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Synthesis and preliminary pharmacological evaluation of the four stereoisomers of (2*S*)-2-(2′-phosphono-3′-phenylcyclopropyl)glycine, the first class of 3′-substituted *trans*$_{C1'-2'}$-2-(2′-phosphonocyclopropyl)glycines

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Abstract—Four stereoisomers of (2*S*)-2-(2′-phosphono-3′-phenylcyclopropyl)glycine were synthesized by a stereocontrolled synthetic procedure and evaluated as mGluRs ligands. The (2*S*,1′*R*,2′*S*,3′*R*)-isomer (PPCG-2) showed to be a group III mGluRs selective ligand endowed with a moderate potency as mGluR4/mGluR6 agonist.

1. Introduction

Cyclopropylphosphonate derivatives have been the focus of interest for chemists because of their potential biological properties. They have been designed as mimics of aminocyclopropane carboxylic acid (ACC) and as such showed to be potent inhibitors of alanine racemase and ACC-deaminase,[1] as analogues of (−)-allonorcoronamic acid[2] and minalcipran,[3] as structural moieties of nucleotides,[4] as potential herbicides or plant growth regulators[5] and as potential insecticides.[6] Combining two of the most important strategies in rational drug design, namely bioisosterism and reduction of the conformational flexibility through ring insertion, we and others turned the attention to phosphonocyclopropyl amino acids as conformationally constrained-bioisosteric analogues of L-glutamic acid (L-Glu), the main excitatory neurotransmitter in the mammalian central nervous system. Thus, phosphonocyclopropyl amino acid **1**, characterized by an appropriate intermediate chain and by the D-configuration at the amino acidic moiety, has been designed by us as a competitive antagonist for the NMDA receptor,[7] whereas (2*S*,1′*R*,2′*S*)-2-(2′- phosphonocyclopropyl)glycine (**2**), a conformationally constrained analogue of L-1-amino-4-phosphonobutanoic acid (L-AP4, **3**), the prototypic selective agonist for the group III family of the glutamate metabotropic receptors (mGluRs), has been shown to be a group III mGluRs agonist with micromolar activity.[8] In the frame of our continuing interest in the development of chemical tools for the characterization of the glutamate receptors and in particular for the metabotropic ones, we became interested in the synthesis of 2,3-disubstituted cyclopropylphosphonates with definite stereochemistry, able to be precursors of 3′-substituted-(2′-phosphonocyclopropyl)glycines, as potential ligands for group III mGluR subtypes. In particular, we reasoned that the introduction of a hydrophobic moiety, such as a phenyl ring, in the 3′-position

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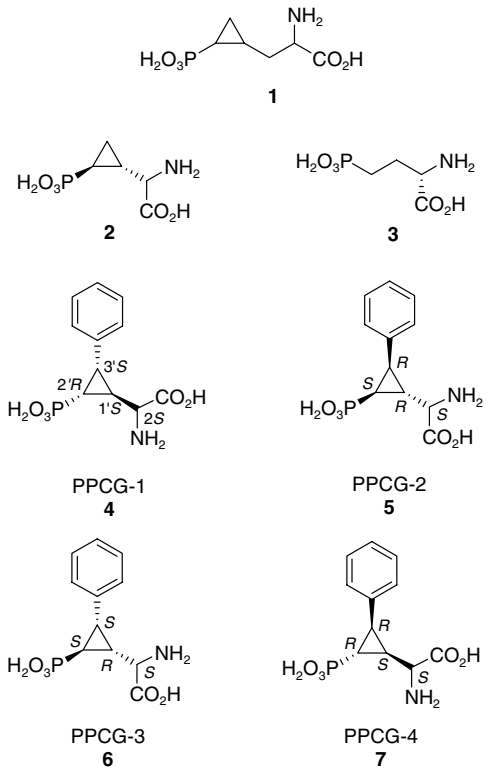


Chart 1.

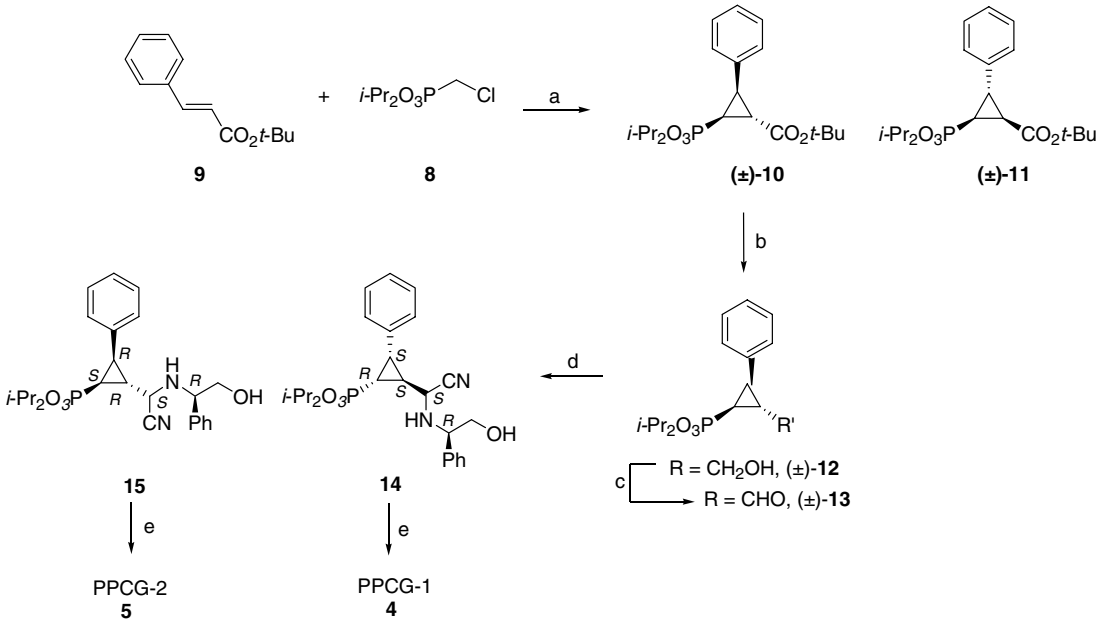
of 2-(2′-phosphonocyclopropyl)glycine can be proved useful for mapping the presence of still unexplored accessory areas in the recognition site of members of this glutamate receptor family.

Taking advantage from the pharmacophore models for group III agonists,[9,10] we addressed our efforts towards the preparation of 3′-substituted-(2′-phosphonocyclopropyl)glycines characterized by the trans-disposition between the pharmacophoric groups, the glycine moiety and the phosphonate group. The synthesis and preliminary biological evaluation of the first representatives of this new class, namely the complete stereolibrary of *trans*$_{C1'-2'}$-(2*S*)-2-(2′-phosphono-3′-phenylcyclopropyl)-glycines (**4**–**7**), are reported herein (Chart 1).

2. Results and discussion

Although a number of synthetic routes to cyclopropylphosphonates have been described in the literature,[11] only few examples of 2,3-disubstituted cyclopropyl-1-phosphonates have been reported.[12] Among them, the stereocontrolled synthesis of 1,2,3-trisubstituted cyclopropane phosphonic acids, reported by Hanessian et al.,[13] involving the addition of chiral phosphonamide-based anions to α,β-unsaturated esters, resulted particularly suitable to our purposes. Because we required all the possible isomers endowed with trans-disposition between the glycine and the phosphonate moieties, the achiral diisopropyl α-chloromethylphosphonate (**8**) was employed in place of the optically active Hanessian's phosphonamide (Scheme 1). Thus, treatment at −78 °C of *E*-*tert*-butyl cinnamate (**9**) with the anion of **8**, generated at −78°C (LDA, THF), afforded two diastereoisomeric diisopropyl (2-*tert*-butoxycarbonyl-3-phenylcyclopropyl)phosphonates [(±)-**10**)] and [(±)-**11**] (2:1 by ^{1}H NMR) in 56% and 19% yields, respectively, after separation by flash chromatography.

The relative stereochemistries of the two racemic mixtures (±)-**10** and (±)-**11** were determined by spectroscopic analysis. A proof of the relative configuration



Scheme 1. Reagents and conditions: (a) (i) LDA, THF, −78 °C, 90′; (ii) flash chromatography (±)-**10** (56%) and (±)-**11** (19%); (b) $LiEt_3BH$, THF, −78 °C, 15′, 81%; (c) PCC, CH_2Cl_2, rt, 24 h, 71%; (d) (i) *R*-(−)-α-phenylglycinol, MeOH, rt, 24 h; (ii) TMSCN, 0 °C, 24 h; (iii) MPLC, **14** (32%) and **15** (14%); (e) (i) $Pb(OAc)_4$, CH_2Cl_2–MeOH, 0 °C, 20′; (ii) 6 N HCl, reflux, 24 h; (iii) ion exchange chromatography, **4** (28%) and **5** (35%).

of C-1–C-2 follows from the H–H coupling constants (J_{1-2}), which are 5.9 and 10.1 Hz for the diastereoisomers (±)-**10**) and (±)-**11**, respectively. Since for the cyclopropane derivatives, $J_{HHcis} > J_{HHtrans}$,[14] the diastereoisomer (±)-**10**, whose coupling constant value is 5.9 Hz, is endowed with trans-disposition between carboxylate and phosphonate groups. On the contrary, (±)-**11** has cis-configuration of the same substituents compatible with a larger coupling constant value. Furthermore, the comparison of H-2–H-3 coupling constant values which are 8.6 and 6.0 Hz for the diastereoisomers (±)-**10** and (±)-**11**, respectively, allows us to suppose a cis-disposition between phosphonate and phenyl group in the diastereoisomer (±)-**10** and the opposite one in (±)-**11**. The stereochemical assignments were supported by NOESY experiments (Fig. 1): in the case of (±)-**10**, strong NOE occurs between H-2 and H-3, whereas NOEs were observed between H-1 and H-2 in the spectrum of (±)-**11**.

Diisopropyl (2-*tert*-butoxycarbonyl-3-phenylcyclopropyl)phosphonate [(±)-**10**], characterized by the desired disposition of the pharmacophoric groups, was then reduced by lithium ethylborohydride in THF at −30 °C to give the corresponding alcohol (±)-**12**, subsequently oxidized by PCC into diisopropyl (2-formyl-3-phenylcyclopropyl)phosphonate [(±)-**13**]. The aldehyde (±)-**13** was submitted to condensation with *R*-α-phenylglycinol and the Schiff base thus formed reacted with trimethylsilyl cyanide to afford a mixture of the four expected α-amino nitriles, as two major (2*S*)- and two minor (2*R*)-components (85:15 by HPLC).[15] Flash chromatography of the reaction mixture allowed a good separation of the desired two more abundant (2*S*)-[(*R*)-(phenylglycinyl)amino]nitriles **14** and **15** in 32% and 14% yields, respectively. The derivative **14** was submitted to oxidative cleavage of the chiral auxiliary, acidic hydrolysis and ion exchange resin chromatography to afford (2*S*,1′*S*,2′*R*,3′*S*)-2-(2′-phosphono-3′-phenylcyclopropyl)glycine (PPCG-1, **4**) in 28% yield. By an analogous procedure, starting from the amino nitrile **15**, (2*S*,1′*R*,2′*S*,3′*R*)-2-(2′-phosphono-3′-phenylcyclopropyl)glycine (PPCG-2, **5**) was obtained in 35% yield.

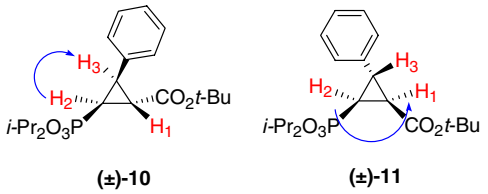
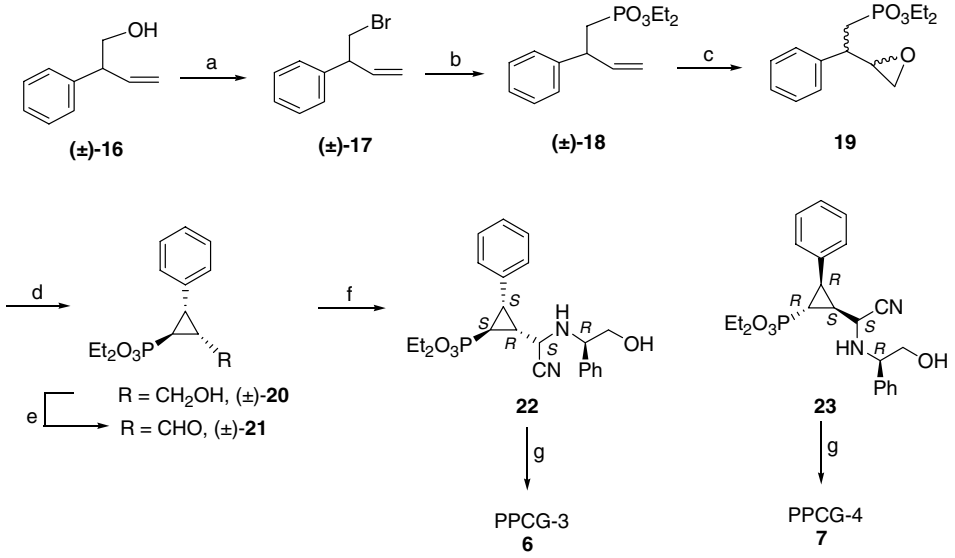


Figure 1. NOESY correlations of the two diastereoisomeric diisopropyl (2-*tert*-butoxycarbonyl-3-phenylcyclopropyl)phosphonates [(±)-**10**)] and [(±)-**11**].

To complete the stereolibrary of *trans*$_{C1'-2'}$-(2*S*)-2-(2′-phosphono-3′-phenylcyclopropyl)glycines, the synthesis of the derivatives endowed with trans-relationship between phosphonate and phenyl group remained to realize. The base-catalyzed intramolecular epoxide opening reaction of γ,δ-epoxybutylphosphonates has been first reported by Oh and colleagues,[4] as a synthetic methodology to produce 2-substituted cyclopropylphosphonates. We recently reported the application of this procedure to the synthesis of (2*S*,1′*R*,2′S)-2-(2′-phosphonocyclopropyl)glycine (**2**).[8] Since the possibility to obtain 2,3-disubstituted cyclopropylphosphonates starting from β-substituted-γ,δ-epoxybutylphosphonates has not yet been explored, we decided to explore this possibility to synthesize the lacking (2*S*)-2-(2′-phosphono-3′-phenylcyclopropyl)glycine isomers (**6** and **7**). To this end, 2-phenylbut-3-en-1-ol [(±)-**16**][16] was treated with carbon tetrabromide and triphenylphosphine to obtain the



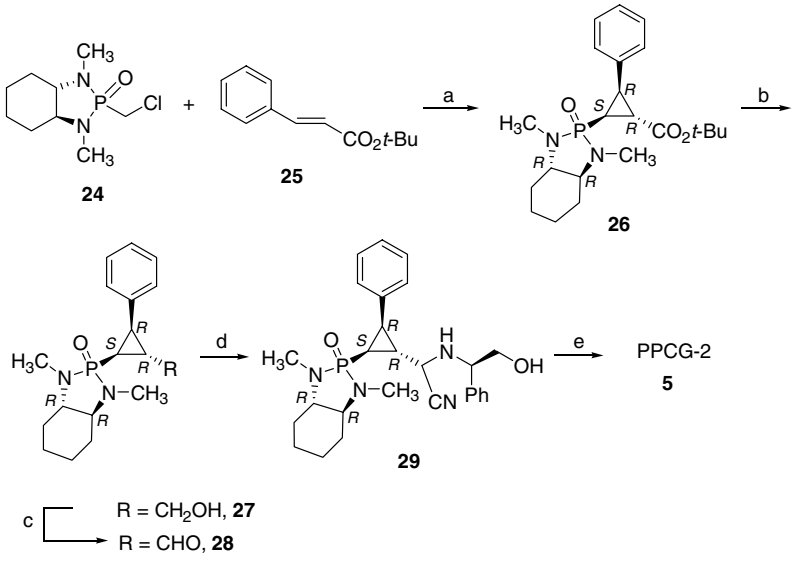
Scheme 2. Reagents and conditions: (a) CBr_4, PPh_3, CH_2Cl_2, rt, 24 h, 80%; (b) $P(OEt)_3$, 150 °C, 7 days, 51%; (c) MCPA, CH_2Cl_2, rt, 48 h, 80%; (d) LiHMDS, THF, −78 to −20 °C, 3 h, 51%; (e) PCC, CH_2Cl_2, rt, 24 h, 67%; (f) (i) *R*-(−)-α-phenylglycinol, MeOH, rt, 24 h; (ii) TMSCN, 0 °C, 24 h; (iii) MPLC, **22** (15%) and **23** (17%); (g) (i) $Pb(OAc)_4$, CH_2Cl_2–MeOH, 0 °C, 20′; (ii) 6 N HCl, reflux, 24 h; (iii) ion exchange chromatography, **6** (46%) and **7** (37%).

corresponding bromide (±)-**17**, then refluxed in triethyl phosphite to afford diethyl 2-phenylbut-3-enylphosphonate (±)-**18** in 55% yield (Scheme 2). Epoxidation of (±)-**18** with *m*-chloroperbenzoic acid in dichloromethane afforded diethyl 2-oxiran-2-yl-2-phenylethylphosphonate (**19**) which was next transformed into trisubstituted cyclopropane (±)-**20** by treatment with LiHMDS at −78 °C.

The cyclisation was highly stereoselective affording (±)-**20** as the only stereoisomer; indeed, no minor isomers could be detected by GC-MS analysis. The relative configuration of the derivative (±)-**20** was assigned by a comparison of its spectroscopic data with those previously obtained from the diastereoisomeric alcohol (±)-**12**. The trans-geometry between the phenyl group and the phosphonate moiety in (±)-**20** was supported by H_3–P coupling constant value ($J_{H_3-P} = 16$ Hz) typical of a cis-disposition of the groups. Starting from the alcohol (±)-**20**, the preparation of the other pair of (2*S*)-2-(2′-phosphono-3′-phenylcyclopropyl)glycines (**6**) and (**7**) was achieved following the synthetic protocol above described for the synthesis of PPCG-1 (**4**) and PPCG-2 (**5**). Thus, oxidation of (±)-**20** into the corresponding aldehyde (±)-**21**, diastereoselective Strecker reaction, cleavage of the chiral auxiliary and final hydrolysis of the α-amino nitriles **22** and **23** provided (2*S*,1′*R*,2′*S*,3′*S*)-2-(2′-phosphono-3′-phenylcyclopropyl)glycine (PPCG-3, **6**) and (2*S*,1′*S*,2′*R*,3′*R*)-2-(2′-phosphono-3′-phenylcyclopropyl)glycine (PPCG-3, **7**) in 28% and 13% overall yield, respectively.

3. Absolute configuration assignment

The absolute configuration assignment to the four diastereoisomeric amino acids **4**–**7** was based upon single-crystal X-ray analysis performed on **23**, one of the two major α-amino nitriles derived from the racemic alde-



Scheme 3. Reagents and conditions: (a) Ref. 13; (b) $LiEt_3BH$, THF, −78 °C, 15′, 84%; (c) PCC, CH_2Cl_2, rt, 1 h, 38%; (d) (i) *R*-(−)-α-phenylglycinol, MeOH, rt, 24 h; (ii) TMSCN, 0 °C, 24 h; (iii) MPLC, 80%; (e) (i) $Pb(OAc)_4$, CH_2Cl_2–MeOH, 0 °C, 20′; (ii) 6 N HCl, reflux, 24 h; (iii) ion exchange chromatography, 45%.

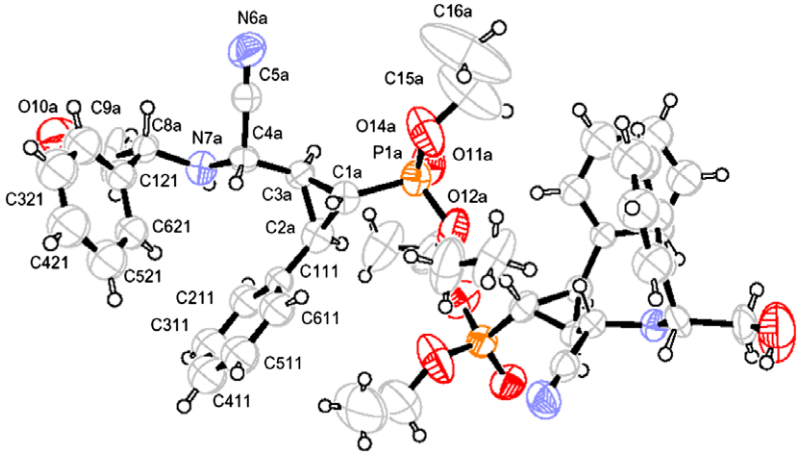


Figure 2. View of the asymmetric unit of the α-amino nitrile **22**. Ellipsoids enclose 50% probability.

hyde (±)-**21**, and on the independent, enantioselective synthesis of (2*S*,1′*R*,2′*S*,3′*R*)-2-(2′-phosphono-3′-phenylcyclopropyl)glycine (**5**) as depicted in Scheme 3. X-ray analysis of the α-amino nitrile **23** (Fig. 2) confirmed the *S*-chirality of the amino nitrilic centre and allowed to fix the absolute configuration at the three cyclopropylic carbon atoms (1′*S*,2′*R*,3′*R*). Conversely, the amino acid **6**, proceeding from the other major α-amino nitrile obtained from the aldehyde (±)-**21**, resulted with the same absolute configuration *S* at C-2 position and opposite one (1′*R*,2′*S*,3′*S*) at the cyclopropylic carbons.

In the impossibility to obtain suitable crystals for X-ray analysis with amino acids derived from aldehyde (±)-**13**, we decided to synthesize the chiral cyclopropyl ester (+)-(1*R*,2*R*,3*S*)-3-*tert*-butyl (1,3-dimethyl-2-oxidooctahydro-1*H*-1,3,2-benzodiazaphosphol-2-yl)-2-phenylcyclopropanecarboxylate (**26**) by following Hanessian's enantioselective procedure.[13] Starting from **26**, by subsequent reduction–oxidation protocol, above reported, the corresponding (1*R*,2*S*,3*R*)-aldehyde **28** was obtained, which was submitted to the diastereoselective Strecker reaction giving only two α-amino nitriles (Scheme 3).

According to the above considerations on the inductive effect of (*R*)-α-phenylglycinol, a more abundant (2*S*,1′*R*,2′*S*,3′*R*)-*N*-[(*R*)-α-phenylglycinyl]glycinonitrile **29** was obtained, which by final deprotection led to (2*S*,1′*R*,2′*S*,3′*R*)-2-(2′-phosphono-3′-phenylcyclopropyl)glycine. A comparison of the spectroscopic data as well as the specific rotatory power values of this compound with those obtained on PPCG-1 (**4**) and PPCG-2 (**5**) enables us to assign to the amino acid **5** the (2*S*,1′*R*,2′*S*,3′*R*) absolute configuration.

4. Biological results

The pharmacological profiles of the four stereoisomers of PPCGs (**4**–**7**) were examined at recombinant mGluR subtypes in functional assays (rmGluR1, rmGluR5, hmGluR2, rmGluR4, and hmGluR7) and binding experiments (rmGluR4 and rmGluR8). As shown in Table 2, only PPCG-2 (**5**) among the four PPCGs showed to bind at mGluR4 subtype with an acceptable affinity (K_i = 24 μM). It should be noticed that compound **5** was also able to bind mGluR8, albeit at a concentration one order of magnitude higher (K_i = 130 μM) than mGluR4. PPCG-3 (**6**) also binds to mGluR8 with the same order of magnitude (K_i = 190 μM) as PPCG-2 (**5**), but it displays more than 20 times weaker binding at mGluR4 (K_i = 630 μM) than PPCG-2 (**5**). Functional measurements (Table 1) revealed that PPCG-2 (**5**) was an agonist at mGluR4 subtype. PPCG-2 (**5**) was also able to activate mGluR6 subtype with the same order of potency. The equivalence of the spatial disposition of the α-amino acidic moiety and the ω-phosphonate group between both the two active isomers of the series, namely PPCG-2 (**5**) and PPCG-3 (**6**), and the corresponding 3′-unsubstituted derivative **2** confirmed the need for a full extended disposition of the pharmacophoric moieties for group III recognition. It is worthy of notice that the introduction of the bulky phenyl group at 3′-position of **2** did not modify the pharmacological profile, thus pointing out a peculiar difference with, for example, group II mGluR ligands, where the introduction of bulky groups over the rigid 2-(2′-carboxycyclopropyl)glycine skeleton invariably changed the functional profile from agonist to antagonist.[15b,20]

Table 2. Binding affinity values expressed as K_i (μM), for PPCGs (**4**-**7**) and (2*S*,1′*R*,2′*S*)-2-(2′-phosphonocyclopropyl)glycine (**2**)

Compound	mGluR4	mGluR8
PPCG-1 (**4**)	>1000	—
PPCG-2 (**5**)	24 ± 4.2	130 ± 3.9
PPCG-3 (**6**)	630 ± 3.2	190 ± 3.8
PPCG-4 (**7**)	>1000	—
PCG-1 (**2**)	7.4 ± 2.7	63 ± 16
L-Glutamate	3.4 ± 0.5	3.4 ± 1.1
L-AP4 (**3**)	0.16 ± 0.02	1.9 ± 0.3

[^{3}H]-L-AP4 and [^{3}H]-LY341495[19] binding experiments where performed on rmGluR4 and rmGluR8 receptor-expressing cell membranes (BHK cells) using a SPA assay.[18] Data are means ± SEM of at least three independent experiments performed in triplicate.

5. Molecular modelling

In order to rationalize the differences in the pharmacological profile of the four diastereoisomeric amino acids **4**–**7**, we have performed molecular modelling studies. Thus, by using the crystal structure of the ligand binding domain (LBD) of mGluR1 as a template (pdb: 1ewk),[21]

Table 1. EC_{50} (μM) values for PPCGs (**4**–**7**) and (2*S*,1′*R*,2′*S*)-2-(2′-phosphonocyclopropyl)glycine (**2**)

Compound	Group I		Group II		Group III	
	mGluR1	mGluR5	mGluR2	mGluR4	mGluR6	mGluR7
PPCG-1 (**4**)	>1000	>1000	>1000	—	>1000	>1000
PPCG-2 (**5**)	>1000	>1000	>1000	59 ± 4.2	51 ± 4.3	>1000
PPCG-3 (**6**)	>1000	>1000	320 ± 3.5	—	—	—
PPCG-4 (**7**)	>1000	>1000	>1000	>1000	—	—
PCG-1 (**2**)	>1000	>1000	>1000	9.4 ± 3.0	13 ± 3.0	700 ± 140
L-Glutamate	7.3 ± 1.0	1.2 ± 0.3	26 ± 2	6.1 ± 1.5	7.6 ± 0.5	>1000
L-AP4 (**3**)	>1000	>1000	>1000	0.51 ± 0.2	0.34 ± 0.07	188 ± 79

Functional data where obtained from CHO cells expressing rmGluR1, rmGluR5 or rmGluR6 or from BHK cells expressing hmGluR2, hmGluR7 or rmGluR4 using previously described methods.[15b,17,18] Potencies were determined by (i) measuring intracellular calcium concentration (group I mGluRs), (ii) GTP(γ)^{35}S stimulation assay (mGluR2) and (iii) measuring cAMP formation (group III mGluRs). The data shown are means ± SEM of at least three independent experiments performed in triplicate.

homology models of both the open and closed forms of the LBD of mGluR4 were constructed. The four ligands **4**–**7** were built up in MOE and, after energy minimization, manually docked into the models of LBD of mGluR4, by using the crystallographically determined position of L-Glu as a guide (Fig. 3).

Inspection of the resulting complexes indicated the presence, in the binding pocket, of a cavity able to accommodate the phenyl ring of PPCG-2 (**5**). This cavity is not present in the LBD of mGluR1, thus reflecting the substitution of the mGluR1 residue tryptophan 110 (W110) by a serine in mGluR4. W110 was recognized by Jingami and colleagues[22] in a site-directed mutagenesis study to be involved in hydrophobic van der Waals interactions with the β- and the γ-carbon of L-Glu in mGluR1. The substitution of the Trp 110 by a serine in mGluR4 results in the disappearance of a space-filling hydrophobic residue thus allowing more sterically demanding ligand side chains to fit in the LBD of mGluR4 receptor subtype with respect to mGluR1 (Fig. 4).

Figure 3. Superimposition of PPCGs (**4**–**7**) on L-Glu (not shown) the side chains are differently orientated according to the absolute configuration of the ring carbons 1′, 2′ and 3′ (colour code of the phenyl groups: PPCG-1 (**4**), red; PPCG-2 (**5**), green; PPCG-3 (**6**), yellow; PPCG-4 (**7**), blue).

Thus, in the model of the LBD of mGluR4, there is a pocket large enough to host the phenyl-moiety of PPCG-type amino acid ligands. This can explain both the observed micromolar affinity of PPCG-2 (**5**) to mGluR4 (K_i = 24 μM) and the stereodiscrimination observed between the diastereomeric amino acids **4**–**7**. Thus, when PPCG-3 (**6**) is superimposed on the position of L-Glu, this cavity is not perfectly accessed by the 3′-substituent. Filling up the cavity by the 3′-phenyl group causes a dislocation of the polar groups NH_2, α-COOH and PO_3H, from their effective binding positions. Furthermore, the lack of activity of PPCG-1 (**4**) and PPCG-4 (**7**) can easily be rationalized by steric clashes of the phenyl moiety with the residues S317, D318, S319, Q211 and Z236 of the mGluR4 receptor model.

6. Conclusions

The stereocontrolled synthesis of the four *trans*$_{C1'-2'}$-(2*S*)-2-(2′-phosphono-3′-phenylcyclopropyl)glycine isomers provided a small library that was employed to assess the steric accessibility of the binding pocket of group III mGluRs. Among the members of the series PPCG-2 (**5**) and PPCG-3 (**6**) displayed affinities as group III mGluRs ligands, albeit with differences in potency and subtype selectivity, while all of them were inactive at group I/II receptor subtypes. These data could be rationalized by docking experiments on the basis of the presence of a cavity in group III receptors that is not present in group I/II. This observation accounts for the stereospecific effect of PPCG-2 (**5**) over the other isomers; for the selectivity of PPCG-2 (**5**) for group III over group I/II receptor subtypes; and for the functional profile of PPCG-2 (**5**) as an agonist at group III. Indeed, filling the cavity with the directionally orientated 3′-phenyl group does not prevent a correct closure of the two lobes of the ligand binding domain of the receptors.

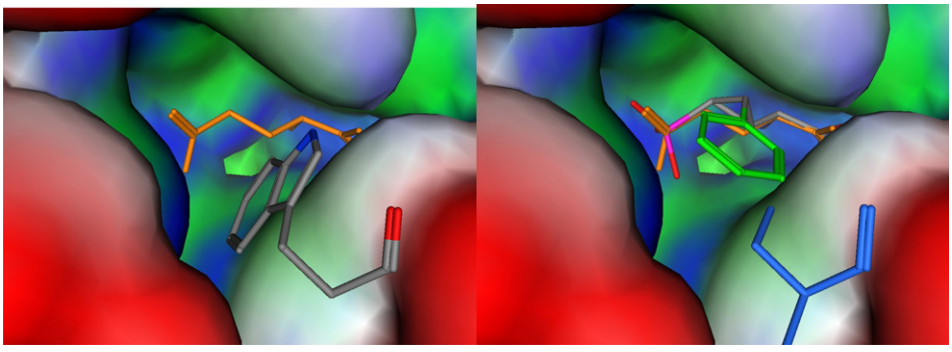


Figure 4. (Left) L-Glu (yellow) and W110 in the crystal of mGluR1. (Right) docking of PPCG-2 (**5**) (element and green phenyl ring) into the homology receptor-model of mGluR4 (in yellow, position of L-Glu in the crystal structure of 1ewk.pdb.) In mGluR4 the substitution of Trp 110 by a less sterically demanding serine allows PPCG-2 (**5**) to bind.

7. Experimental

All reagents were of analytical grade and purchased from Sigma–Aldrich (Milano, Italy). Flash chromatography was performed on Merck silica gel (0.040–0.063 mm). Melting points were determined in open capillary tubes on a Büchi 535 electrothermal apparatus and are uncorrected. ^{1}H-, ^{31}P- and ^{13}C NMR spectra were registered on a Bruker AC 200 or Bruker AC 400 using $CDCl_3$ as solvent unless otherwise indicated. Chemical shifts are reported in ppm. The abbreviations used are as follows: s, singlet; d, doublet; dd, double doublet; bs, broad signal. Optical rotations were recorded on a Jasco Dip-360 digital polarimeter. The analytical HPLC analyses were carried out on a Shimadzu (Kyoto, Japan) Workstation Class LC-10 equipped with a CBM-10A system controller, two LC-10AD high pressure binary gradient delivery systems, a SPD-10A variable-wavelength UV–vis detector and a Rheodyne 7725i injector (Rheodyne Inc., Cotati, CA, USA) with a 20-μl stainless steel loop. Cation- and anion-exchange resin chromatographies were performed with Dowex 50WX2-200 and Dowex 1X8-200, respectively.

7.1. (±)-(1*R*,2*S*,3*R*)- and (±)-(1*S*,2*S*,3*S*)-*tert*-butyl 2-(diisopropoxyphosphoryl)-3-phenyl cyclopropanecarboxylates [(±)-10 and (±)-11]

A cold (−78 °C) solution of **8** (2.40 g, 11.2 mmol) in THF (25 ml) was added to a magnetically stirred cooled (−78 °C) solution of LDA [from addition of 2.5 M *n*Bu-Li in hexane (8.8 mL) to a solution of dry diisopropylamine (1.80 g, 18.1 mmol) in THF (32 mL)]. After 15 min, a cooled (−78 °C) solution of **9** (3.00 g, 14.7 mmol) in THF (32 mL) was added dropwise in 15 min. Stirring was continued for 1.5 h at −78 °C, then the reaction mixture was quenched with saturated NH_4Cl solution (40 mL) and allowed to warm to room temperature. The resulting mixture was then extracted with AcOEt (3×60 mL), the combined organic phases were dried over anhydrous Na_2SO_4, filtered and evaporated to give a residue which was purified by flash chromatography. Elution with EtOAc–light petroleum (3:7) afforded (±)-**10** (2.40 g, 56% yield). ^{1}H NMR (200 MHz) δ 1.1 (m, 12H, P[OCH(CH_3)$_2$]$_2$), 1.42 (s, 9H, $CO_2C(CH_3)_3$), 1.74 (ddd, J = 2.7, 5.9, and 8.6 Hz, 1H, 2-C*H*), 2.62 (dt, J = 5.8 and 15.5 Hz, 1H, 1-C*H*), 2.80 (ddd, J = 5.8, 10.3, and 15.5 Hz, 1H, 3-C*H*), 4.28 (m, 1H, P[OC*H*(CH$_3$)$_2$]), 4.45 (m, 1H, P[OC*H*(CH$_3$)$_2$]), 7.1–7.34 (m, 5H, aromatics); ^{13}C NMR (50 MHz) δ 23.05 (d, J_{CP} = 192 Hz), 23.67 (4d, J_{CP} = 4 Hz), 25.10, 27.97, 29.83 (d, J_{CP} = 5 Hz), 70.32 (2d, J_{CP} = 6 Hz), 81.37, 126.91, 127.78, 129.21, 134.80, 171.00; ^{31}P NMR (80 MHz) δ 22.32. Further elution with the same solvents yielded (±)-**11** (0.80 g, 19% yield). ^{1}H NMR (200 MHz) δ 1.26 (m, 12H, P[OCH(CH_3)$_2$]$_2$), 1.44 (s, 9H, $CO_2C(CH_3)_3$), 1.55 (ddd, J = 0.6, 7.3 and 10.1 Hz, 1H, 2-C*H*), 2.18 (ddd, J = 6.0, 10.1 and 11.2 Hz, 1H, 1-C*H*), 3.01 (ddd, J = 6.0, 7.3 and 17.4 Hz, 1H, 3-C*H*), 4.7 (m, 2H, P[OC*H*(CH$_3$)$_2$]$_2$), 7.0–7.5 (m, 5H, aromatics); ^{13}C NMR (50 MHz) δ 24.20 (d, J_{CP} = 192 Hz), 23.91 (3d, J_{CP} = 5 Hz), 27.59, 28.00, 30.03 (d, J_{CP} = 6 Hz), 70.51 (2d, J_{CP} = 6 Hz), 81.23, 126.23, 126.85, 128.48, 138.39, 167.78; ^{31}P NMR (80 MHz) δ 22.63.

7.2. (±)-(1*S*,2*R*,3*R*)-Diisopropyl 2-(hydroxymethyl)-3-phenylcyclopropylphosphonate [(±)-12]

A 1 M solution of lithium triethylborohydride in THF (7.8 mL) was added to a cooled (−78 °C), magnetically stirred solution of (±)-**10** (1.00 g, 2.61 mmol) in dry THF (33 mL). After 15 min, the reaction mixture was acidified with 2 N HCl (10 mL) and allowed to warm to room temperature. The aqueous layer was extracted with EtOAc (2×60 mL), the combined organic phases dried over anhydrous Na_2SO_4, filtered and evaporated to give a residue which was purified by flash chromatography. Elution with AcOEt–MeOH (95:5) afforded (±)-**12** (0.66 g, 81% yield). ^{1}H NMR (400 MHz) δ 1.04 (m, 12H, P[OCH(CH_3)$_2$]$_2$), 1.18 (ddd, J = 2.4, 6.2 and 9.6 Hz, 1H, 1-C*H*), 2.22 (m, 1H, 2-C*H*), 2.37 (ddd, J = 6.2, 9.6 and 12.8 Hz, 1H, 3-C*H*), 3.62 (dd, J = 6.1 and 11.4 Hz, 1H, CH_aOH), 3.73 (dd, J = 5.7 and 11.4 Hz, 1H, CH_bOH), 4.23 (m, 1H, P[OC*H*(CH$_3$)$_2$]), 4.45 (m, 1H, P[OC*H*(CH$_3$)$_2$]), 7.12–7.32 (m, 5H, aromatics); ^{13}C NMR (100 MHz) δ 19.20 (d, J_{CP} = 195 Hz), 23.76 (m), 25.19 (d, J_{CP} = 3 Hz), 26.76 (d, J_{CP} = 6 Hz), 64.46, 69.98, 126.49, 127.63, 129.39, 136.20; ^{31}P NMR (160 MHz) δ 25.90.

7.3. (±)-(1*S*,2*R*,3*R*)-Diisopropyl 2-formyl-3-phenylcyclopropylphosphonate [(±)-13]

A solution of (±)-**12** (0.66 g, 2.13 mmol) in dry CH_2Cl_2 (18 mL) was added dropwise in 10 min to a magnetically stirred suspension of PCC (0.68 g, 1.90 mmol) in dry CH_2Cl_2 (12 mL). After 12 h, the reaction mixture was diluted with Et_2O (35 mL), filtered and the solvent evaporated off. Filtration of the residue through a Florisil® pad yielded (±)-**13** (0.47 g, 71% yield). ^{1}H NMR (400 MHz) δ 1.09 (m, J = 6.0 Hz, 12H, P[OCH(CH_3)$_2$]$_2$), 1.94 (dd, J = 5.9 and 9.4 Hz, 1H, 1-C*H*), 2.94 (m, 2H, 2-C*H* and 3-C*H*), 4.29 (m, 1H, P[OC*H*(CH$_3$)$_2$]), 4.44 (m, 1H, P[OC*H*(CH$_3$)$_2$]), 7.22–7.34 (m, 5H, aromatics), 9.48 (d, J = 4.2 Hz, 1H, C*H*O); ^{13}C NMR (100 MHz) δ 23.02 (d, J_{CP} = 193 Hz), 23.78 (2d + 1t, J_{CP} = 3 Hz), 30.53 (d, J_{CP} = 5 Hz), 32.36, 70.63, 127.29, 127.95, 129.19, 133.91, 198.14; ^{31}P NMR (160 MHz) δ 20.96.

7.4. (2*S*,1′*S*,2′*R*,3′*S*)- and (2*S*,1′*R*,2′*S*,3′*R*)-*N*-[(*R*) − α-Phenylglycinyl]-2-[2′-diisopropylphosphono-3′-phenylcyclopropyl]glycinonitriles (14 and 15)

(*R*)-α-Phenylglycinol (0.92 g, 6.67 mmol) was added to a solution of (±)-**13** (2.07 g, 6.67 mmol) in MeOH (50 mL), and the resulting solution was magnetically stirred at room temperature for 24 h. After cooling to (0 °C), TMSCN (1.31 g, 13.2 mmol) was added, and the resulting mixture was stirred for 24 h at room temperature. Evaporation of the solvent gave a residue which was submitted to a preliminary purification by flash chromatography (EtOAc) in order to remove the residue (*R*)-α-phenylglycinol. The mixture (2.8 g) of **14** and **15**, thus obtained, was then submitted to MPLC.

Elution with *n*-hexane–EtOAc (45:55) afforded the corresponding *N*-substituted-α-aminonitrile **14** (0.49 g, 32% yield). ^{1}H NMR (200 MHz) δ 1.10 (m, 12 H, P[OCH(C*H*$_3$)$_2$]$_2$), 1.41 (dd, J = 6.3 and 9.9 Hz, 1H, 1′-C*H*), 2.38 (m, 1H, 2′-C*H*), 2.52 (ddd, J = 6.4, 9.9 and 13.1 Hz, 1H, 3′-C*H*), 3.59 (m, 2H, 2-CH and CH_aOH), 3.74 (dd, J = 3.8 and 11.0 Hz, 1H, CH_bOH), 4.10 (dd, J = 3.8 and 9.2 Hz, 1H, NHC*H*Ph), 4.26 (m, 1H, P[OC*H*(CH$_3$)$_2$]), 4.47 (m, 1H, P[OC*H*(CH$_3$)$_2$]), 7.15–7.34 (m, 10H, aromatics); ^{13}C NMR (50 MHz) δ 18.47 (d, J_{CP} = 194 Hz), 23.88 (2d, J_{CP} = 3 Hz), 24.82, 26.76 (d, J_{CP} = 5 Hz), 49.94, 63.19, 67.07, 70.67 (2d, J_{CP} = 6 Hz), 117.98, 127.06, 127.41, 127.74, 128.30, 128.87, 129.44, 134.96, 135.08, 138.20; ^{31}P NMR (80 MHz) δ 23.78; $[\alpha]_D^{20}$ − 12.54 (*c* 2.62, CHCl$_3$). Further elution with the same solvents gave **15** (0.180 g, 14% yield). ^{1}H NMR (200 MHz) δ 1.14 (m, 12H, P[OCH(C*H*$_3$)$_2$]$_2$), 1.36 (dd, J = 6.2 and 10.2 Hz, 1H, 1′-C*H*), 2.45 (m, 2H, 2′-C*H* and 3′-C*H*), 3.45 (d, J = 6.4 Hz, 1H, 2-CH), 3.60 (m, 1H, CH_aOH), 3.74 (dd, J = 4.0 and 11.0 Hz, 1H, CH_bOH), 4.10 (m, 1H, NHC*H*Ph), 4.27 (m, 1H, P[OC*H*(CH$_3$)$_2$]), 4.47 (m, 1H, P[OC*H*(CH$_3$)$_2$]), 7.14-7.35 (m, 10H, aromatics); ^{13}C NMR (50 MHz) δ 19.67 (d, J_{C-P} = 194 Hz), 23.81, 24.63, 26.59–26.68 (d, J_{C-P} = 5.7 Hz), 50.49, 63.13, 67.01, 70.57, 117.95, 127.07, 127.53, 127.73, 127.94, 128.48, 128.97, 129.24, 129.44, 134.83, 137.64. ^{31}P-NMR (160 MHz) δ 23.27; $[\alpha]_D^{20}$ − 65.46 (*c* 1.41, CHCl$_3$).

7.5. (2*S*,1′*S*,2′*R*,3′*S*)-2-(2′-Phosphono-3′-phenylcyclopropyl)glycine (PPCG-1, 4)

Lead tetraacetate (0.49 g, 1.1 mmol) was added to a cooled (0 °C) magnetically stirred solution of **14** (0.42 g, 0.92 mmol) in anhydrous MeOH/CH$_2$Cl$_2$ (2:1, 48 mL). After 20 min, pH 7.7 phosphate buffer (70 mL) was added and the resulting mixture was filtered on a Celite pad. The solvent was then removed in vacuo and the residue thus obtained heated at 95 °C in 6 N HCl (5 mL) for 24 h. After evaporation of the solvent, the residue was purified by ion exchange resin chromatography. Elution with 2 N AcOH yielded **4** (0.093 g, 28% yield). ^{1}H NMR (200 MHz, D$_2$O) δ 1.60 (dd, J = 5.6 and 10 Hz, 1H, 2′-C*H*), 2.08 (m, 1H, 1′-C*H*), 2.63 (m, 1H, 3′-C*H*), 3.58 (d, J = 10 Hz, 1H, 2-C*H*), 7.04–7.11 (m, 5H, aromatics); ^{13}C NMR (50 MHz, D$_2$O) δ 20.07 (d, J_{CP} = 184.5 Hz), 21.73, 27.44-27.54 (d, J_{CP} = 5 Hz), 55.90, 127.03, 128.19, 128.97, 134.92, 170.64; ^{31}P NMR (80 MHz, D$_2$O) δ 21.97. $[\alpha]_D^{20}$ + 80.62 (*c* 2.85, H$_2$O).

7.6. (2*S*,1′*R*,2′*S*,3′*R*)-2-(2′-Phosphono-3′-phenylcyclopropyl)glycine (PPCG-2, 5)

Lead tetraacetate (0.21 g, 0.47 mmol) was added to a cooled (0 °C) magnetically stirred solution of **15** (0.18 g, 0.40 mmol) in anhydrous MeOH/CH$_2$Cl$_2$ (2:1, 21 mL). After 20 min, pH 7.7 phosphate buffer (15 mL) was added and the resulting mixture was filtered on a Celite pad. The solvent was then removed in vacuo and the residue thus obtained heated at 95 °C in 6 N HCl (5 mL) for 24 h. After evaporation of the solvent, the residue was purified by ion exchange resin chromatography. Elution with 2 N AcOH yielded **5** (0.049 g, 35% yield). ^{1}H NMR (200 MHz, D$_2$O) δ 1.42 (dd, J = 3.7 and 10.1 Hz, 1H, 2′-C*H*), 2.02 (m, 1H, 1′-C*H*), 2.71 (m, 1H, 3′-C*H*), 3.55 (d, J = 10 Hz, 1H, 2-C*H*), 7.07–7.14 (m, 5H, aromatics); ^{13}C NMR (50 MHz, D$_2$O) δ 18.15, 21.91, 27.54, 56.07, 127.06, 128.20, 129.07, 135.08, 170.69; ^{31}P NMR (80 MHz, D$_2$O) δ 21.72; $[\alpha]_D^{20}$ − 32.20 (*c* 1.3, H$_2$O).

7.7. (±)-1-Bromo-2-phenyl-3-butene [(±)-17]

Carbon tetrabromide (37.87 g, 114.21 mmol) and triphenylphosphine (19.97 g, 76.14 mmol) were added to a stirred solution of (±)-**16** (11.26 g, 76.14 mmol) in dry CH$_2$Cl$_2$ (39 mL). After 12 h, the solvent was removed in vacuo and the residue thus obtained, purified by flash chromatography. Elution with light petroleum afforded (±)-**17** (12.84 g, 80% yield). ^{1}H NMR (200 MHz) δ 3.69 (m, 3H, 1-CH_2 and 2-C*H*), 5.18 (m, 2H, 4-CH_2), 6.03 (m, 1H, 3-C*H*) 7.2–7.37 (m, 5H, aromatics).

7.8. (±)-Diethyl-2-phenylbut-3-enylphosphonate [(±)-18]

A magnetically stirred mixture of (±)-**17** (10.3 g, 48.8 mmol) and triethylphosphite (60 mL) was heated at 150 °C for 7 days. Excess of triethylphosphite was distilled off and the residue purified by flash chromatography. Elution with *n*-hexane–AcOEt (1:1) gave (±)-**18** (6.7 g, 51% yield). ^{1}H NMR (200 MHz) δ 1.10 (t, J = 6.0 Hz, 3H, P(OCH$_2$C*H*$_3$), 1.16 (t, J = 6.0 Hz, 3H, P(OCH$_2$C*H*$_3$)), 2.13 (dd, J = 2.8 and 7.3 Hz, 1H, 1-CH_a), 2.22 (dd, J = 3.2 and 7.4 Hz, 1H, 1-CH_b), 3.87 (m, 5H, P(OC*H*$_2$CH$_3$)$_2$ and 2-C*H*), 4.99 (m, 2H, 4-CH$_2$), 5.96 (m, 1H, 3-C*H*), 7.13–7.29 (m, 5H, aromatics); ^{13}C NMR (50 MHz) δ 16.17, 16.27, 30.33–33.12 (d, J_{CP} = 139.5 Hz), 43.76, 61.28, 61.38, 114.42, 126.64, 127.59, 128.51, 141.07-141.30 (d, J_{CP} = 11.5 Hz), 142.92–143.12 (d, J_{CP} = 10.2 Hz); ^{31}P NMR (80 MHz) δ 30.79.

7.9. Diethyl 2-oxiran-2-yl-2-phenylethylphosphonate (19)

A solution of (±)-**18** (2.90 g, 10.8 mmol) in CH$_2$Cl$_2$ (45 mL) was added dropwise to a magnetically stirred solution of 77% *m*-chloroperbenzoic acid (3.05 g, 14.4 mmol) in CH$_2$Cl$_2$ (25 mL). After 48 h the excess of peracid was destroyed by addition of 10% Na$_2$SO$_3$ (35 mL). The organic layer was separated and washed with 5% NaHCO$_3$ (35 mL) then with water (30 mL), dried over anhydrous Na$_2$SO$_4$ and the solvent removed in vacuo. The residue, thus obtained was purified by flash chromatography. Elution with EtOAc–light petroleum (7:3) afforded **19** (2.46 g, 80% yield).^{1}H NMR (200 MHz) δ 1.12 (m, 6H, P(OCH$_2$C*H*$_3$)$_2$), 2.13 (m, 2H, 1-CH$_2$), 2.47 (dd, J = 2.4 and 4.8 Hz, 1H, CH_aO of major diastereoisomer), 2.53 (dd, J = 2.5 and 6.7 Hz, 1H, CH_aO of minor diastereoisomer), 2.70 (m, 1H, CH_bO of both the diastereoisomers), 3.09 (m, 1H, OC*H*), 3.94 (m, 10H, P(OC*H*$_2$CH$_3$)$_2$ and 2-C*H*), 7.17–7.30 (m, 10H, aromatics); ^{13}C NMR (50 MHz) δ 16.16, 27.7 (d, J_{CP} = 160 Hz), 28.6 (d, J_{CP} = 140 Hz), 42.14, 43.2, 46.58, 47.3, 55.22, 55.5, 56.5, 61.45, 127.23, 127.97, 128.49; ^{31}P NMR (80 MHz) δ 30.39, 30.49.

7.10. (±)-(1*S*,2*R*,3*S*)-Diethyl 2-(hydroxymethyl)-3-phenylcyclopropylphosphonate [(±)-20]

1 M LiHMDS (3.9 mL) was added to a cooled (−78 °C), magnetically stirred solution of **19** (0.48 g, 1.69 mmol). The reaction mixture was then allowed to warm to −50 °C and stirred at this temperature for 3 h. The reaction mixture was quenched with saturated NH_4Cl solution (40 mL), allowed to warm to room temperature and extracted with AcOEt (3×60 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and evaporated to give a residue which was purified by flash chromatography. Elution with AcOEt–acetone (8:2) afforded **(±)-20** (0.25 g, 51% yield). ^{1}H NMR (400 MHz) δ 1.37 (m, 7H, $P(OCH_2CH_3)_2$ and 1-C*H*), 2.01 (m, 1H, 2-C*H*), 2.16 (br s, 1H, O*H*), 2.84 (ddd, J = 6.4, 9.1 and 16.0 Hz, 3-C*H*), 3.46 (d, J = 6.9 Hz, 1H, CH_2OH), 4.18 (m, 4H, $P(OCH_2CH_3)_2$), 7.26–7.33 (m, 5H, aromatics); ^{13}C NMR (50 MHz) δ 14.29 (d, J_{CP} = 197 Hz), 16.41, 16.47, 25.52 (d, J_{CP} = 5 Hz), 26.02 (d, J_{CP} = 3.5 Hz), 61.04 (d, J_{CP} = 4 Hz), 62.08, 62.18, 126.93, 128.43, 128.86, 136.59; ^{31}P NMR (80 MHz) δ 29.70.

7.11. (±)-(1*S*,2*R*,3*S*)-Diethyl 2-formyl-3-phenylcyclopropylphosphonate [(±)-21]

A solution of (±)-**20** (1.10 g, 3.06 mmol) in dry CH_2Cl_2 (35 mL) was added dropwise in 10 min to a stirred suspension of PCC (1.27 g, 5.9 mmol) in dry CH_2Cl_2 (25 mL). After 12 h, the reaction mixture was diluted with Et_2O (55 mL), filtered and the solvent evaporated off. Filtration of the residue through a Florisil® pad yielded (±)-**21** (0.73 g, 67% yield). ^{1}H NMR (200 MHz) δ 1.30 (t, J = 7.0 Hz, 3H, $P(OCH_2CH_3)$, 1.31 (t, J = 7.0 Hz, 3H, $P(OCH_2CH_3)$), 2.26 (m, 1H, 1-C*H*), 2.59 (m, 1H, 2-C*H*) 3.17 (m, 1H, 3-C*H*), 4.09 (m, 4H, $P(OCH_2CH_3)_2$) 7.10–7.30 (m, 5H, aromatics), 8.87 (d, J = 6.0 Hz, 1H, C*H*O); ^{13}C NMR (100 MHz) δ 17.25 (d, J_{CP} = 192.5 Hz), 16.54, 29.77, 32.64, 127.7, 128.8, 129.1, 133.27, 197.6; ^{31}P NMR (80 MHz) δ 25.76.

7.12. (2*S*,1′*R*,2′S,3′S)- and (2*S*,1′S,2′*R*,3′*R*) − *N*-[(*R*) − α-Phenylglycinyl]-2-[2′-diethylphosphono-3′-phenylcyclopropyl]glycinonitriles (22 and 23)

(*R*)-(α)-Phenylglycinol (0.35 g, 2.59 mmol) was added to a magnetically stirred solution of (±)-**21** (0.73 g, 2.59 mmol) in MeOH (25 mL) and the resulting solution was stirred at room temperature for 24 h. After cooling to 0 °C, TMSCN (0.51 g, 5.16 mmol) was added, and the resulting mixture was stirred for 24 h at room temperature. Evaporation of the solvent gave a residue which was submitted to a preliminary purification by flash chromatography (EtOAc) in order to remove the residue (*R*)-α-phenylglycinol. The mixture (0.9 g) of **22** and **23**, thus obtained, was then submitted to MPLC. Elution with *n*-hexane–acetone (6:4) afforded **22** (0.17 g, 15% yield): ^{1}H NMR (200 MHz) δ 1.30 (m, 7H, $P(OCH_2CH_3)_2$ and 2′-C*H*), 2.08 (m, 1H, 1′-C*H*), 2.40 (d, J = 9.8 Hz, 1H, 2-C*H*), 2.84 (m, 2H, 3′-C*H* and O*H*), 3.51 (t, J = 12.0 Hz, 1H, CH_aOH), 3.67 (dd, J = 4.0 and 12.0 Hz, 1H, CH_bOH), 3.89 (dd, J = 4.0 and 12.0 Hz, 1H, C*H*CH_2OH), 4.16 (m, 4H, $P(OCH_2CH_3)_2$), 6.90–6.96 (m, 5H, aromatics), 7.09–7.33 (m, 5H, aromatics); ^{13}C NMR (50 MHz) δ 15.49 (d, J_{CP} = 191.4 Hz), 16.39, 26.54, 46.32–46.40 (d, J_{CP} = 4 Hz), 62.38–62.50 (d, J_{CP} = 6 Hz), 62.57–62.70 (d, J_{CP} = 6 Hz), 62.86, 66.97, 118.71, 127.47, 128.10, 128.38, 128.52, 128.65, 128.87, 133.22, 138.30; ^{31}P NMR (80 MHz) δ 27.83; $[\alpha]_D^{20}$ − 110.9 (*c* 3.35, $CHCl_3$). Further elution with the same solvents gave **23** (0.19 g, 17% yield): ^{1}H NMR (200 MHz) δ 1.30 (m, 7H, $P(OCH_2CH_3)_2$ and 2′-C*H*), 2.06 (m, 1H, 1′-C*H*), 2.63 (d, J = 10.0 Hz, 1H, 2-C*H*), 2.90 (m, 1H, 3′-C*H*), 3.36 (dd, J = 9.2 and 10.7 Hz, 1H, CH_aOH), 3.55 (dd, J = 4.0 and 10.6 Hz, 1H, CH_bOH), 3.90 (dd, J = 4.0 and 9.0 Hz, 1H, C*H*CH_2OH), 4.12 (m, 4H, $P(OCH_2CH_3)_2$), 6.61–6.65 (m, 2H, aromatics), 6.91–7.26. (m, 8H, aromatics); ^{13}C NMR (50 MHz) δ13.01 (d, J_{CP} = 191.6 Hz), 16.42, 26.65, 27.03, 47.10–47.03 (d, J_{CP} = 3.5 Hz), 62.31, 62.42, 62.91; ^{31}P NMR (80 MHz) δ 27.87; $[\alpha]_D^{20}$ − 24.99 (*c* 2.5, $CHCl_3$).

7.13. (2*S*,1′*R*,2′*S*,3′*S*)-2-(2′-Phosphono-3′-phenylcyclopropyl)glycine (PPCG-3, 6)

Lead (IV) acetate (0.07 g, 0.16 mmol) was added to a cooled (0 °C) magnetically stirred solution of **22** (0.083 g, 0.19 mmol) in anhydrous CH_2Cl_2/MeOH (2:1, 9 mL). After 20 min, pH 7.7 phosphate buffer (5 mL) was added and the resulting mixture was filtered on a Celite pad. The solvent was then removed in vacuo and the residue thus obtained heated at 95 °C in 6 N HCl (5 mL) for 24 h. After evaporation of the solvent, the residue was purified by ion exchange resin chromatography. Elution with 2 N AcOH yielded **6** (0.018 g, 46% yield). ^{1}H NMR (400 MHz, D_2O + HCl) δ 1.85 (m, 2H, 1′-C*H* and 2′-C*H*), 2.75 (m, 1H, 3′-C*H*), 3.10 (d, J = 10.0 Hz, 1H, 2-C*H*), 7.12–7.17 (m, 5H, aromatics); ^{13}C NMR (50 MHz, D_2O) δ 15.26 (d, J_{CP} = 185 Hz), 23.73, 26.57, 51.67, 127.46, 128.32, 128.89, 133.26, 169.65; ^{31}P NMR (80 MHz, D_2O) δ 21.20; $[\alpha]_D^{20}$ − 16.43 (*c* 0.78, 6 N HCl).

7.14. (2*S*,1′*S*,2′*R*,3′*R*)-2-(2′-Phosphono-3′-phenylcyclopropyl)glycine (PPCG-4, 7)

Lead (IV) acetate (0.150 g, 0.34 mmol) was added to a cooled (0 °C) magnetically stirred solution of **23** (0.121 g, 0.28 mmol) in anhydrous CH_2Cl_2/MeOH (2:1, 15 mL). After 20 min, pH 7.7 phosphate buffer (10 mL) was added and the resulting mixture was filtered on a Celite pad. The solvent was then removed in vacuo and the residue thus obtained heated at 95 °C in 6 N HCl (8 mL) for 36 h. After evaporation of the solvent, the residue was purified by ion exchange resin chromatography. Elution with 2 N AcOH afforded **7** (0.055 g, 37% yield). ^{1}H NMR (200 MHz, D_2O) δ 1.66 (m, 1H, 1′-C*H*), 1.82 (m, 1H, 2′-C*H*), 2.60 (m, 1H, 3′-C*H*), 3.09 (d, J = 12.0 Hz, 1H, 2-C*H*), 7.15–7.26 (m, 5H, aromatics); ^{13}C NMR (50 MHz, D_2O) δ 17.11 (d, J_{CP} = 180 Hz), 24.34, 25.59, 51.05, 127.62, 128.44, 128.89, 133.59, 171.48; ^{31}P NMR (80 MHz, D_2O) δ 22.02; $[\alpha]_D^{20}$ + 154.50 (*c* 0.88, H_2O).

7.15. (1*R*,2*S*,3*R*)-[2-(1,3-Dimethyl-2-oxidooctahydro-1*H*-1,3,2-benzodiazaphosphol-2-yl)-3-phenylcyclopropyl]methanol (27)

A 1-M solution of lithium triethylborohydride in THF (1.48 mL) was added to a cooled (−78 °C), magnetically stirred solution of **26** (0.30 g, 0.74 mmol) in dry THF (12 mL). After 15 min, the reaction mixture was quenched with saturated aqueous NH_4Cl (10 mL) and allowed to warm to room temperature. The aqueous layer was extracted with EtOAc (2×12 mL), the combined organic phases dried over anhydrous Na_2SO_4, filtered and evaporated to give a residue which was purified by flash chromatography. Elution with AcOEt–MeOH (90:10) afforded **27** (0.21 g, 84% yield). ^{1}H NMR (200 MHz) δ 1.07 (m, 5H, 2×CH_2 and 1-C*H*), 1.79 (m, 4H, 2 × CH_2), 2.02 (d, J = 11.6 Hz, 3H, N-CH_3), 2.42 (m, 7H, N-CH_3, 2-C*H*, 3-C*H* and 2×C*H*), 3.64 (dd, J = 6.4 and 11.6 Hz, 1H, CH_aOH), 3.87 (dd, J = 5.3 and 11.6 Hz, 1H, CH_bOH), 7.17-7.42 (m, 5H, aromatics); ^{13}C-NMR (50 MHz) δ 20.70 (d, J_{CP} = 153 Hz), 24.17, 26.60 (d, J_{CP} = 4.3 Hz), 28.00, 28.16, 28.36, 28.55, 29.10, 63.65 (d, J_{CP} = 7.4 Hz), 65.05, 126.59, 127.94, 129.53, 136.90; ^{31}P-NMR (80 MHz) δ 57.86; $[\alpha]_D^{20}$ − 108.76 (c 0.80, CH_2Cl_2).

7.16. (1*R*,2*S*,3*R*)-[2-(1,3-dimethyl-2-oxidooctahydro-1*H*-1,3,2-benzodiazaphosphol-2-yl)-3-phenylcyclopropanecarbaldehyde (28)

A solution of **27** (0.202 g, 0.59 mmol) in dry CH_2Cl_2 (5 mL) was added dropwise in 2 min to a magnetically stirred suspension of PCC (0.14 g, 0.65 mmol) in dry CH_2Cl_2 (3 mL). After 1 h, the reaction mixture was diluted with Et_2O (15 mL), filtered and the solvent evaporated off to give crude **28** (0.075 g, 38% yield), used for the next step without any purification due to its instability.

7.17. (2*S*,1′*R*,2′*S*,3′*R*)-*N*-[(*R*)-α-Phenylglycinyl]-2-[2′-(1,3-dimethyl-2-oxidooctahydro-1*H*-1,3,2-benzodiazaphosphol-2-yl)-3′-phenylcyclopropyl]glycinonitrile (29)

(*R*)-(α)-Phenylglycinol (0.0562 g, 0.41 mmol) was added to a magnetically stirred solution of **28** (0.075 g, 0.23 mmol) in MeOH (3 mL) and the resulting solution was stirred at room temperature for 24 h. After cooling to 0 °C, TMSCN (0.02 g, 0.23 mmol) was added, and the resulting mixture was stirred for 24 h at room temperature. Evaporation of the solvent gave a residue which was purified by flash chromatography. Elution with AcOEt–MeOH (90:10) afforded **29** (0.044 g, 80% yield). ^{1}H NMR (400 MHz) δ 1.00 (m, 3H, CH_2 and 2′-C*H*), 1.48 (m, 2H, CH_2), 1.79 (m, 2H, CH_2), 1.91 (m, 2H, CH_2), 2.05 (d, J = 5.8 Hz, 3H, N-CH_3), 2. 36 (d, J = 5.4 Hz, 3H, N-CH_3), 2.55 (m, 4H, 2′-CH, 3′-CH, and 2×CH_2), 3.50 (d, J = 5.62 Hz, 2-CH), 3.58 (m, 1H, CH_aOH), 3.75 (m, 2H, CH_bOH and C*H*Ph), 7.26–7.40 (m, 10H, aromatics); ^{13}C NMR (100 MHz) δ 20.06 (d, J_{CP} = 150 Hz), 24.12, 26.04, 27.99 (d, J_{CP} = 4.7 Hz), 28.31, 28.68 (d, J_{CP} = 9.6 Hz), 29.14, 49.90, 62.45, 65.04 (d, J_{CP} = 5.0 Hz), 67.30, 118.46, 127.03, 127.49, 128.10, 128.87, 129.38, 135.70, 138.04; ^{31}P NMR (160 MHz) δ 41.10; $[\alpha]_D^{20}$ − 115.37 (c 0.50, CH_2Cl_2).

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