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Synthesis of (2*S*,1′*S*,2′*S*)-2-methyl-2-(carboxycyclopropyl)glycine and (*S*)-2-amino-2-methyl-4-phosphonobutyric acid from L-alanine

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Abstract: The synthesis of two isotype-selective antagonists for metabotropic glutamate receptors, (2*S*,1′*S*,2′*S*)-2-methyl-2-(carboxycyclopropyl)glycine and (*S*)-2-amino-2-methyl-4-phosphonobutyric acid from L-alanine is described. © 1997 Elsevier Science Ltd. All rights reserved.

Molecular cloning has revealed the existence of at least eight subtypes of metabotropic glutamate receptors (mGluRs). Based on sequence similarities, transduction mechanism and agonist preference these subtypes have been divided into three groups. The development of novel mGluR subtype selective antagonists is of great interest for understanding further the functions and coupling mechanisms of in situ mGluRs.[1] Recently, (2*S*,1′*S*,2′*S*)-2-methyl-2-(carboxycyclopropyl)glycine (MCCG, **1**) and (*S*)-2-amino-2-methyl-4-phosphonobutyric acid (*S*-α-MAP4, **2**) were described as novel mGluRs antagonists with a different subtype selectivity, respectively.[2] Since they were discovered, these two compounds have received much attention in studying the different roles of mGluR subtypes.[3–5] Surprisingly, their chemical synthesis has not been reported. As part of continuing efforts to develop more potent and selective antagonists for mGluR subtypes,[6] we developed a general, enantiomerically selective synthesis of these two compounds.

As detailed in Scheme 1 and Scheme 2, we used trans-2-phenyloxazolidinone **3** which could be obtained from L-alanine in large quantities according to known procedures[7] as our starting material for synthesizing MCCG and (*S*)-MAP4. After treatment of **3** with lithium hexamethyldisilazide at −78°C, the generated anion was trapped with 2-bromoethyl triflate to produce **4** in 61% yield as a single isomer. Other alkylation reagents with two functional groups such as 1,2-dibromoethane, $BrCH_2CH_2OTHP$ and ICH_2CH_2OTHP were found not suitable for this coupling reaction. In these cases the starting material was recovered after quenching. The stereochemistry of **4** was confirmed by its NOSEY spectrum, which revealed an NOE between the 4-methyl and 2-phenyl groups. Next, the bromide **4** was converted to the corresponding iodide **5**, which was subjected to a Michaelis–Becher reaction[8] to afford **6** in 83% yield. It was found that heating **5** with trimethyl phosphite at reflux only gave the recovered starting material. After removing all the protecting groups by refluxing **6** in 6 N HCl, the crude **2** was produced as its hydrochloride salt. Treatment of this salt with propylene oxide followed by recrystallation from ethanol afforded (*S*)-MAP4 in 76% yield.

Trans-2-phenyloxazolidinone **3** was converted to the corresponding enolate by treatment with lithium hexamethyldisilazide. The Michael addition of this enloate to methyl (E)-3-bromopropenoate[9] followed by elimination of HBr afforded α,β-unsaturated ester **7** in 65% yield. ^1H NMR showed that only trans isomer was formed. At this stage we could use the palladium-catalyzed cycloaddition of diazomethane to olefin to build our three-membered ring.[10] Accordingly, treatment of the ester **7** with excess diazomethane led to a mixture of **8** and **9** in a ratio of 3/4. The two isomers could be separated by column chromatography and they showed in the ^1H NMR spectra a pattern of signals suitable for the study of their relative stereochemistry by NOE difference spectroscopy. On the basis of the

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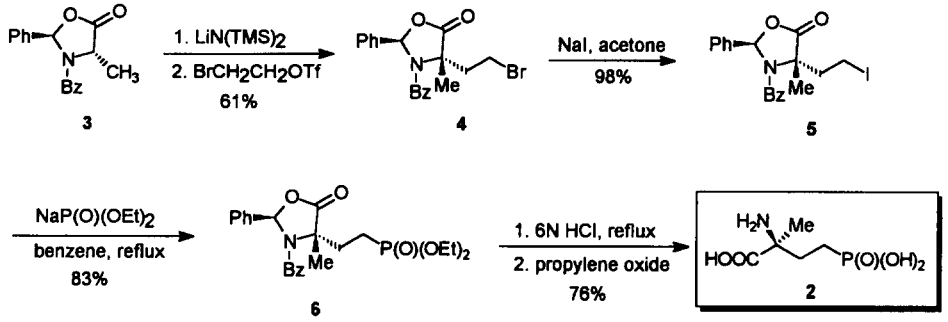
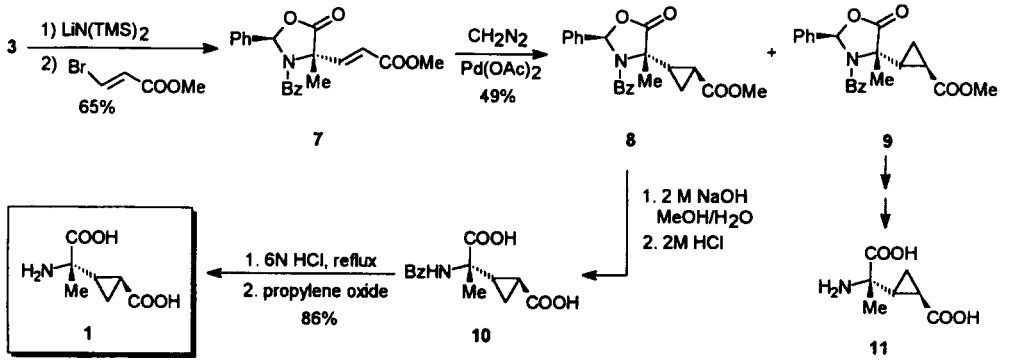


Scheme 1.



Scheme 2.

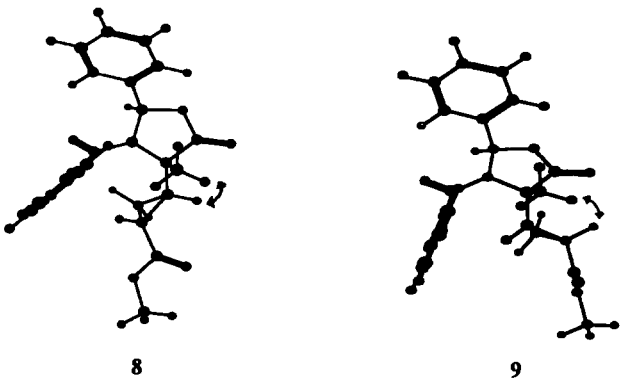


Figure 1. PM3-optimized minimum energy conformations (MMX force field) found for models of compounds **8** and **9**, showing characteristic NOEs.[11]

sets of observed NOEs (supported by force field and semiempirical calculations,[11,13–16] Figure 1), a (1*S*,1′*S*,2′*S*)-stereochemistry was concluded for compound **8**, while a (1*S*,1′*R*,2′*R*)-configuration was assigned for compound **9**. These results were further confirmed by conversion of **8** to known **1**.

Hydrolysis of **8** with sodium hydroxide in ethanol and water produced diacid **10**, which was refluxed in 6 N HCl to afford crude **1** as a hydrochloride salt. Treatment of this salt with propylene oxide followed by chromatography (C_{18} reverse-phase column) to give **1** ($[\alpha]^{25}_D=-57.6$ (c 0.65, H_2O)), reported[12] $[\alpha]^{25}_D=-55.9$ (c 0.18, H_2O). In a similar manner, the compound **9** was converted to **11** in 81% yield ($[\alpha]^{25}_D=+77.3$ (c 0.67, H_2O)).

In conclusion, alkylation of trans-2-phenyloxazolidinone **3** with 2-bromoethyl triflate followed by installing a phosphonate group through the Michaelis–Becker reaction allowed a direct and stereocontrolled access to (*S*)-α-MAP4, while Michael addition of trans-2-phenyloxazolidinone **3** to methyl (E)-3-bromopropenoate followed by cyclopropanation to unsaturated ester leads to the formation of MCCG. The application of the present synthetic protocols to the preparation of MCCG and (*S*)-α-MAP4 analogues thereby developing more potent ligands for metabotropic receptors is currently under progress.

Experimental section

General procedures

Melting points are uncorrected. IR spectra were measured on a Schimadzu 440 spectrometer. ^{1}H NMR spectra were recorded with TMS as an internal strandard at a Brucker AM-300 spectrometer. MS spectra were determined on a Finnigan 4201 spectrometer. Optical rotations were obtained on a Perkin–Elmer 241 Autopol polarimeter. THF was distilled from a deep blue ketyl prior to use. All reactions were run in flame-dried glassware under nitrogen atmosphere unless stated otherwise.

(2R,4S)-3-Benzoyl-4-bromoethyl-4-methyl-2-phenyl-1,3-oxazolidin-5-one **4**

A solution of **3** (8.10 g, 28.6 mmol) in THF (600 mL) was cooled to −78°C. To this stirring solution was added lithium hexamethyldisilazide (1 M in hexane, 30 mL, 30 mmol) dropwise and then the stirring was continued for 40 min at −78°C. After 2-bromoethyl triflate (8.02g, 28.6 mmol) in 20 mL of THF was added dropwise, the mixture was maintained at −78°C for 3 h and then stirred overnight at room temperature. The solvent was evaporated and the residue was partitioned between saturated NH_4Cl (100 mL) and ethyl acetate (400 mL). The organic layer was separated, washed with brine, dried over Na_2SO_4. After removing the solvent, the residue was chromatographed (silica gel, 1/5 ethyl acetate/petroleum ether as eluent) to afford 6.84 g (61% yield) of **4** as a white crystal. $[\alpha]^{25}_D$=+220 (c 1 $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35–7.12 (m, 8H), 6.98 (d, *J*=7.2 Hz, 2H), 6.72 (s, 1H), 3.61–3.42 (m, 2H), 3.10 (m, 1H), 2.65 (m, 1H), 1.98 (s, 3H); MS m/z 388 (M^++H^+), 367, 308, 280, 240, 174, 130, 105, 77. HRMS calcd for $C_{19}H_{18}BrNO_3$: 387.047, Found: 387.050.

(2R,4S)-3-Benzoyl-4-diethylphosphonateethyl-4-methyl-2-phenyl-1,3-oxazolidin-5-one **6**

A mixture of **4** (6.61 g, 17.1 mmol) and sodium iodide (15.3 g, 116 mmol) in dry acetone (200 mL) was stirred at 50°C for 14 h. After removing the solvent, the residue was diluted with 500 mL of ethyl acetate and washed with water, brine respectively. The organic layer was dried over Na_2SO_4 and then concentrated to dryness to afford 7.26 g of crude **5**. In another bottle, sodium hydride (60%, 1.34 g, 33.5 mmol) and 100 mL of dry benzene were placed. To this suspension solution was added diethylphosphite (4.4 mL, 34.1 mmol) in a dropwise manner. The resultant mixture was stirred for 30 min and then a solution of 7.26 g of crude **5** in 50 mL of dry benzene was added slowly. After heating at 50°C for 5 h, the solution was diluted with 300 mL of ethyl acetate, washed with water and brine respectively and dried over Na_2SO_4. Evaporation of the solvent followed by chromatography (silica gel, 2/1 ethyl acetate/petroleum ether as eluent) afforded 6.17 g (83% yield from **4**) of **6**. $[\alpha]^{25}_D$=+89.1 (c 1 $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38–6.90 (m, 10H), 6.19 (s, 1H), 4.41–4.10 (m, 6H), 3.25 (m, 1H), 2.45 (m, 1H), 2.05 (s, 3H), 1.40 (m, 6H); MS m/z 445 (M^+), 444, 430, 400, 340, 308, 280, 220, 192, 158, 131, 105, 91, 77. HRMS calcd for $C_{23}H_{28}NO_6P$: 445.165, Found: 445.166.

(S)-2-Amino-2-methyl-4-phosphonobutyric acid **2**

The phosphonate **3** (2.60 g, 5.84 mmol) and 6 N HCl (50 mL) were placed in a sealed tube and the mixture was stirred at 100°C for 48 h. After cooling to room temperature the resultant mixture was partitioned between 100 mL of ethyl acetate and 100 mL of water. The aqueous layer was separated and concentrated under reduced pressure to dryness and the residue was dissolved in 40 mL of ethanol before 10 mL of propylene oxide was added. After heating at reflux for 10 minute, the solution was stood overnight. The resulting solid was collected and recrystallized from 20 mL of ethanol to afford

1.08 g of **2** (76% yield). $[\alpha]^{25}_D$=−12.3 (c 0.31, MeOH); ^{1}H NMR (300 MHz, D_2O) δ 4.59–4.47 (m, 2H), 2.60 (m, 2H), 1.63 (s, 3H); MS (m/z) 116 (M^+−81), 88.

(2R,4S)-3-Benzoyl-4-[(3-methoxy)carbonyl-(1E)-propenyl]-4-methyl-2-phenyl-1,3-oxazolidin-5-one **7**

To a solution of **3** (8.5 g, 30 mmol) in THF (600 mL) was added 1 M lithium hexamethyldisilazide (33 mL, 33 mmol) at −78°C. After the reaction mixture was stirred for 40 min at −78°C, a solution of methyl (E)-3-bromopropenoate (5.0 g, 33 mmol) in THF (30 mL) was added dropwise at the same temperature. The resultant solution was stirred for another 1 h at −78°C, and then allowed to warm to room temperature overnight. After treating with buffer solution (pH=7, 50 mL), THF was evaporated via rotavapor and the residue was extracted with ethyl acetate (3×200 mL). The combined organic layer was dried over Na_2SO_4, and concentrated. The residual oil was chromatographed (silica gel, 1/4 ethyl acetate/petroleum ether as eluent) to give 7.1 g (65% yield) of **7**. $[\alpha]^{25}_D$=+189 (c 0.18 $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34–7.09 (m, 10H), 7.04 (d, *J*=15.9 Hz, 1H), 6.80 (s, 1H), 6.09 (d, *J*=15.9 Hz, 1H), 3.76 (s, 3H), 2.05 (s, 3H); MS m/z 365 (M^+), 231, 216, 172, 140, 105, 77, 51. HRMS calcd for $C_{21}H_{19}NO_5$: 365.126, Found: 365.125.

Cyclopropanation of **7**

To a suspension solution of **7** (7.0 g, 19 mmol), $Pd(OAc)_2$ (214 mg, 0.95 mmol) and ether (250 mL) was added, in a dropwise manner, a solution of CH_2N_2 in ether (100 mL) at room temperature over 30 min. The mixture was then filtered and the filtrate was concentrated in vacuo to give an oily residue, which was chromatographed (silica gel, 1/9 ethyl acetate/petroleum as eluent) to afford 1.5 g of **8** (21% yield) and 2.0 g of **9** (28%). The compound **8**: $[\alpha]^{25}_D$=+93.1 (c 0.1 $CHCl_3$); IR (film) 2955, 1795, 1732, 1660 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36–6.99 (m, 10H), 6.65 (s, 1H), 3.72 (s, 3H), 2.44 (m, 1H), 2.00 (s, 3H), 1.76 (dt, *J*=9.3, 5.1 Hz, 1H), 1.45 (d, *J*=8.2 Hz, 1H), 1.32 (dd, *J*=10.2, 5.1 Hz, 1H); MS m/z 379 (M^+), 230, 160, 159, 122, 100, 99, 77. HRMS calcd for $C_{22}H_{21}NO_5$: 379.141, Found: 379.139. The compound **9**: $[\alpha]^{25}_D$=+113 (c 0.1 $CHCl_3$); IR (film) 2950, 1796, 1730, 1659 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35–6.95 (m, 10H), 6.59 (s, 1H), 3.70 (s, 3H), 2.46 (m, 1H), 2.21 (dt, *J*=8.7, 4.8 Hz, 1H), 2.04 (s, 3H), 1.31 (dt, *J*=9.7, 5.1 Hz, 1H), 1.03 (ddd, *J*=8.7, 6.7, 5.1 Hz, 1H); MS m/z 379 (M^+), 230, 160, 159, 122, 100, 99, 77. HRMS calcd. for $C_{22}H_{21}NO_5$: 379.141, Found: 379.141.

(2S,1′S,2′S)-2-Methyl-2-(carboxycyclopropyl)glycine **1**

To a solution of **8** (1.1 g, 2.9 mmol) in 50 mL of MeOH was added 2 N NaOH (3.0 mL, 6.0 mmol) and then the mixture was stirred for 30 min at room temperature. The solution was diluted with 50 mL of water and extracted with ether (3×50 mL). The aqueous layer was cooled to 0°C and treated with 2 N HCl to pH=3. The acidic solution was extracted with ethyl acetate (5×70 mL) and the combined organic layers were dried over Na_2SO_4. After removing the solvent, the residue was transferred to a sealed tube and 6 N HCl (15 mL) was added. This mixture was heated at 100°C for 48 h and then extracted with ethyl acetate (3×10 mL). The aqueous layer was evaporated to dryness under reduced pressure and the residue was dissolved in 10 mL of anhydrous ethanol. After 5 mL of propylene oxide was added, the mixture was heated at reflux for 15 min. After removal of the solvents the residue was dissolved with a small amount of water and chromatographed (C_{18} reverse-phase column, H_2O as eluent) to afford 430 mg of **1** (86%). $[\alpha]^{25}_D$=−57.6 (c 0.65 H_2O); ^{1}H NMR (300 MHz, D_2O) δ 1.68–1.73 (m, 2H), 1.40 (s, 3H), 1.10–1.20 (m, 2H); MS m/z 173 (M^+), 156, 88, 43.

In a similar manner, amino acid **11** was obtained in 81% yield. $[\alpha]^{25}_D$=+77.3 (c 0.67 H_2O); ^{1}H NMR (300 MHz, D_2O) δ 1.87–1.80 (m, 1H), 1.74–1.68 (m, 1H), 1.30 (s, 3H), 1.23–1.16 (m, 1H), 1.11–1.06 (m, 1H); MS m/z 379 (M^+), MS m/z 173 (M^+), 156, 88, 43.

Acknowledgements

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References

1. Knopfel, T.; Kuhn, R.; Allgeier, H. *J. Med. Chem.*, **1995**, *38*, 1418. Ornstein, P. L.; Schoepp, D. D.; Monn, J. A. *Current Pharmaceutical Design*, **1995**, *1*, 355. Knopfel, T.; Gasparini, F. *Drug Discovery Today*, **1996**, *1*, 103.
2. Jane, D. E.; Jones, P. L. St. J.; Pook, P. C.-K.; Tse, H.-W.; Watkins, J. C. *Br. J. Pharmac.*, **1994**, *112*, 809.
3. Knopfel, T.; Lukic, S.; Leonardt, T.; Flor, P. J.; Kuhn, R.; Gasparini, F. *Neuropharmacology*, **1995**, *34*, 1099.
4. Salt, T. E.; Eaton, S. A. *Neuroscience*, **1995**, *65*, 5.
5. Bushell, T. J.; Jane, D. E.; Tse, H. W.; Watkins, J. C.; Davies, C. H.; Garthaite, J.; Collingride, G. L. *Neuropharmacology*, **1995**, *34*, 239.
6. a) Ma, D.; Tian, H. *Tetrahedron Asymmetry*, **1996**, *7*, 1567. b) Ma, D.; Tian, H. *et al.*, unpublished results.
7. Fadel, A.; Salaun, J. *Tetrahedron Lett.*, **1987**, *28*, 2243.
8. Engel, R. *Synthesis of Carbon–Phosphous Bonds*, CRC Press, Inc., Boca Raton, FL, **1988**. Baraldi, P. G.; Guarneri, M.; Morder, F.; Pollini, G. P.; Simoni, D. *Synthesis*, **1982**, 653.
9. Weir, J. R.; Patel, B. A.; Heck, R. F. *J. Org. Chem.*, **1980**, *45*, 4926.
10. Shimamoto, K.; Ishida, M.; Shinozaki, H.; Ohfune, Y. *J. Org. Chem.*, **1991**, *56*, 4167.
11. Minimum energy conformations for models of all possible (1*S*,1′*S*,2′*S*)- and (1*S*,1′*R*,2′*R*)-products were located using MM+ force field as implemented in HyperChem V3.0 (see ref. 13). The geometries of the most important conformations were fully optimized by semi-empirical molecular orbital calculations, using PM3 Hamiltonians (see ref. 14) included in MOPAC V6.0 (see ref. 15) in Sybyl V6.0a (see ref. 16). The refined geometries in the gas phase were in agreement with the conformation in solution deducted from ^{1}H NOE spectroscopy. For compounds **8** and **9**, rotamers can better account for the observed NOEs as showed with arrows in Figure 1.
12. We thank Dr Zhang Weiyi, Research Biochemicals International, provided the data for **1**.
13. HyperChem version 3.0 Hypercube, Inc.
14. PM3: see, Stewart, J. J. P. *J. Comp. Chem.*, **1990**, *10*, 209.
15. MOPAC version 6.0. Stewart. J. J. P.. United States Air Force Academy.
16. Sybyl version 6.0a. Tripos Associates, Inc.

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