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Asymmetric synthesis of conformationally constrained L-AP4 analogues using chiral sulfinyl auxiliary

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Abstract: Constrained L-AP4 analogues, (2*S*,1'*R*,2'*S*)- and (2*S*,1'*S*,2'*R*)-2-(2'-phosphonocyclopropyl) glycines as well as their phenyl analogues (2*S*,1'*S*,2'*R*,3'*S*)-2-(2'-phosphono-3'-phenylcyclopropyl) glycine (PPCG-1) and (2*S*,1'*R*,2'*S*,3'*R*)-2-(2'-phosphono-3'-phenylcyclopropyl) glycine (PPCG-2) were synthesized. The stereogenic centers in cyclopropane ring were formed under sulfinyl group control, in asymmetric cyclopropanation of enantiomerically pure α-phosphoryl vinyl sulfoxides. The sulfinimine-mediated asymmetric Strecker reaction allowed to introduce aminoacid moiety.

Keywords: glycine analogues; asymmetric cyclopropanation; sulfinyl auxiliary; sulfonium ylides; Strecker reaction; sulfinimines.

1. Introduction

(*S*)-Glutamic acid (Glu) (**1**) is the major excitatory neurotransmitter in the central nervous system (CNS), and activates both ionotropic and metabotropic excitatory amino acid (EAA) receptors. Glu is involved in most brain functions such as learning, memory, motor control, vision and pain sensitivity. It is generally agreed that all classes of EAA receptors play important roles in the CNS, and that ligands affecting ionotropic as well as metabotropic[1] receptors would serve as useful therapeutic targets in relation to various neurological disorders. Therefore, the development of selective ligands for glutamate receptors allows a fine modulation of the glutamatergic pathways and may provide an appropriate therapeutic approach for the treatment of neurodegenerative pathologies such as Alzheimer's or Huntington's disease, or neuropsychiatric disorders as Parkinson's desease or neuronal damage resulting from cerebral ischemia and epilepsy.[2]

More potent analogues can be designed by manipulation of a functional group, stereochemistry or a conformational constrain, since flexible molecules suffer from a significant loss in entropy upon binding to receptors. Many strategies have been devised to reduce or eliminate the conformational flexibility of the natural ligand. However, the most widely used technique is ring insertion, since constrained amino acids closely mimic the bioactive conformation of natural neurotransmitters. For this reason, intensive studies have been performed on the synthesis of three to six-membered carbocyclic analogues.[3,4] Among all these analogues, the carboxycyclopropylglycines (CCG) represent the most important source of active analogues for the Glu receptors. For instance, *trans*-

(2*S*,1'*S*,2'*S*)-2-(2'-carboxycyclopropyl)gly (L-CCG-I **2**) has been shown to be a potent agonist of group II mGluRs, while the *cis*-isomer (**3**) is a potent and selective NMDA agonist.[5]

Bioisosteric replacement of substituents is another way to improve pharmacological properties, and thus create more effective drugs and prodrugs. Special interest in the phosphonic acid group is associated, among other issues, with its tetrahedral structure, where the planar and less bulky carboxylic acid (CO_2H) is replaced by a tetrahedral phosphonic acid functionality (PO_3H_2). α-Aminophosphonic acids, structurally analogous to α-amino acids, are important compounds which exhibit interesting biological activities by themselves or as components of peptidomimetics, particularly in research involving the modification of physiological processes in living organisms.

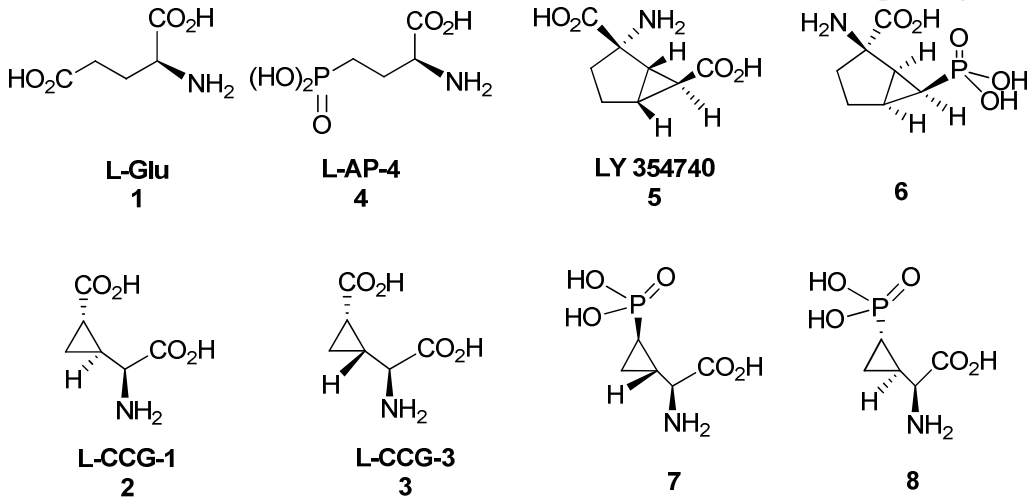


Fig. 1. Selected L-Glu analogues

(2*S*)-2-Amino-4-phosphonobutanoic acid L-AP4 (**4**) acts as an agonist for the group III metabotropic glutamate receptors, although with a lack of selectivity between the different mGluR group III subtypes.[6]

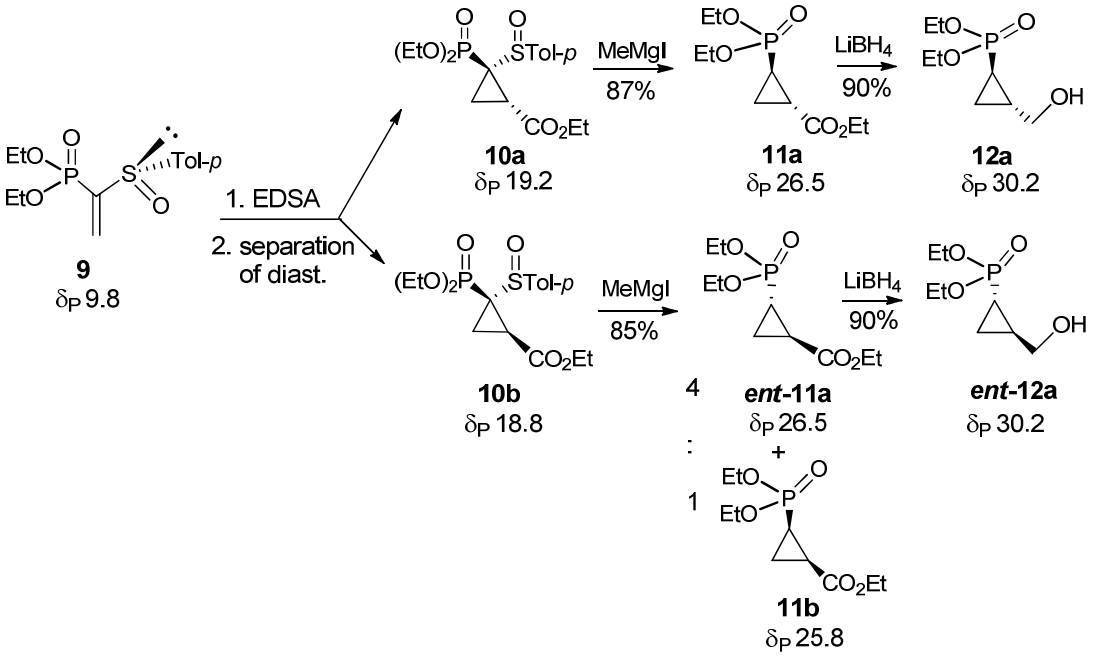
Combining both techniques: conformational restriction and isosterism became a reasonable way of searching for effective potential selective mGluRs agonists. According to this concept, the synthesis of enantiomerically pure (2*S*,3*R*,4*R*)-ethoxycarbonylcyclopropyl phosphonoglycine[7] and 4-phosphonophenylglycine 4-PPG, were elaborated; the latter turned out to be a potent and selective group III mGluRs agonist.[8] Recently we described the synthesis of optically active bicyclic aminophosphonic acid **6**, which is an analogue of one of the most potent and selective group II agonist, LY354740 (**5**).[9]

Continuing our studies on asymmetric cyclopropanation mediated by a chiral sulfinyl group and its application to the synthesis of biologically active compounds, we decided to apply our methodology as a key step in the preparation of phosphonate analogues of carboxycyclopropylglycines.[10] In 2006

Pellicciari and coworkers[11] evaluated the synthesized phosphonocyclopropylaminoacids (PCG) as mGluR ligands and proved their activity as group III mGluRs agonists. One year later, the same group published[12] their results on the stereocontrolled synthesis of 3'-phenyl substituted analogues (PPCG) and evaluation 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. These publications prompted us to disclose our own results concerning the synthesis of those ligands. This approach is based on our previous work and applies a different methodology, which allowed to use less expensive materials and gave the desired products in higher overall yield.

2. Results and discussion

In the approach to the synthesis of PCG we utilized our methodology for the synthesis of enantiomericaly pure cyclopropylphosphonates, based on the reaction of (*S*)-(+)-(1-diethoxyphosphoryl)vinyl *p*-tolyl sulfoxide with sulfonium ylides.[13] We have found[14] that cyclopropanation using ethyl (dimethylsulfuranylidene)acetate (EDSA) occurs in a highly diastereoselective manner with facial stereoselectivity up to 12:1.[15] The major diastereomer obtained in this reaction, (1*S*,2*S*)-(1-diethoxyphosphoryl-2-ethoxycarbonyl)cyclopropyl *p*-tolyl sulfoxide, was converted in two steps into enantiopure **12a** (Scheme 1). Desulfurization performed on the second diastereomer **10b**, where carboethoxy and phosphoryl groups are in *cis* relationship,[16] gave, under the same conditions, a mixture of *ent*-**11a** and **11b**, which were separated by column chromatography. The formation of *ent*-**11a** in this reaction is due to inversion of the configuration at C(1) and thermodynamic control, affording a more stable *trans*-isomer as the major product (Scheme 1).



Scheme 1.

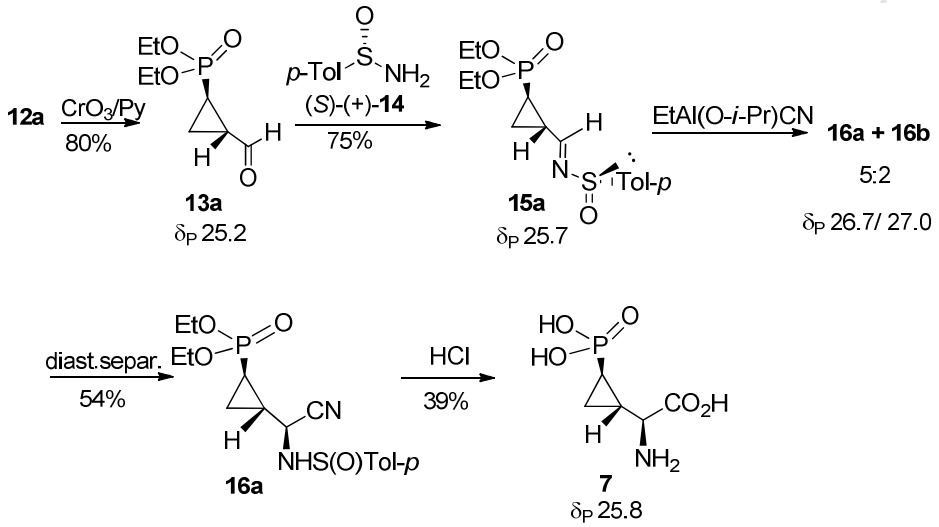
Alcohol **12a**, obtained by ester **11a** reduction was then oxidized by CrO_3 in pyridine to the aldehyde **13a** in 80% yield. Analogous conversions were performed on its enantiomer, leading to *ent*-**13a** (Scheme 2)**.**

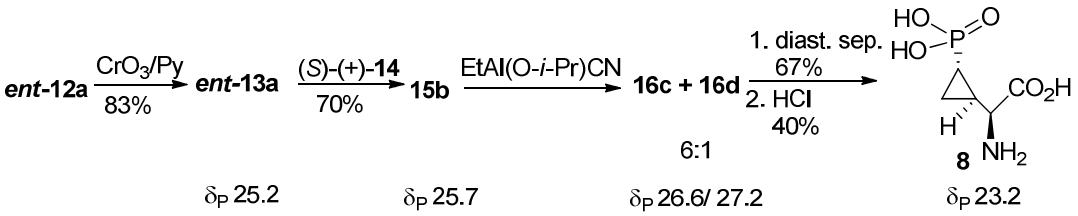
To introduce the amino acid moiety at this stage, we decided to apply the asymmetric Strecker synthesis involving the highly diastereoselective addition of ethylaluminum cyano alkoxide ["EtAl(OR)CN"] to non-racemic sulfinimines developed by Davis.[17] It was established that the configuration of the sulfinyl group controls cyanide addition: Re-face addition to sulfinimines of (*S*)-configuration gives (S,S_S)-amino nitriles as the major diastereoisomers.

For this purpose, the sulfinimine **15a** was prepared by condensing commercially available (*S*)-(+)-*p*-toluenesulfinamide (**14**) with the cyclopropyl aldehyde **13a** in the presence of $Ti(OEt)_4$ running the reaction overnight (Scheme 2). After purification and removal of the unreacted aldehyde, the isolated yield of **15a** was 75%. Next, Strecker reaction was performed by addition of ethylaluminum cyanoisopropoxide [EtAl(O-*i*-Pr)CN], prepared by treatment of 2 equiv of diethylaluminum cyanide with 1.0 equiv of *i*-PrOH, to a solution of the sulfinimine **15a** at –78 °C. Quenching at low temperature afforded the mixture of (2*S*,1'*S*,2'*R*)- and (2*R*,1'*S*,2'*R*)-aminonitriles **16a** and **16b** in 5 to 2 ratio (43% *de*). We assume that the major diastereomer **16a**, isolated after chromatography, has *S* configuration on a newly created center, which is consistent with Davis' hypothesis[17b] about the coordination of EtAl(O-*i*-Pr)CN to the sulfinyl oxygen and intramolecular delivery of CN moiety.

Hydrolysis of the aminonitrile **16a** occurs efficiently, without epimerization, on heating in 6.0 N HCl to afford the corresponding amino acid **7** (Scheme 2).

To obtain the more potent diastereomer **8**, the same sequence of transformations was performed using cyclopropyl aldehyde ***ent*-12a** as a starting material. Sulfinamide ***ent*-13a** was subjected to diastereoselective Strecker reaction affording corresponding (2*S*,1'*R*,2'*S*)- and (2*R*,1'*R*,2'*S*)-aminonitriles **16c** and **16d.** To our delight, the asymmetric induction was much higher in this case and the ratio of diastereomers attained 6 : 1 (71.4% *de*). Separation of the major diastereomer **16c** and final hydrolysis of the amino nitriles, when a cleavage of the chiral auxiliary takes place, afforded desired (2*S*,1'*R*,2'*S*)-2-(2'-phosphonocyclopropyl)glycine **8** (PCG-1).





Scheme 2.

The absolute configuration of the substituted cyclopropane ring was tentatively assigned by us earlier, based on the model of transition state for the cyclopropanation reaction of chiral 1-phosphorylvinyl sulfoxides.[13b,18] During the transformations which lead to cyclopropylglycines **7** and **8**, this configuration is retained. Formation of a new chiral center during Strecker reaction is evidently controlled by the stereogenic sulfinyl group, with a moderate "match" effect for sulfinimine **15b**. Configuration of this center was assigned by analogy to other reactions of this

type, where (*S*,S_S)-amino nitriles are formed as the major diastereoisomers from sulfinimines of (*S*)-configuration.

For further modifications of cyclopropane ring in order to obtain phenyl substituted -(2'-phosphonocyclopropyl) glycines we used *E*-(*S*)-(1-dimethoxyphosphoryl-2-phenyl)vinyl *p*-tolyl sulfoxide as a starting material for cyclopropanation. The presence of an additional substituent on carbon 2 in this sulfoxide caused an increase of diastereoselectivity during cyclopropanation with ethyl (dimethylsulfuranylidene)acetate. Though three new stereogenic centres of chirality were formed under the control of the chiral *p*-toluenesulfinyl group, the cyclopropane **17E** was formed as a mixture of only two diastereomers in an 8:1 ratio.[19] Our former investigations evidenced that the major diastereomer of cyclopropylphosphonate **17E** obtained in this reaction was easily separated by column chromatography and converted into the corresponding methyl ester **17** in quantitative yield by transesterification with methanol under basic conditions. Desulfurization of the latter was performed by treatment with sodium amalgam. Under the reaction conditions applied, the cyclopropanephosphonate **18** was obtained as a 3:1 mixture of two diastereomers **18a** and **18b**, which were easily separated by column chromatography. Based on the homo- and heteronuclear two-dimensional NMR and a three-bond carbon–phosphorus coupling constants, as well as on NOE measurements,[13] the diastereomers were found to have an opposite configuration at the α-phosphonate carbon atom.[14] The major diastereomer (+)-**18a** was formed with retention of configuration (Fig. 2).

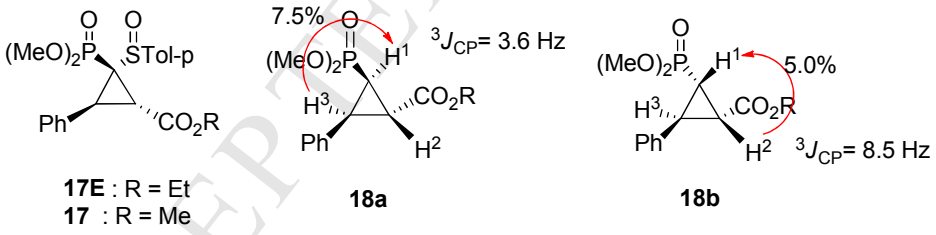
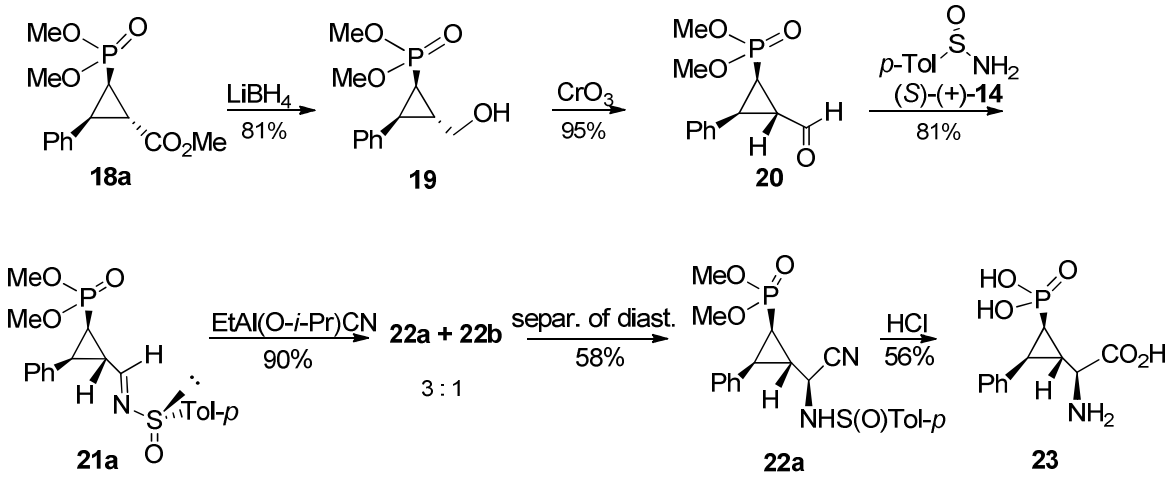


Fig. 2.

Cyclopropyl phosphonate **18a**, with *trans* relationship of the ester group to both remaining substituents was effectively reduced to appropriate alcohol **19**. Oxidation of **19** by CrO_3 in pyridine in dichloromethane at room temperature led in 95% yield to the aldehyde **20.**



Scheme 3.

In order to obtain the appropriate cyclopropylaminoacid, we again used sulfinimine-mediated asymmetric Strecker synthesis to introduce the aminoacid moiety. Condensation of **20** with (*S*)-(+)-*p*-toluenesulfinamide (**14**) formed sulfimine **21a**, which was reacted with ethylaluminum cyanoisopropoxide [EtAl(O-*i*-Pr)CN], affording a mixture of aminonitriles **22a** and **22b** in 3:1 ratio. The major diastereomer (*2S,1'S,2'R,3'S*)-**22a,** which was separated by column chromatography, was subjected to hydrolysis leading to PPCG-1 **23** in reasonable 56% yield (Scheme 3).

To obtain diastereomer (2*S*,1'*R*,2'*S*,3'*R*) PPCG-2 **24** showing agonistic activity[12], the sequence of transformations presented above should be performed using the opposite enantiomer of **20** (*ent*-**20**).

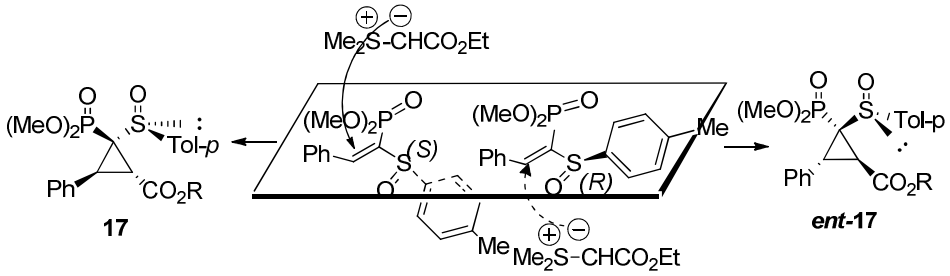
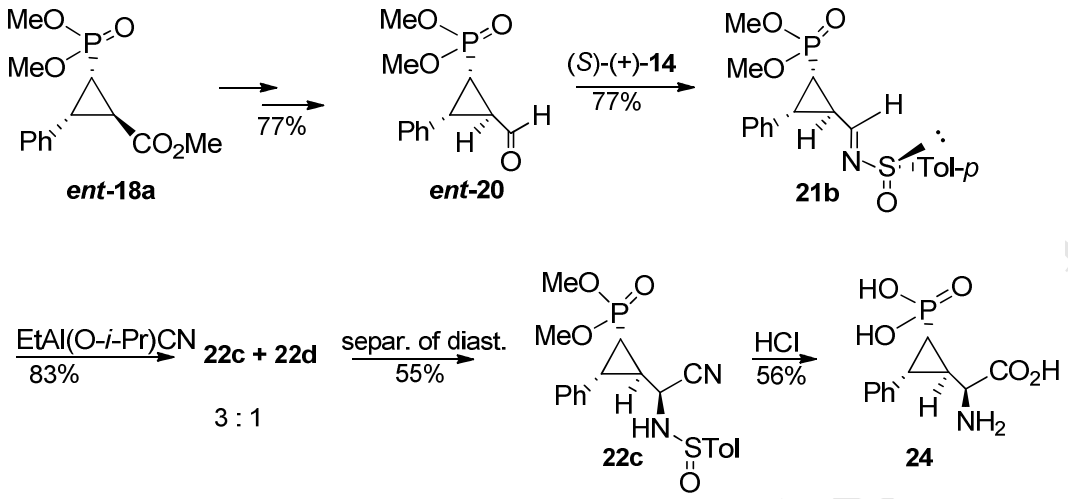


Fig. 3.

Therefore, cyclopropanation reaction was performed on vinyl sulfoxide with *R* configuration on the sulfinyl group. The opposite configuration on sulfur caused that the approach of EDSA to the carbon-carbon double bond, which takes place preferentially from the less hindered diastereotopic face occupied by the lone electron pair of sulfur, in *E*-(*R*)-(1-dimethoxyphosphoryl-2-phenyl)vinyl *p*-tolyl sulfoxide, occurs from the opposite side (bottom-face attack) (Figure 3). In this way the (1*R*,2*R*,3*S*,R_S) cyclopropyl sulfoxide *ent*-**17** was formed as the major product and after desulfurization afforded *ent*-**18a**, used for further transformations.



Scheme 4.

Diastereoselective Strecker reaction and final hydrolysis of the α-amino nitrile **22c** provided (*2S,1'R,2'S,3'R*)-2-(2'-phosphono-3'-phenylcyclopropyl)glycine (PPCG-2, **24**) in 18.2% overall yield, starting from the easily available (1*R*,2*S*,3*R*)-methyl 2-(dimethoxyphosphoryl)-3-phenylcyclopropanecarboxylate ***ent*-18a** (Scheme 4).

Although configuration of stereogenic center during the synthesis was assigned by analogy to other Strecker reactions, the spectral data of (2'-phosphonocyclopropyl) glycines, as well as their phenyl analogues, which were obtained by us, are consistent with those described in the literature.[11,12] In this way the presented transformations, leading to known products, provide another confirmation of the former configurational assignment.

3. Summary

The stereocontrolled synthesis of the *trans*-(2*S*,1'*R*,2'*S*)- and (2*S*,1'*S*,2'*R*)-2-(2'-phosphonocyclopropyl) glycines (PCG-2, **7**) and (PCG-1, **8**) and appropriate phenyl analogues (2*S*,1'*S*,2'*R*,3'*S*)-2-(2'-phosphono-3'-phenylcyclopropyl) glycine (PPCG-1, **23**) and (2*S*,1'*R*,2'*S*,3'*R*)-2-(2'-phosphono-3'-phenylcyclopropyl) glycine (PPCG-2, **24**) was elaborated. The stereogenic centers in cyclopropane ring were formed under sulfinyl group control, utilizing asymmetric synthesis of cyclopropylphosphonates using enantiomerically pure α-phosphoryl vinyl sulfoxides. The sulfinimine-mediated asymmetric Strecker reaction allowed to introduce aminoacid moiety. Hydrolysis of appropriate aminonitriles was easily accomplished, simply by heating in acidic medium, avoiding toxic reagents. Although sulfinyl auxiliary was used twice during transformations

to cyclopropyl glycines, it improved efficiency of the synthesis, since separation of diastereomers was easier to perform.

4. Experimental section

4.1. General

^{1}H, ^{13}C and ^{31}P NMR spectra were recorded on a Bruker DRX 500, Bruker MSL 300 and Bruker AC 200 Spectrometers using deuterochloroform as a solvent. Mass spectra were recorded on Finnigan MAT95. The optical rotations were measured on a Perkin–Elmer 241 MC photopolarimeter at 20 ^{o}C. The microanalyses were performed on an Elemental Analyzer EA 1108. TLC was carried out on silica gel plates (Merck F254) and Silica Gel 60 (70–230 ASTM) was used for chromatography. THF was freshly distilled over potassium/benzophenone

4.2. Preparation of 1-(diethoxyphosphoryl)-2-(formyl)cyclopropane

In a single-neck round-bottom flask was placed a solution of alcohol (0.322 g, 1.55 mmol, 1 eq) in CH_2Cl_2 (10 mL), then CrO_3 in pyridine (1.549 g, 0.0155 mol, 10 eq) was added and stirred overnight. At this time CH_2Cl_2 was evaporated and the resulting precipitate dissolved in Et_2O (5 mL). The suspension was filtered through Celite, and concentrated to give pure aldehyde.

4.2.1. (1*R*, 2*S*)-1-(Diethoxyphosphoryl)-2-(formyl)cyclopropane 13a

A colorless oil. Yield: 0.254 g (80%), $[\alpha]_D^{20}$ = –61 (*c* 3.0, acetone); IR (KBr) 2985, 1725, 1230 cm^{-1}; ^{31}P NMR (81 MHz, $CDCl_3$): δ 25.2; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.80–0.98 (m, 2H, 3'-C*H*$_2$), 1.30 (t, *J* = 7.1 Hz, 3H, C*H*$_3$CH$_2$O), 1.32 (t, *J* = 7.1 Hz, 3H, C*H*$_3$CH$_2$O), 1.40–1.55 (m, 1H, 2'-C*H*), 1.56–1.66 (m, 1H, 1'-C*H*), 4.06–4.23 (m, 4H, CH$_3$C*H*$_2$O), 9.25 (d, *J* = 4.3 Hz, 1H, C*H*O); ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.4 (d, *J* = 196.5 Hz), 16.3 (d, *J* = 5.9 Hz), 26.1, 26.2, 62.4 (d, *J* = 6.1), 198.2 (d, *J* = 4.3 Hz); MS (CI) m/z = 207 $(M + H)^+$; HR MS(EI) 206. 0711. calcd for $C_8H_{15}O_4P$. Found: 206. 0708.

4.3. Preparation of *N*-(2-diethoxyphosphoryl)cyclopropylmethylidene-*p*-toluenesulfinamide

In a dried single-neck round-bottom flask equipped with magnetic stirring bar, rubber septum, and an argon baloon was dissolved (*S*)-(+)-*p*-toluensulfinamide (0.377 g, 22.1 mmol, 1.8 eq) in dry CH_2Cl_2, then was added aldehyde (0.254 g, 12.3 mmol, 1 eq) and $Ti(OEt)_4$ (2.805 g, 0.015 mol,

3.61 mL, 12.5 eq), and the mixture was stirred overnight. At this time to the reaction mixture water was added. The suspension was filtered through Celite, and washed with CH_2Cl_2 (5 mL). The organic and aqueous phases was separated, and the aqueous phase was extracted with CH_2Cl_2 (5 x 5 mL). The combined organic phases was dried over $MgSO_4$, and concentrated to give crude sulfinimine, which was washed with petroleum ether to remove excess of (*S*)-(+)-*p*-toluensulfinamide and purified by column chromatography (diethyl ether : acetone, 20:1).

4.3.1. (1*S*, 2*R*, S_s)-2-(diethoxyphosphoryl)-cyclopropylmethylidene-*p*-toluenesulfinamide 15a

A colorless oil. Yield: 0.316 g (75%), $[\alpha]_D^{20}$ = −155 (*c* 3.5, acetone); IR (KBr) 3030, 2975, 2860, 1560, 1230, 1025 cm^{-1}; ^{31}P NMR (81 MHz, $CDCl_3$): δ 25.7; ^1H NMR (200 MHz, $CDCl_3$): δ 0.80–0.98 (m, 2H, 3'-C*H*$_2$), 1.21–1.29 (m, 1H, 2'-C*H*), 1.31 (t, *J* = 7.1 Hz, 3H, C*H*$_3$CH$_2$O), 1.32 (t, *J* = 7.1 Hz, 3H, C*H*$_3$CH$_2$O), 1.50–1.55 (m, 1H, 1'-C*H*), 2.39 (s, 3H, $C_6H_4CH_3$), 4.01–4.17 (m, 4H, CH$_3$C*H*$_2$O), 7.29 (d, *J* = 8.0 Hz, H_{Ar}), 7.52 (d, *J* = 7.9 Hz, H_{Ar}), 7.68 (d, *J* = 7.2, 1H, C*H*=N); ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.4 (d, *J* = 196.4 Hz), 16.3 (d, *J* = 5.9 Hz), 21.2, 26.1, 30.2, 62.3, 124.4, 125.3, 129.5, 129.8, 165.6; MS (CI) m/z = 344 $(M + H)^+$; HR MS(EI) 343.1007 calcd for $C_{15}H_{22}NO_4PS$. Found: 343.1014.

4.3.2. (1*R*, 2*S*, S_s)-2-(diethoxyphosphoryl)-cyclopropylmethylidene-*p*-toluenesulfinamide 15b

A colorless oil. Yield: (70%), $[\alpha]_D^{20}$ = +152 (*c* 1.2, acetone); IR (film) 3030, 2980, 2875, 1560, 1230, 1025 cm^{-1}; ^{31}P NMR (81 MHz, $CDCl_3$): δ 25.7; ^1H NMR (200 MHz, $CDCl_3$): δ 0.84–1.29 (m, 2H, 3'-C*H*$_2$), 1.21–1.29 (m, 1H, 2'-C*H*), 1.30 (t, *J* = 7.1 Hz, 3H, C*H*$_3$CH$_2$O), 1.32 (t, *J* = 7.1 Hz, 3H, C*H*$_3$CH$_2$O), 1.45–1.69 (m, 1H, 1'-C*H*), 2.40 (s, 3H, $C_6H_4CH_3$), 4.02–4.18 (m, 4H, CH$_3$C*H*$_2$O), 7.30 (d, *J* = 8.1 Hz, H_{Ar}), 7.53 (d, *J* = 8.2 Hz, H_{Ar}), 7.69 (d, *J* = 7.4 Hz, 1H, C*H*=N); ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.3 (d, $J_{C\text{-}P}$ = 190.2 Hz), 16.1 (d, $J_{C\text{-}P}$ = 5.5 Hz), 21.1, 26.1,30.4, 62.1, 124.3, 125.6, 128.7, 129.3, 165.4; MS (CI) m/z = 344 $(M + H)^+$; HR MS(EI) 343.1007 calcd for $C_{15}H_{22}NO_4PS$. Found: 343.1001.

4.4. Preparation of [(*S*)-*N*-*p*-toluenesulfinyl]-2-amino-2-[diethoxyphosphorylcyclopropyl]-ethanenitrile 16

In an oven-dried double-neck round-bottom flask equipped with a magnetic stirring bar, a rubber septum, and an argon balloon was placed the solution of sulfininime (0.140 g, 0.409 mmol, 1 eq) in THF (7 mL) and cooled to −78 ^oC. In a separate single-neck round-bottom flask equipped with magnetic stirring bar, a rubber septum, and an argon balloon was added a solution of diethylaluminium cyanide (0.211 g, 0.189 mmol, 0.25 mL, 4.6 eq) in THF (2 mL). The solution was

cooled to −78 °C, and *i*-PrOH (0.051 g, 0.818 mmol, 0.064 mL, 2 eq) was added. The mixture was allowed to reach room temperature, stirred for 30 min, and cannulated to the solution of sulfinimine at −78 °C. After the reaction the mixture was brought to room temperature, and stirred for 24 h, it was cooled to −78 °C, and quenched with saturated NH_4Cl solution (5 mL). The suspension was filtered through Celite, extracted with EtOAc (5 x 5 mL), washed with brine (3 x 5 mL), dried over $MgSO_4$ and concentrated to give a mixture of aminonitriles (diastereomeric ratio: 5 : 2) (83%), which was purified by column chromatography (acetyl acetate : diethyl ether : Et_3N, 1:1: traces)

4.4.1. (2*S*)-[(*S*)-*N*-*p*-toluenesulfinyl]-2-amino-(1'*S*,2'*R*)-2-[diethoxyphosphorylcyclopropyl]-ethanenitrile 16a

A colorless oil. Yield: 0.081g (54%), $[\alpha]_D^{20}$ = +41 (*c* 0.75, acetone); IR (film) 3440, 3030, 2980, 2230, 1230, 1020 cm^{-1}; ^{31}P NMR (81 MHz, $CDCl_3$): δ 26.7; ^1H NMR (200 MHz, $CDCl_3$): δ 1.05 (t, *J* = 7.3 Hz, 3H, C*H*$_3$CH$_2$O), 1.22 (t, *J* = 7.0 Hz, 3H, C*H*$_3$CH$_2$O), 1.00–1.38 (m, 3H, 1'-C*H*, 3'-C*H*$_2$), 1.77–1.87 (m, 1H, 2'-C*H*), 2.37 (s, 3H, C*H*$_3$C$_6$H$_5$), 3.81 (dd, *J* = 8.7, 6.5 Hz, 1H, C*H*CN), 4.01–4.12 (m, 4H, CH$_3$C*H*$_2$O), 5.83 (d, *J* = 8.8 Hz, 1H, N*H*), 7.28 (d, *J* = 8.1 Hz, 2H$_{Ar}$), 7.54 (d, *J* = 8.1 Hz, 2H$_{Ar}$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 9.9 (d, *J* = 34.2 Hz), 14.7 (d, J_{C-P}= 194.5 Hz), 16.3, 20.5, 21.3, 29.6, 43.6, 62.4 (m), 116.9, 126.1, 129.9,139.3, 142.2; MS (CI) m/z = 371 $(M + H)^+$; HR MS(FAB) 370.1116 calcd for $C_{16}H_{23}N_2O_4PS$. Found: 370.1111.

4.4.2. (2*S*)-[(*S*)-*N*-*p*-toluenesulfinyl]-2-amino-(1'*R*,2'*S*)-2-[diethoxyphosphorylcyclopropyl]-ethanenitrile 16c

A colorless oil. Yield: (67%), $[\alpha]_D^{20}$ = +44 (*c* 1, acetone); IR (KBr) 3430, 3030, 2980, 2225, 1225, 1030 cm^{-1}; ^{31}P NMR (81 MHz, $CDCl_3$): δ 26.6; ^1H NMR (200 MHz, $CDCl_3$): δ 0.99–1.10 (m, 3H, 2'-C*H*, 3'-C*H*$_2$), 1.28 (t, *J* = 7.3 Hz, 3H, C*H*$_3$CH$_2$O), 1.40 (t, *J* = 7.3 Hz, 3H, C*H*$_3$CH$_2$O), 1.89–1.94 (m, 1H, 1'-C*H*), 2.41 (s, 3H, C*H*$_3$C$_6$H$_5$), 3.87 (dd, *J* = 7.3, 6.9 Hz, 1H, C*H*CN), 4.01–4.12 (m, 4H, CH$_3$C*H*$_2$O), 5.43 (d, *J* = 6.9 Hz, 1H, N*H*), 7.28 (d, *J* = 8.1 Hz, 2H$_{Ar}$), 7.53 (d, *J* = 8.2 Hz, 2H$_{Ar}$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 8.6 (3'*C*), 9.4 (d, J_{C-P} = 194.3 Hz, 2'*C*), 16.3 (d, J_{C-P}=5.5 Hz, *C*H$_3$CH$_2$O), 20.4 (1'*C*), 21.2, 43.3 (*C*-CN), 62.3 (d, J_{C-P}= 5.8 Hz, CH$_3$*C*H$_2$O), 116.7 (*C*N), 126.0 (*C*$_{Ar-H}$), 130.0 (*C*$_{Ar-H}$), 139.1 (*C*$_{Ar-C}$), 142.5 (*C*$_{Ar-S}$); MS (CI) m/z = 371 $(M + H)^+$; HR MS(FAB) 370.1116 calcd for $C_{16}H_{23}N_2O_4PS$. Found: 370.1122.

4.5. Procedure for hydrolysis of the aminonitriles to amino acids

In single-neck round-bottom flask equipped with magnetic stirring bar and a water condenser were placed the appropriate aminonitrile (0.0811g, 0.219 mmol, 1eq) and 6N HCl aq, (6 mL). The solution was refluxed for 24 h. The reaction mixture was cooled to room temperature and extracted

with diethyl ether (5 x 5 mL), and the aqueous phase was concentrated. The crude product was purified by preparative TLC (methanol, 2% of acetic acid).

4.5.1. (2*S*,1'*S*,2'*R*)-2-(2'-phosphonocyclopropyl)glycine 7

A white powder, m.p. 246–248 °C. Yield: 16,8 mg (39%), $[\alpha]_D^{20}$ = –9.3 (c 0.72, H_2O); IR (KBr) 3100, 2985, 2130, 1230 cm^{-1}; ^{31}P NMR (81 MHz, D_2O): δ 25.8; ^{1}H NMR (200 MHz, D_2O): δ 0.95–1.12 (m, 2H, 3'-C*H*$_2$), 1.25–1.27 (m, 1H, 1'-C*H*), 1.39–1.48 (m, 1H, 2'-C*H*), 3.43 (d, *J* = 10.1 Hz, 2-C*H*); ^{13}C NMR (125 MHz, D_2O): δ 8.7, 12.5 (d, J_{C-P} = 184.6 Hz), 16.7, 56.0, 170.8; MS (CI) m/z = 195 $(M + H)^+$ HR MS(FAB) 195.0296 calcd for $C_5H_{10}NO_5P$. Found: 195.0274.

4.5.2. (2*S*,1'*R*,2'*S*)-2-(2'-phosphonocyclopropyl)glycine 8

A white powder, m.p. 235–237 °C. Yield: (40%), $[\alpha]_D^{20}$ = +78.5 (*c* 0.95, H_2O); IR (KBr) 3100, 2980, 2120, 1230 cm^{-1}; ^{31}P NMR (81 MHz, D_2O): δ 23.2; ^{1}H NMR (200 MHz, D_2O): δ 1.00–1.06 (m, 2H, 3'-C*H*$_2$), 1.10–1.17 (m, 1H, 1'-C*H*), 1.43–1.50 (m, 1H, 2'-C*H*), 3.36 (d, *J* = 9.5 Hz, 2-C*H*); ^{13}C NMR (125 MHz, D_2O): δ 8.9, 12.2 (d, J_{C-P} = 183.5 Hz), 16.9, 56.3, 171.1; MS (CI) m/z = 195 $(M + H)^+$ HR MS(FAB) 195.0296 calcd. for $C_5H_{10}NO_5P$. Found: 195.0304

4.6. Preparation of 1-dimethoxyphosphoryl-2-carbomethoxy-3-phenylcyclopropane

To the solution of 772 mg (2 mmol) of 1-dimethoxyphosphoryl-1-*p*-tolylsulfinyl-2-carbomethoxy-3-phenylcyclopropane in methanol (20 mL) Na_2HPO_4 (1.5 g) was added as a buffer. To this mixture, cooled to –20 °C, sodium amalgam (1 g) was added and reaction mixture was stirred for 1 h and then allowed to warm up to 0 °C. At this temperature 10 mL of water was added and solution was extracted with chloroform (5 x 20 mL) The combined organic phases was dried over $MgSO_4$, and concentrated to give crude product (444 mg, 78% yield). The crude product was purified by chromatography.

4.6.1. (1*R*,2*S*,3*S*)- 1-Dimethoxyphosphoryl-2-carbomethoxy-3-phenylcyclopropane 18a

A colorless oil 280 mg (50 % yield). $[\alpha]_D^{20}$ +47.7 (c 1.7, acetone); IR (KBr) 3030, 1770, 1580, 1530, 1235, 1210, 1020 cm^{-1}; ^{31}P NMR (80 MHz, $CDCl_3$) δ_P = 25.8 ppm; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.93 (ddd, 1H, J_{P-H} = 3.0 Hz, J_{H-H} = 10.1, 5.8 Hz, C*H*P), 2.78 (ddd, 1H, J_{P-H} = 15.5 Hz, J_{H-H} = 5.8, 5.6, Hz, C*H*CO_2), 2.98 (ddd, 1H, J_{P-H} = 15.7 Hz, J_{H-H} = 10.1, 5.7 Hz, C*H*Ph), 3.37 (d, 3H, *J* = 10.9 Hz, C*H*$_3$OP), 3.40 (d, 3H, J_{P-H} = 11.0 Hz, C*H*$_3$OP), 3.76 (s, 3H, C*H*$_3O_2C$), 7.21–7.37 (m, 5H, C_6H_5); ^{13}C NMR (50 MHz, $CDCl_3$) 21.8 (d, J_{C-P} = 193.6 Hz), 23.6 (*C*CO_2), 29.8 (d, J_{C-P} = 6.2 Hz, *C*Ph), 52.0 (d, J_{C-P} = 6.0 Hz), 52.3 (d, J_{C-P} = 6.5 Hz), 52.4, 127.3, 128.1, 129.0, 134.4 (d, J_{C-}

$_P$ = 6.2 Hz), 172.1 (d, J_{C-P} = 3.6 Hz, *C*=O),; MS (CI) m/z = 285 $(M + H)^+$; Anal. Calcd for $C_{13}H_{17}O_5P$ C, 54.93; H, 6.03; Found C, 54.75; H, 5.98.

NOE: $H^3 \rightarrow H^1$ 7.5%;

4.6.2. (1*S*,2*S*,3*S*)- 1-Dimethoxyphosphoryl-2-carbomethoxy-3-phenylcyclopropane 18b

A colorless oil 135 mg (23.7 % yield). $[\alpha]_D^{20}$ +16.7 (c 2.3, acetone); IR (KBr) 3035, 1765, 1220 cm^{-1}; ^{31}P NMR (80 MHz, $CDCl_3$) δ_P = 26.4 ppm; ^1H NMR (500 MHz, $CDCl_3$) δ: 1.68 (ddd, 1H, J_{P-H} = 1.2 Hz, J_{H-H} = 9.9, 7.2 Hz, C*H*P), 2.36 (ddd, 1H, J_{P-H} = 11.0 Hz, J_{H-H} = 9.9, 5.9 Hz, C*H*CO_2), 3.16 (ddd, 1H, J_{P-H} = 17.5, J_{H-H} = 7.2, 5.9 Hz, C*H*Ph), 3.77 (d, 3H, *J* = 11.1 Hz, C*H*$_3$OP), 3.77 (s, 3H, C*H*$_3O_2$C), 3.78 (d, 3H, *J* = 11.0 Hz, C*H*$_3$OP), 7.11–7.35 (m, 5H, C_6H_5); ^{13}C NMR (50 MHz, $CDCl_3$) 22.4 (d, J_{C-P} = 194.1 Hz), 28.3 (d, J_{C-P} = 6.0 Hz), 28.7 (d, J_{C-P} = 2.5 Hz), 52.3, 52.7 (d, J_{C-P} = 6.2 Hz), 52.9 (d, J_{C-P} = 6.1 Hz), 96.1, 126.4, 127.3, 128.7, 137.5 (d, J_{C-P} = 3.2 Hz), 169.5 (d, J_{C-P} = 8.5 Hz, *C*=O),; MS (CI) m/z = 257 $(M + H)^+$; HR MS calcd for $C_{13}H_{17}PO_5$. Found 256.0853.

NOE: $H^2 \rightarrow H^1$ 5%

4.7. Preparation of 1-dimethoxyphosphoryl-2-hydroksymethyl-3-phenylcyclopropane

To the solution of methyl 2-(dimethoxyphosphoryl)-3-phenylcyclopropanecarboxylate (624 mg, 3 mmol) and methanol (0.4 mL) in THF (15 mL) was added slowly $LiBH_4$ (5eq, 7.5 mL, 2 M solution in THF). The reaction was stirred vigorously for 24 hours at room temperature, and then 10 ml of water was added. The mixture was a acidified by the addition of 5% solution of HCl aq to pH 3 and extracted (5 x 10 mL) with $CHCl_3$. The combined organic layers were dried with anhydrous $MgSO_4$ and evaporated. Product was purified by column chromatography on silica gel (diethyl ether).

4.7.1. (1*R*,2*S*,3*S*)- 1-Dimethoxyphosphoryl-2-hydroksymethyl-3-phenylcyclopropane 19

A colorless oil 400 mg (yield 81%). $[\alpha]_D$ +64.5 (c 3.7, acetone); IR (KBr) 3640, 3030, 2985, 1590, 1510, 1320, 1230 cm^{-1}; ^{31}P NMR (80 MHz, $CDCl_3$) δ_P = 29.5 ppm; ^1H NMR (200 MHz, $CDCl_3$) δ: 1.26–1.34 (m, 1H, C*H*P), 2.16–2.40 (m, 1H, C*H*), 2.43–2.62 (m, 1H, C*H*), 3.36 (d, 3H, *J* = 11.0 Hz, C*H*$_3$OP), 3.39 (d, 3H, *J* = 11.0 Hz, C*H*$_3$OP), 3.57–3.66 (m, 1H, C*H*$_2$OH), 3.79–3.88 (m, 1H, C*H*$_2$OH), 7.18–7.36 (m, 5H, C_6H_5); ^{13}C NMR (50 MHz, $CDCl_3$) 17.6 (d, J_{C-P} = 195 Hz), 25.1 (d, J_{C-P} = 4.0 Hz), 26.3 (d, J_{C-P} = 5.4 Hz), 51.9 (d, J_{C-P} = 6.1 Hz), 52.2 (d, J_{C-P} = 6.5 Hz), 64.2 (d, J_{C-P} = 34.4 Hz), 126.8, 127.9, 129.3, 136.2 (d, J_{C-P} = 6.6); MS (CI) m/z = 257 $(M + H)^+$; HR MS(EI) 256.0861 calcd for $C_{12}H_{15}O_4P$. Found 256.0853.

4.8. Preparation of dimethoxyphosphoryl 2-formyl-3-phenylcyclopropane

To the solution of 1-dimethoxyphosphoryl-2-hydroksymethyl-3-phenylcyclopropane (508 mg, 2 mmol) in 25 mL of dichloromethane, complex of CrO_3 in pyridine (800 mg) was added and stirred 12 hours at room temperature. Reaction was monitored by TLC and finished until the spot of alcohol disappeared. Solvent was evaporated and brown precipitate was washed with diethyl ether (3 x 10 mL) and filtrated by Celite. Filtrate was evaporated in vacuum. Crude product was purified by flash chromatography using diethyl ether as eluent.

4.8.1. (1*R*,2*S*,3*S*)-Dimethoxyphosphoryl-2-formyl-3-phenylcyclopropane 20

A colorless oil 486 mg (95 % yield) $[\alpha]_D^{20}$ +136.4 (c 10.5, acetone); IR (film) 3030, 2985, 1740, 1610, 1590, 1520, 1230 cm^{-1}; ^{31}P NMR (80 MHz, $CDCl_3$) δ_P = 24.8 ppm; ^1H NMR (200 MHz, $CDCl_3$) δ: 2.01–2.10 (m, 1H, C*H*P), 2.95–3.12 (m, 2H, C*H*), 3.38 (d, 3H, *J* = 10.8 Hz, CH_3OP), 3.41 (d, 3H, *J* = 10.8 Hz, CH_3OP), 7.23–7.35 (m, 5H, C_6H_5), 9.58 (d, 1H, *J* = 3.1 Hz, C*H*O); ^{13}C NMR (50 MHz, $CDCl_3$) 23.2 (d, $J_{C\text{-}P}$ = 195.8 Hz), 30.2 (d, $J_{C\text{-}P}$ = 4.6 Hz), 32.0, 52.5 (d, $J_{C\text{-}P}$ = 6.0 Hz), 52.6 (d, $J_{C\text{-}P}$ = 6.3 Hz), 127.6, 128.3, 129.1, 133.8, 197.8; MS (CI) m/z = 255 $(M + H)^+$; HR MS(EI) 254.0697 calcd for $C_{12}H_{15}O_4P$. Found 254.0692.

4.9. Preparation of *N*-(2-dimethoxyphosphoryl)-(3-phenyl)cyclopropylmethylidene-*p*-toluenesulfinamide

To the mixture of aldehyde (254 mg, 1 mmol, 1eq) and (+)- (*S*)-*p*-tolylsulfinamide (310 mg, 2 mmol, 2eq) in CH_2Cl_2 (30 mL) was added slowly $Ti(OEt)_4$ (7eq). Reaction was stirred for 24 hours at room temperature and quenched at 0 ^oC by slow addition of 20 mL of water. White gel was filtrated by Celite and washed with CH_2Cl_2 (2 x 20 mL). Water phase was extracted (2 x 15 mL) with CH_2Cl_2 and combined organic fraction was dried over $MgSO_4$. Solvent was evaporated in vacuum and crude product was purified by column chromatography on silica gel (Et_2O) to remove unreacted sulfinamide.

4.9.1. (1*S*,2*R*,3*S*,S_S) *N*-(2-Dimethoxyphosphoryl)-(3-phenyl)cyclopropylmethylidene-*p*-toluenesulfinamide 21a

Product was isolated as colorless oil 310 mg (79 % yield). $[\alpha]_D$ +157.4 (c 2.0, acetone); IR (film) 3030, 2985, 1620, 1585, 1460, 1230, 1025 cm^{-1}; ^{31}P NMR (80 MHz, $CDCl_3$) δ_P = 25.3 ppm; ^1H

NMR (200 MHz, $CDCl_3$) δ: 2.01–2.10 (m, 1H, C*H*P), 2.95–3.12 (m, 2H, C*H*), 3.38 (d, 3H, *J* = 10.8 Hz, CH_3OP), 3.41 (d, 3H, *J* = 10.8 Hz, CH_3OP), 7.23–7.35 (m, 5H, C_6H_5), 9.58 (d, 1H, *J* = 3.1 Hz, C*H*O); ^{13}C NMR (50 MHz, $CDCl_3$) 19.3 (d, $J_{C\text{-}P}$ = 194 Hz), 21.5, 25.4, 27.6, 44.1, 52.4 (d, $J_{C\text{-}P}$ = 6.0 Hz), 52.6 (d, $J_{C\text{-}P}$ = 6.3 Hz), 126.4, 127.0, 128.2, 128.3, 129.1, 131.1, 138.1, 142.7, 166.3. Anal. calcd for $C_{19}H_{22}NO_4PS$ C, 58.30; H, 5.67; Found C, 58.51; H, 5.58;

4.9.2. (1*R*,2*S*,3*S*,S_S) *N*-(2-Dimethoxyphosphoryl)-(3-phenyl)cyclopropylmethylidene-*p*-toluenesulfinamide 21b

A colorless oil. Yield 77%; $[\alpha]_D$ −136.1 (c 2.1, acetone); IR (film) 3030, 2985, 1620, 1575, 1510, 1460, 1230, 1025 cm^{-1}; ^{31}P NMR (80 MHz, $CDCl_3$) δ_P = 25.2 ppm; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.01–2.11 (m, 1H, C*H*P), 2.96–3.11 (m, 2H, C*H*), 3.37 (d, 3H, *J* = 10.8 Hz, CH_3OP), 3.40 (d, 3H, *J* = 10.8 Hz, CH_3OP), 7.21–7.34 (m, 5H, C_6H_5), 9.58 (d, 1H, *J* = 3.1 Hz, C*H*O); ^{13}C NMR (50 MHz, $CDCl_3$) 19.5 (d, $J_{C\text{-}P}$ = 191 Hz), 21.3, 25.7, 27.1, 44.5, 52.2 (d, $J_{C\text{-}P}$ = 6.0 Hz), 52.8 (d, $J_{C\text{-}P}$ = 6.2 Hz), 126.4, 127.1, 128.3, 129.2, 129.3, 131.3, 138.2, 142.8, 166.2. Anal. Calcd for $C_{19}H_{22}NO_4PS$ C, 58.30; H, 5.67; Found C, 58.56, H, 5.54.

4.10. Preparation of [(*S*)-*N*-*p*-toluenesulfinyl]-2-amino-2-[2'-dimethoxyphosphoryl-3'-phenyl]cyclopropyl-ethanenitrile

To the solution of Et_2AlCN (202 mg 1.82 mmol, 2 eq) was added *i*-PrOH (60 mg 0.91 mmol, 1 eq) in 20 mL THF at –78 ^{o}C. The mixture was warmed to room temperature and stirred for 30 minutes. Next, reaction was cooled to –78 ^{o}C and added to cyclopropylsulfinimine (354 mg 0.91 mmol).. After then, the mixture was warmed to r.t. and stirred vigorously for 24 hours. The reaction was quenched –78 ^{o}C by addition of 10 mL of sat. NH_4Cl. The mixture was filtrated by Celite. The water phase was extracted with ethyl acetate (3 x 20 mL). Combined organic phase was washed with sat. NaCl and dried over $MgSO_4$. The solvent was evaporated. The crude product was obtained as a mixture of two diastereomers in 3:1 ratio (83% yield) and purified by column chromatography (ethyl acetate/petroleum ether/Et_3N 1 : 1 : traces).

4.10.1. (2*S*,1'*S*,2'*R*,3'*S*,S_S)-[(*N*-*p*-toluenesulfinyl)-2-amino]-2-[2'-dimethoxyphosphoryl-3'-phenyl]cyclopropyl-ethanenitrile 22a

The major diastereomer was isolated as yellow oil 220 mg (58 % yield). $[\alpha]_D^{20}$ +200.2 (c 2.1,

acetone); IR (film) 3430, 3030, 2985, 2230, 1600, 1580, 1440, 1230, 1025 cm^{-1}; ^{31}P NMR (80 MHz, $CDCl_3$) δ_P = 26.6 ppm; ^1H NMR (500 MHz, $CDCl_3$) δ: 1.54 (dd, 1H, *J* = 10.1, 6.1 Hz, C*H*), 2.42 (s, 3H, $C_6H_4CH_3$), 2.51 (ddd, 1H, *J* = 16.1, 6.1, 6.1 Hz, C*H*), 2.73 (ddd, *J* = 13.6, 10.1, 6.1 Hz, 1H, C*H*), 3.38 (d, 3H, *J* = 11.2 Hz, CH_3OP), 3.40 (d, 3H, *J* = 11.2 Hz, CH_3OP), 4.30 (dd, 1H, *J* = 6.5, 6.5 Hz C*H*), 5.52 (d, 1H, *J* = 6.5 Hz C*H*), 7.21–7.36 (m, 7H (C_6H_5 + 2H $C_6H_4CH_3$)), 7.61 (d, 2H, *J* = 8.1 Hz, $C_6H_4CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) 18.0 (d, J_{C-P} = 195.6 Hz), 21.4, 25.8, 27.9, 43.6, 52.4 (d, J_{C-P} = 6.0 Hz), 52.5 (d, J_{C-P} = 6.3 Hz), 116.3, 126.1, 127.4, 128.2, 129.1, 130.0, 134.2, 138.3, 142.5; MS (EI) m/z = 419 $(M)^+$; Anal. Calcd for $C_{20}H_{23}N_2O_4PS$ C, 57.41; H, 5.54; S 7.66; Found C, 57.21; H, 5.68, S 7.79.

4.10.2. (2*S*,1'*R*,2'*S*,3'*R*,S_S)-[(*N*-*p*-toluenesulfinyl)-2-amino]-2-[2'-dimethoxyphosphoryl-3'-phenyl]cyclopropyl-ethanenitrile 22c

A colorless oil. Yield 55%; $[\alpha]_D^{20}$ +38.5 (c 2.0, acetone); IR (film) 3440, 3030, 2985, 2230, 1610, 1575, 1450, 1230, 1025 cm^{-1}; ^{31}P NMR (80 MHz, $CDCl_3$) δ_P = 26.5 ppm; ^1H NMR (500 MHz, $CDCl_3$) δ: 1.62 (dd, 1H, *J* = 10.1, 6.0 Hz, C*H*), 2.43 (s, 3H, $C_6H_4CH_3$), 2.52 (ddd, 1H, *J* = 16.2, 13.7, 6.0 Hz, C*H*), 2.72 (ddd, 1H, *J* = 13.7, 10.1, 6.0 Hz, C*H*), 3.36 (d, 3H, *J* = 11 Hz, CH_3OP), 3.43 (d, 3H, *J* = 11 Hz, CH_3OP), 4.00 (dd, 1H, *J* = 7.5, 7.5 Hz C*H*), 5.43 (d, 1H, *J* = 7.5 Hz C*H*), 7.22–7.37 (m, 7H, (C_6H_5 + 2H $C_6H_4CH_3$)), 7.61 (d, 2H, *J* = 8.1 Hz, $C_6H_4CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) 19.8 (d, J_{C-P} = 194.5 Hz), 21.4; 26.2, 28.0, 43.9, 52.4 (d, J_{C-P} = 7.1 Hz), 116.8, 126.2, 127.5, 128.3, 129.0, 130.1, 134.3, 138.7, 142.5; MS (CI) m/z = 419 $(M + H)^+$; Anal. Calcd for $C_{20}H_{23}N_2O_4$ PS C, 57.41; H, 5.54; S, 7.66; Found C, 57.23; H, 5.64; S, 7.76

4.11. Preparation of 2-(2'-phosphono-3'-phenylcyclopropyl)glycine.

Cyclopropane **22** (77 mg 0.184 mmol) was dissolved in 10 mL of 6N HCl and heated at 95 °C for 24 hours. The solution was evaporated in vacuum. Product was purified by resin Dowex – X 50W.

4.11.1. (2*S*,1'*S*,2'*R*,3'*S*)-2-(2'-Phosphono-3'-phenylcyclopropyl)glycine 23

A white powder, m.p. 247–251 °C. 28 mg (56 % yield). $[\alpha]_D^{20}$ +79.5 (c 1.1, H_2O); IR (KBr) 3120, 3030, 2985, 2120, 1630, 1520, 1440, 1230, cm^{-1}; ^{31}P NMR (80 MHz, D_2O) δ_P = 21.9 ppm; ^1H NMR (200 MHz, D_2O) δ: 1.45 (dd, 1H, *J* = 10.0, 6.4, C*H*), 2.02–2.12 (m, 1H, C*H*), 2.53–2.59 (m, 1H, C*H*), 3.61 (d, 1H, *J* = 10.1 Hz, N*H*), 7.09–7.35 (m, 5H C_6H_5); ^{13}C NMR (50 MHz, D_2O) 21.1, 21.7 (d, J_{C-P} = 189.7 Hz), 27.4, 27.9, 57.8, 127.1, 128.5, 129.7, 136.8, 173.1; MS (CI) m/z = 272 $(M + H)^+$ HR MS(FAB) 271.0609 calcd for $C_{11}H_{14}NO_5P$. Found: 271.0621.

4.11.2. (2*S*,1'*R*,2'*S*,3'*R*)-2-(2'-Phosphono-3'-phenylcyclopropyl)glycine 24

A white powder m.p. 229–234 ^{o}C. $[\alpha]_D^{20}$ –31.8 (c 1.0, H_2O); IR (KBr) 3130, 3030, 2980, 2120, 1640, 1590, 1520, 1440, 1230, cm^{-1}; ^{31}P NMR (80 MHz, D_2O) δ_P = 21.8 ppm; ^{1}H NMR (200 MHz, D_2O) δ: 1.45 (dd, 1H, *J* = 10.0, 3.7 Hz, C*H*), 1.96–2.10 (m, 1H, C*H*), 2.53–2.59 (m, 1H, C*H*), 3.59 (d, 1H, *J* = 10.0 Hz, N*H*), 7.08–7.25 (m, 5H, C_6H_5); ^{13}C NMR (50 MHz, D_2O) 19.2, 21.9, (d, $J_{C\text{-}P}$ = 189.7 Hz), 27.5, 27.9, 57.8, 127.1, 128.5, 129.2, 135.8, 170.1; MS (CI) m/z = 272 $(M + H)^+$. HR MS(FAB) 271.0609 calcd for $C_{11}H_{14}NO_5P$. Found: 271.0614.

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Notes and references

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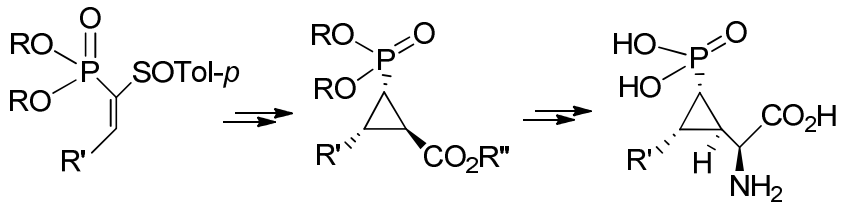
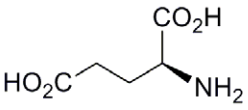
Graphical abstract





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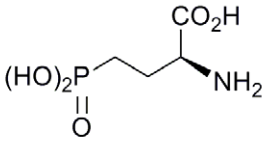

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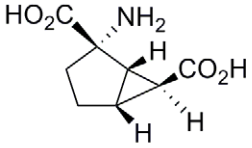

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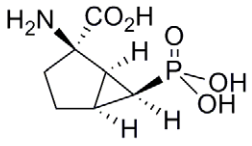

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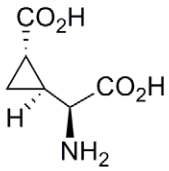

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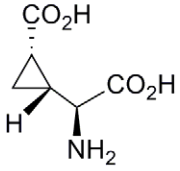

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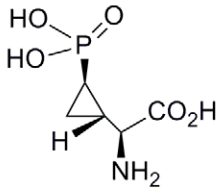

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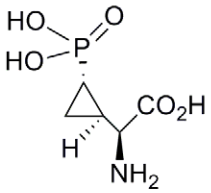

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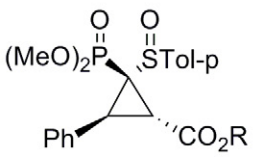

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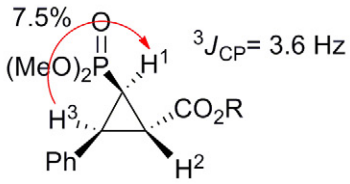
17 : R = Me



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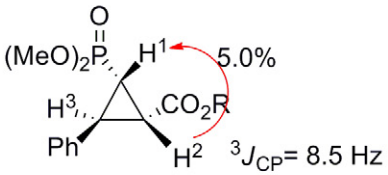

18b