol) of (*R*)-4-hydroxyphenylglycine **1** was dissolved in 75 ml of 2 M NaOH and then a solution of 35.7 g of $CuSO_4 \cdot 5H_2O$ (0.15 mol) in 40 ml of water was added to the stirred solution. After stirring of this mixture for a further 20 min, 75 ml of 2 M NaOH, 560 ml of methanol and 22 ml (0.19 mol) of benzyl bromide were added. The resulting solution was stirred vigorously for 3 h and then the blue precipitate was filtered off, and washed with 200 ml of methanol–water (3.5 : 1). After trituration of the precipitate with 10 ml of 1 M hydrochloric acid, the mixture was filtered again and the operation was repeated several times until the precipitate turned white. This solid was washed successively with 50 ml of NH_4OH, 50 ml of water and 50 ml of methanol, and dried *in vacuo* to afford crude title compound **2**. Without further purification, this amino acid was used directly for the next step; δ_H(300 MHz; CD_3SOCD_3) 7.45 (m, 5 H, $C_6H_5CH_2$), 7.28 (d, $J_{2,3}$ 7.8, 2 H, ArH), 6.91 (d, $J_{3,2}$ 7.8, 2 H, ArH), 5.14 (s, 2 H, PhCH_2) and 5.08 (s, 1 H, CHNH_2).

(*R*)-4-Benzyloxyphenyl-*N*-methylglycinamide 3

Through a suspension of (*R*)-4-benzyloxyphenylglycine (40.0 g, 0.156 mol) in 350 ml of anhydrous methanol was introduced gaseous hydrogen chloride until no more gas was absorbed. The resulting solution was stirred overnight at room temperature before the solvent was removed. The residue was dissolved with 50 ml of methanol and the solution was concentrated again to remove remaining hydrochloride. Without further purification, this ester was dissolved in 100 ml of anhydrous methanol. To this solution, cooled to 0 °C, was added 300 ml of methylamine in ethanol (300 ml). After the addition the solution was stirred for 30 h at room temp. The solvent was removed on a Rotavapor and the residue was treated with 100 ml of methylene dichloride. The resulting suspension was filtered and the filtrate was concentrated. Column chromatography (silica gel; elution with 20 : 1 methylene dichloride–methanol) of the residual oil afforded compound **3** (26.0 g, 71%) as a solid, mp 103–105 °C;

$[\alpha]_D^{22}$ −22.3 (*c* 0.22, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3380 (NH), 3030 (ArH) and 1650 (CO); δ_H(300 MHz; $CDCl_3$) 7.46–7.27 (m, 7 H, ArH), 7.05 (br s, 1 H, NH), 6.79 (d, $J_{3,2}$ 8.5, 2 H, ArH), 5.08 (s, 2 H, PhCH_2), 4.54 (m, 1 H, C*H*NH_2), 2.84 (d, *J* 4.9, 3 H, NHCH_3) and 1.65 (br s, 2 H, NH_2); *m*/*z* (EI) 254 (M^+ − 16) (Found: M^+ − CONHMe, 212.109. $C_{14}H_{14}NO$ requires *m*/*z*, 212.108).

(2*R*,5*R*)-1-Benzoyl-5-(4-benzyloxyphenyl)-2-*tert*-butyl-3-methylimidazolidin-4-one 4

A mixture of compound **3** (26.0 g, 96 mmol), trimethylacetaldehyde (13 ml, 120 mmol) and 80 ml of *n*-pentane was refluxed with removal of water (Dean–Stark) for 3 h. After being cooled the resulting suspension was concentrated at reduced pressure and the residual oil was dissolved in 30 ml of anhydrous methanol and then 60 ml of methanol saturated with gaseous HCl was added at 0 °C. After being stirred for 3 h at room temp., the solution was concentrated to dryness. The residue was dissolved in 30 ml of anhydrous methanol and the solution was concentrated again to remove remaining hydrochloride. The resultant yellow solid was dissolved in 250 ml of methylene dichloride and then 200 ml of triethylamine was added, with cooling in an ice–water-bath. After the mixture had been stirred for 20 min, 35 ml (300 mmol) of benzoyl chloride was added and the solution was stirred for 6 h at room temp. To quench the reaction 200 ml of ice–water was added. The organic layer was separated and the aqueous layer was extracted with methylene dichloride (3 × 150 ml). The combined organic layers were washed successively with water and brine, dried over Na_2SO_4, and concentrated. The residue was loaded on a column of silica gel and eluted with 1:3 ethyl acetate–light petroleum to afford *compound* **4** (37.5 g, 88% from **3**), mp 203–205 °C (Found: C, 75.52; H, 6.67; N, 6.12. $C_{28}H_{30}N_2O_3$ requires C, 75.98; H, 6.83; N, 6.33%); $[\alpha]_D^{22}$ −137.5 (*c* 1.02, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3030 (ArH), 1700 (CO) and 1650 (CO); δ_H(300 MHz; $CDCl_3$) 7.49–7.16 (m, 12 H, ArH), 6.57 (m, 2 H, ArH), 5.85 (s, 1 H, ArC*H*N), 5.05 (s, 1 H, Bu^{t}C*H*), 4.95 (s, 2 H, PhCH_2), 3.17 (s, 3 H, NCH_3) and 1.14 (s, 9 H, Bu^t); *m*/*z* (EI) 385 (M^+ − 57).

(2*R*,5*S*)-1-Benzoyl-5-(4-benzyloxyphenyl)-2-(*tert*-butyl)-3,5-dimethylimidazolidin-4-one 5

To a solution of compound **4** (17.2 g, 38.9 mmol) in 400 ml of anhydrous THF was added a solution of LDA (40 mmol) in THF at −78 °C. The resulting solution was stirred for 1 h at the same temperature and then methyl iodide (4 ml, 65 mmol) was added. Stirring was continued for 2 h at −78 °C before the solution was warmed to room temp. Saturated aq. ammonium chloride (400 ml) was added to quench the reaction. The organic layer was separated and the aqueous layer was extracted with methylene dichloride. The combined organic layers were washed successively with water and brine, and dried over anhydrous Na_2SO_4. After removal of the solvent, the residual oil was chromatographed (silica gel; 1:3 ethyl acetate–light petroleum as eluent) to afford *title compound* **5** (16.2 g, 92%), mp 202–204 °C (Found: C, 75.98; H, 7.13; N, 5.81. $C_{29}H_{32}N_2O_3$ requires C, 76.29; H, 7.06; N, 6.14%); $[\alpha]_D^{22}$ +141.3 (*c* 1.33, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3050 (ArH), 1690 (CO) and 1650 (CO); δ_H(90 MHz; $CDCl_3$) 7.6–7.4 (m, 12 H, ArH), 6.9 (d, *J* 8.4, 2 H, ArH), 5.4 (s, 1 H, Bu^{t}C*H*), 5.0 (s, 2 H, PhCH_2), 3.0 (s, 3 H, NCH_3), 1.7 (s, 3 H, CH_3) and 0.8 (s, 9 H, Bu^t); *m*/*z* (EI) 399 (M^+ − 57).

Triflate 6

A mixture of the benzyl ether **5** (16.3 g, 35.7 mmol), 0.5 g of 10% Pd/C and 250 ml of methanol was stirred under hydrogen (ordinary pressure) for 3 h. After filtration to remove Pd/C, the filtrate was concentrated to furnish the deprotected product, which was dissolved in 250 ml of anhydrous methylene dichloride, and this was followed by addition of 2,6-dimethylpyridine (2,6-lutidine) (5 ml, 42.9 mmol) and 4-(dimethylamino)pyridine (DMAP) (1.32 g, 10.8 mmol). The stirred solution was cooled to −30 °C and triflic anhydride (Tf_2O) (9 ml, 53.5 mmol) was added. After being stirred for 2 h the solution was warmed to room temp. and was then poured into 150 ml of ice–water. The organic layer was separated, washed with water, dried over anhydrous Na_2SO_4, and concentrated. The residual oil was allowed to pass through a short column of silica gel with elution by 1:4 ethyl acetate–light petroleum to afford compound **6** (17.4 g, 95%). Without further purification, this triflate was directly used for the next step.

Pd-catalyzed coupling of triflate 6 with diethyl hydrogen phosphite

A mixture of triflate **6** (1.23 g, 2.48 mmol), tetrakis(triphenylphosphine)palladium (0.61 g, 0.51 mmol), diethyl hydrogen phosphite (1.9 ml, 14.5 mmol) and 4 ml of triethylamine was heated at 100 °C under nitrogen for 8 h. After having cooled to room temp. the mixture was partitioned between 100 ml of ethyl acetate and 50 ml of water. The organic layer was separated, washed successively with water and brine, dried over anhydrous Na_2SO_4, and concentrated by Rotavapor. Chromatography of the residual oil with 1:2 ethyl acetate–light petroleum as eluent afforded phosphonate **7** (1.01 g, 84%); $[\alpha]_D^{22}$ +141.3 (*c* 1.33, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3050 (Ar–H), 1776 (C=O), 1728 (C=O) and 1410 (Ar–P); δ_H(300 MHz; $CDCl_3$) 8.10 (m, 4 H, ArH), 7.43 (m, 5 H, ArH), 5.52 (s, 1 H, Bu^{t}C*H*), 4.15 (q, *J* 7.6, 4 H, OC$H_2$$CH_3$), 3.15 (s, 3 H, NCH_3), 1.91 (s, 3 H, CH_3), 1.36 (t, *J* 7.6, 6 H, OCH_2CH_3) and 0.86 (s, 9 H, Bu^t); *m*/*z* (EI) 429 (M^+ − 57) (Found: M^+ − Bu^t, 429.160. $C_{22}H_{26}N_2O_5P$ requires *m*/*z*, 429.158).

(*S*)-α-Methyl-4-phosphonophenylglycine [(*S*)-MPPG]

The phosphonate **7** (0.48 g, 0.99 mmol) and 10 ml of 6 M HCl were placed in a sealed tube. This mixture was heated at 160 °C for 24 h. After being cooled to room temp. it was extracted with methylene dichloride (3 × 10 ml). The aqueous layer was concentrated to dryness at reduced pressure and the resulting pale yellow solid was loaded onto an ion-exchange column (Dowex 50WX2-200) and eluted with water to afford (*S*)-MPPG (0.19 g, 78%); $[\alpha]_D^{22}$ +58 (*c* 0.014, 6 M HCl); ν_{max}(KBr)/cm^{-1} 3857–2050br (CO_2H, NH, OH), 1612 (NH_3^+) and 1548 (CO_2^-); δ_H(300 MHz; D_2O) 7.73 (dd, $J_{P\text{-}H}$ 12.4, $J_{3,2}$ 8.3, 2 H, 3,5-ArH), 7.55 (dd, $J_{2,3}$ 8.3, $J_{P\text{-}H}$ 2.8, 2 H, 2,6-ArH) and 1.75 (s, 3 H, CH_3); *m*/*z* (FAB) 246 (M^+).

Nitrile 8

To a solution of triflate **6** (1.30 g, 2.61 mmol) and TMSCN (0.52 g, 5.22 mmol) in 6 ml of triethylamine was added tetrakis(triphenylphosphine)palladium (0.15 g, 0.13 mmol). The resulting mixture was stirred at reflux for 6 h under nitrogen, when TLC indicated complete conversion to nitrile. The solution was partitioned between 150 ml of methylene dichloride and 50 ml of water. The organic layer was separated, washed successively with water and brine, and dried over Na_2SO_4. After removal of solvent, the residual oil was chromatographed to afford nitrile **8** (0.95 g, 98%), $[\alpha]_D^{22}$ +167 (*c* 0.019, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 2235 (CN), 1702 (CO) and 1648 (CO); δ_H(300 MHz; $CDCl_3$) 8.09 (d, $J_{3,2}$ 8.3, 2 H, ArH), 7.64 (d, $J_{2,3}$ 8.3, 2 H, ArH), 7.44 (m, 5 H, ArH), 5.37 (s, 1 H, Bu^{t}C*H*), 3.10 (s, 3 H, NCH_3), 1.99 (s, 3 H, CH_3) and 0.62 (s, 9 H, Bu^t); *m*/*z* (EI) 376 (M^+) (Found: M^+ − Bu^t, 318.122. $C_{19}H_{16}N_3O_2$ requires *m*/*z*, 318.124).

(*S*)-α-Methyl-4-(tetrazol-5-yl)phenylglycine [(*S*)-MTPG]

A mixture of the nitrile **8** (200 mg, 0.55 mmol) and azidotributylstannane (366 mg, 1.1 mmol) was heated at 80 °C under N_2 for 12 h. After being cooled to room temp. it was treated with 6 M HCl. The resulting mixture was stirred for 2 h and was then concentrated to dryness *in vacuo*. The residue was placed in a sealed tube and 5 ml of 6 M HCl were added. After the mixture

had been heated at 160 °C for 24 h it was cooled to room temp. and extracted with methylene dichloride (3 × 10 ml). The aqueous layer was concentrated and the residue was purified on an ion-exchange column (Dowex 50WX2-200; elution with water) to afford (*S*)-MTPG (89 mg, 66%), $[\alpha]_D^{22}$ −72.4 (*c* 0.009, 6 M HCl); ν_{max}(KBr)/cm^{-1} 3400–2340br (CO_2H, NH_2), 1620 (NH_3^+) and 1531 (CO_2^-); δ_H(300 MHz; D_2O) 7.87 (d, $J_{3,2}$ 8.2, 2 H, ArH), 7.48 (d, $J_{2,3}$ 8.2, 2 H, ArH) and 1.78 (s, 3 H, CH_3); *m*/*z* (FAB) 272 ($M^+ + K^+$).

Pd-catalyzed carbonylation of triflate 6

To a solution of triflate **6** (17.4 g, 35.4 mmol), 1,3-bis-(diphenylphosphino)propane (DPPP) (1.51 g, 3.64 mmol) and palladium diacetate (0.51 g, 2.25 mmol) in 100 ml of anhydrous ethanol were added 20 ml of triethylamine. The mixture was stirred under carbon monoxide (1 atm) at 70 °C for 3 h. After being cooled to room temp., the mixture was partitioned between 400 ml of water and 600 ml of methylene dichloride. The organic layer was separated, washed successively with water and brine, and dried over Na_2SO_4. After removal of the solvent the residual oil was chromatographed (silica gel; elution with 1 : 3 ethyl acetate–light petroleum) to afford *ester* **9** (14.4 g, 97%), mp 58–60 °C (Found: C, 69.74; H, 7.11; N, 6.20. $C_{25}H_{30}N_2O_4$ requires C, 71.06; H, 7.16; N, 6.63%); $[\alpha]_D^{22}$ +147.5 (*c* 1.48, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3050 (ArH), 1710 (CO) and 1650 (CO); δ_H(300 MHz; $CDCl_3$) 8.05 (m, 4 H, ArH), 7.52 (m, 5 H, ArH), 5.49 (s, 1 H, C*H*Bu^t), 4.45 (q, *J* 7.2, 2 H, $CO_2CH_2CH_3$), 3.08 (s, 3 H, NCH_3), 1.95 (s, 3 H, CH_3), 1.24 (t, *J* 7.2, 3 H, $CO_2CH_2CH_3$) and 0.81 (s, 9 H, Bu^t); *m*/*z* (EI) 365 ($M^+ - 57$).

(*S*)-4-Carboxyphenyl-α-methylglycine

The ester **9** (2.0 g, 4.7 mmol) and 30 ml of 6 M HCl were placed in a sealed tube. This mixture was heated at 150 °C for 18 h, by which time the solution had clarified. After being cooled to room temp. it was extracted with methylene dichloride (3 × 30 ml). The aqueous layer was concentrated to dryness at reduced pressure and the resulting pale yellow solid was dissolved in 40 ml of ethanol. To this solution were added 10 ml of propylene oxide and the mixture was heated at 50 °C for 10 min. After storage overnight, the precipitate was filtered off, washed with ethanol, and dried *in vacuo* to afford (*S*)-αM4CPG (0.82 g, 83%), $[\alpha]_D^{25}$ +90 (*c* 0.53, 6 M HCl) {lit.,[3] $[\alpha]_D^{18}$ +93 (*c* 0.53, 6 M HCl)}; ν_{max}(KBr)/cm^{-1} 3424–2500 (NH, CO_2H), 1687 (C=O), 1602 (NH_3^+) and 1540 (CO_2^-); δ_H(300 MHz; $CDCl_3$) 7.88 (d, $J_{3,2}$ 8.4, 2 H, ArH), 7.50 (d, $J_{2,3}$ 8.4, 2 H, ArH) and 1.94 (s, 3 H, CH_3); *m*/*z* (FAB) 210 (M^+).

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