EurJOC
European Journal of Organic Chemistry

A Journal of ChemPubSoc Europe

Accepted Article

Title: Highly diastereoselective synthesis of cyclic α-aminophosphonic and α-aminophosphinic acids from glycyl-L-proline 2,5-diketopiperazine

Authors: Mario Ordonez, Fernando Torres-Hernández, and José Luis Viveros-Ceballos

To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.201901439

Link to VoR: http://dx.doi.org/10.1002/ejoc.201901439

Supported by ACES Asian Chemical Editorial Society

WILEY-VCH

WILEY-VCH

FULL PAPER

Highly diastereoselective synthesis of cyclic α-aminophosphonic and α-aminophosphinic acids from glycyl-L-proline 2,5-diketopiperazine

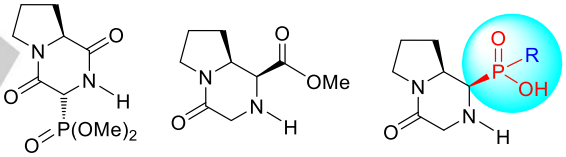
Mario Ordóñez*, Fernando Torres-Hernández and José Luis Viveros-Ceballos

Abstract: This paper describes the first diastereoselective synthesis of cyclic α-aminophosphonic and α-aminophosphinic acids from glycyl-L-proline 2,5-diketopiperazine (*S*)-**6** prepared according to the usual peptide coupling procedures. The highlights of this contribution is the chemoselective reduction of the carbamate-imide activated carbonyl group in the *N*-Boc 2,5-diketopiperazine (*S*)-**11** to generate the unstable hemiaminals (1*R*,8a*S*)-**12** and (1*S*,8a*S*)-**13**, followed by the highly diastereoselective nucleophilic addition of trimethyl phosphite or dimethyl phenylphosphonite to the chiral carbenium ion (*S*)-**5**. Acid hydrolysis of the phosphonate and phosphinate functionalities with simultaneous cleavage of the *tert*-butyl carbamate protecting group led to the target compounds. The high diastereoselectivity in the nucleophilic addition of trivalent phosphorus to the chiral carbenium ion (*S*)-**5** is in agreement with our precedent reports.

Introduction

α-Aminophosphonic and phosphinic acids represent an important class of organophosphorus compounds widely used as inhibitors or false substrates of therapeutically valuable protesases,[1] which is attributable to the well-known capacity of phosphonic and phosphinic groups to simulate the tetrahedral transition state of enzymatic peptide bond hydrolysis.[2] Particularly, a large number of azaheterocyclic derivatives have been prepared and incorporated into small peptides as conformationally restricted bioisosteres of natural amino acids.[3] Although the synthesis of these compounds has been approached by different strategies,[4] the addition of P-nucleophiles to chiral carbenium ions readily obtained from cyclic amides has proven to be one of the most suitable methods.[5]

On the other hand, 2,5-diketopiperazines (2,5-DKP) are optically active cyclodipeptides abundantly distributed in the nature and are easily synthesized from available α-amino acids, which represent privileged structures as templates for the preparation of structurally diverse bioactive heterocycles.[6] Among different methods developed for the selective functionalization of 2,5-DKP precursors,[7] the generation of endocyclic carbenium ions derived from the C-2 carbonyl group has been widely employed for the intramolecular construction of the 2,6-bridged piperazine-3-one scaffold present in tetrahydroisoquinoline alkaloids;[8] however, the stereoselective addition of external nucleophiles to these intermediates has remained virtually unexplored.



(3*S*,8a*S*)-**1** (1*S*,8a*S*)-**2** (1*R*,8a*S*)-**3**; R = OH (1*R*,8a*S*)-**4**; R = Ph

Figure 1. Relevant 2,5-diketopiperazines derivatives and target molecules.

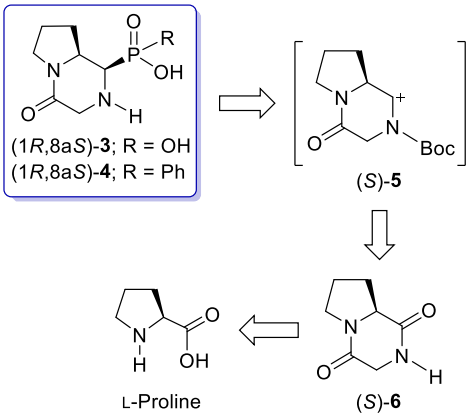
Taking into account the high potential of conformationally constrained phosphorus α-amino acid analogs,[1] the relevance of 2,5-diketopiperazines bearing the phosphonate moiety group like the compound **1**[9] as well as the importance of the stereochemistry in the drug-receptor interactions,[10] we here describe the stereoselective synthesis of the novel cyclic α-aminophosphonic acid (1*R*,8a*S*)-**3** and cyclic α-aminophosphinic acid (1*R*,8a*S*)-**4** analogs of the corresponding methyl ester (1*S*,8a*S*)-**2** (Figure 1),[11] from the glycyl-L-proline 2,5-diketopiperazine (*S*)-**6** [cyclo(Gly-L-Pro), cGP], through the diastereoselective phosphonylation of the cyclic chiral carbenium ion (*S*)-**5** as a key step.

Centro de Investigaciones Químicas – IICBA,
Universidad Autónoma del Estado de Morelos,
Av. Universidad 1001, 62209 Cuernavaca, Morelos, Mexico
E-mail: palacios@uaem.mx
fernando.torresher@uaem.edu.mx
jlvc@uaem.mx
https://www.ciquaem.mx/ordonez-palacios-jose-mario
https://www.ciquaem.mx/torres-hernandez-fernando
https://www.ciquaem.mx/viveros-ceballos-jose-luis

Supporting information for this article is given via a link at the end of the document

Results and Discussion

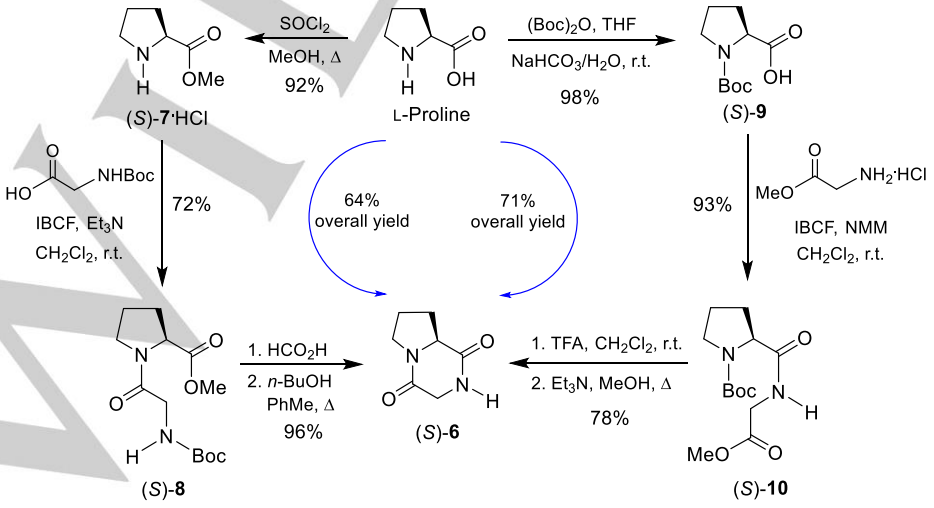
For the synthesis of the novel cyclic α-aminophosphonic and α-aminophosphinic acids (1*R*,8a*S*)-**3** and (1*R*,8a*S*)-**4**, we proposed the chiral 2,5-diketopiperazine (*S*)-**6** easily obtained from L-proline as a key starting material, considering that one of the methodologies for the synthesis of cyclic α-aminophosphonate derivatives is the addition of trialkyl phosphites to cyclic carbenium ions, which can be obtained from the corresponding cyclic amides (Scheme 1).



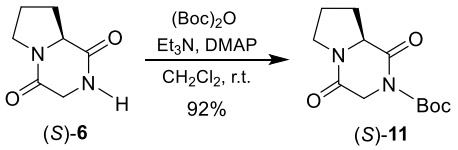
Scheme 1. Retrosynthetic analysis of (1*R*,8a*S*)-**3** and (1*R*,8a*S*)-**4**.

Taking into account the previous analysis, we first addressed the preparation of the glycyl-L-proline 2,5-diketopiperazine (*S*)-**6**. Various methods have been reported for the synthesis of 2,5-DKPs[7] and one of the most common involves the coupling of an *N*-protected α-amino acid with an α-amino acid ester, followed by removal of the *N*-protecting group and cyclization. Therefore, making use of this methodology, the coupling reaction of *N*-Boc protected glycine with L-proline methyl ester hydrochloride (*S*)-**7** easily obtained, in dichloromethane using isobutyl chloroformate (IBCF) as a coupling reagent and triethylamine at room temperature, afforded the dipeptide (*S*)-**8** in 72% yield. Cleavage of the *N*-Boc bond in (*S*)-**8** with formic acid, followed by intramolecular cyclization under thermal conditions, provided the key starting material 2,5-diketopiperazine (*S*)-**6** in 96% yield [64% overall yield from L-proline]. Additionally, was also possible to invert the order of the peptide coupling to obtain the 2,5-diketopiperazine (*S*)-**6**. In this context, the reaction of *N*-Boc-L-proline (*S*)-**9** obtained in excellent yield from L-proline, with glycine methyl ester hydrochloride, isobutyl chloroformate and *N*-methylmorpholine in dichloromethane at room temperature, gave the dipeptide (*S*)-**10** in 93% yield, which by cleavage of the *N*-Boc protective group with TFA followed by treatment with Et_3N in methanol under thermal conditions, produced the 2,5-diketopiperazine (*S*)-**6** in 78% yield [71% overall yield from L-proline] (Scheme 2).

In the next stage, selective activation of one of the carbonyl groups in the 2,5-diketopiperazine (*S*)-**6** was performed by its transformation into a carbamate-imide derivative that would allow its reduction into an hemiaminal using mild reducing agents, since the *tert*-butoxycarbonyl protecting group acts as an electron acceptor, enhancing the electrophilicity of otherwise less electrophilic C-2 carbonyl group. Thus, the 2,5-diketopiperazine (*S*)-**6** was reacted with $(Boc)_2O$, triethylamine and 4-(dimethylamino)pyridine (DMAP) in dichloromethane at room temperature, to obtain the *N*-Boc 2,5-diketopiperazine (*S*)-**11** in 92% yield (Scheme 3).



Scheme 2. Synthesis of the glycyl-L-proline 2,5-diketopiperazine (*S*)-**6**.

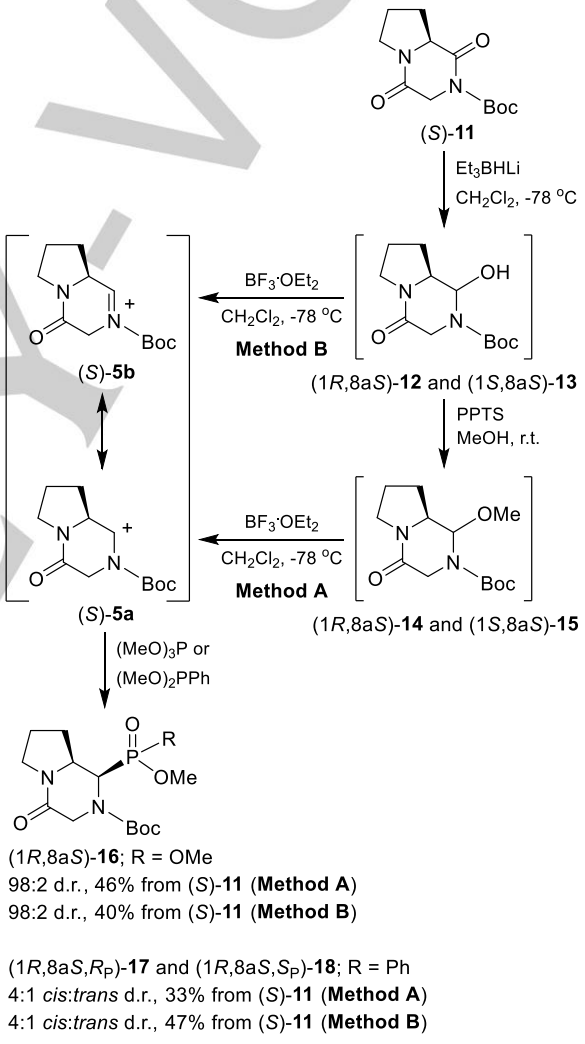


Scheme 3. Preparation of the *N*-Boc 2,5-diketopiperazine (*S*)-**11**.

Once the 2,5-diketopiperazine with the appropriate imide system (*S*)-**11** was prepared, we undertook its transformation into the α-aminophosphonate and phosphinate functionalities by a three-step process without isolation of the intermediates. Thus, the selective reduction of carbamate-imide function in the *N*-Boc 2,5-diketopiperazine (*S*)-**11** with lithium triethyl borohydride (Et_3BHLi) in dichloromethane at -78 ºC, gave the diastereoisomeric mixture of unstable hemiaminals (1*R*,8a*S*)-**12** and (1*S*,8a*S*)-**13**. Considering the well-known hemiaminal derivatization to its methyl ether as carbenium ion precursor in the synthesis of α-amino acid derivatives,[12] we carried out the treatment of the unisolated hemiaminals (1*R*,8a*S*)-**12** and (1*S*,8a*S*)-**13** with methanol and catalytic amounts of pyridinium *p*-toluenesulfonate (PPTS), to obtain the corresponding hemiaminal methyl ethers (1*R*,8a*S*)-**14** and (1*S*,8a*S*)-**15**, which by reaction with trimethyl phosphite in the presence of boron trifluoride diethyl ether ($BF_3{\cdot}OEt_2$) in dichloromethane at -78 ºC, afforded the cyclic *N*-Boc α-aminophosphonate (1*R*,8a*S*)-**16** in 46% overall yield from (*S*)-**11** and 98:2 diastereoisomeric ratio, presumably through the phosphonylation of the carbenium ion (*S*)-**5**. On the other hand, when dimethyl phenylphosphonite was used as trivalent phosphorus nucleophile in this last step, the cyclic *N*-Boc α-aminophosphinates (1*R*,8a*S*,R_P)-**17** and (1*R*,8a*S*,S_P)-**18** were obtained in 33% overall yield from (*S*)-**11** and 4:1 *cis*:*trans* diastereoisomeric ratio (Scheme 4, Method A). It is noteworthy to mention that although the reduction of C-2 carbonyl group proceeds with low diastereoselectivity probably due to the reduced nucleophile size (hydride), the diastereoselectivity of this stage does not affect the stereochemical outcome of the global route, since the stereochemistry of this center is lost during Lewis acid mediated elimination (Scheme 4).

The diastereoisomeric ratio was determined by ^{31}P NMR spectroscopy at 202 MHz, and the absolute configuration of the α-aminophosphonate (1*R*,8a*S*)-**16** was established by X-ray diffraction (Figure 2).[13]

Additionally, aiming to reduce the number of steps of the procedure and taking into account reports that describe that Lewis acids can mediate the direct addition of nucleophiles to hemiaminals,[14] we carried out the reduction of the carbamate-imide function in the *N*-Boc protected 2,5-diketopiperazine (*S*)-**11** with Et_3BHLi in dichloromethane at -78 ºC, obtaining the corresponding hemiaminals (1*R*,8a*S*)-**12** and (1*S*,8a*S*)-**13**, which without further purification were reacted with the appropriate phosphorus nucleophile in the presence of $BF_3{\cdot}OEt_2$ in dichloromethane at -78 ºC, obtaining the corresponding cyclic organophosphorus compounds (1*R*,8a*S*)-**16** or (1*R*,8a*S*,R_P)-**17** and (1*R*,8a*S*,S_P)-**18** in 40 and 47% overall yield from (*S*)-**11**, respectively, with identical diastereoselectivities (Scheme 4, Method B).



Scheme 4. Synthesis of (1*R*,8a*S*)-**16**, (1*R*,8a*S*,R_P)-**17** and (1*R*,8a*S*,S_P)-**18** via the carbenium ion intermediate (*S*)-**5**.

Despite what was expected, the preferred formation of *cis* diastereoisomers (Schemes 4) can be explained by depicting a carbenium ion intermediate (*S*)-**5a**[15] as indicated in Figure 3, in which the *tert*-butoxycarbonyl protecting group adopts a *trans*

orientation with respect to the pyrrolidine ring. Thus, *cis* products arise from a kinetically controlled process where nucleophiles prefer to approach the carbenium carbon center from the *Re* face (less hindered face).

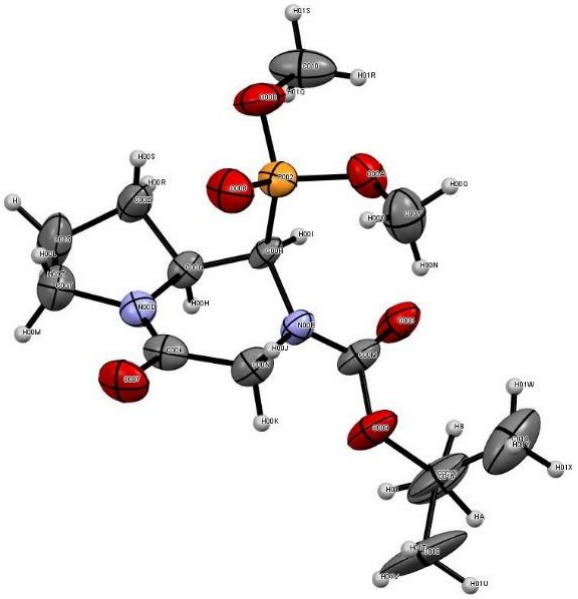


Figure 2. Single-crystal X-Ray analysis structure of (1*R*,8a*S*)-**16**.

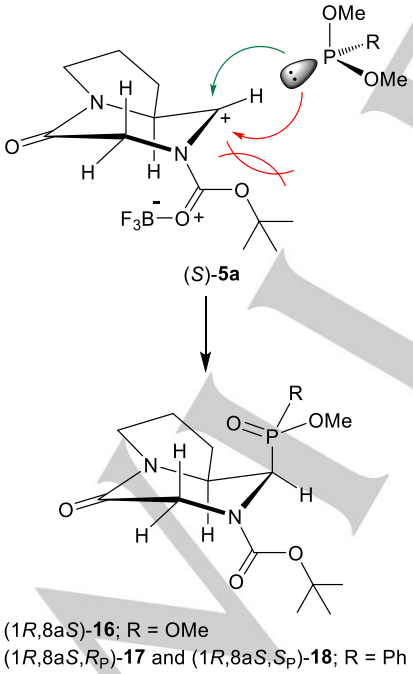
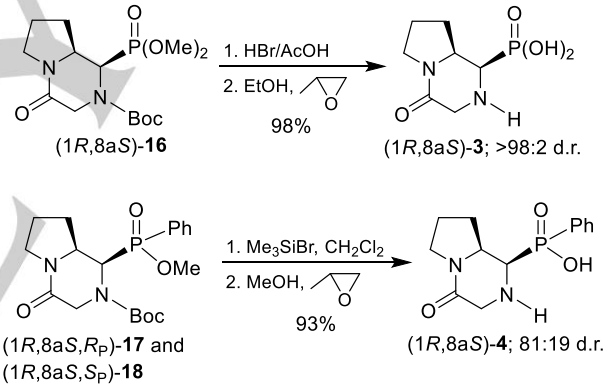


Figure 3. Proposed mechanism for the addition of phosphorus nucleophiles to chiral carbenium ion (*S*)-**5a**.

Finally, the cleavage of *tert*-butoxycarbonyl protecting group in (1*R*,8a*S*)-**16** with simultaneous hydrolysis of phosphonic ester moiety was accomplished by reaction with a 33% solution of hydrogen bromide in acetic acid, followed by the treatment with propylene oxide in ethanol, obtaining the cyclic α-aminophosphonic acid (1*R*,8a*S*)-**3** in quantitative yield as a single diastereoisomer. Surprisingly, these conditions did not work to meet the hydrolysis of the *N*-Boc α-aminophosphinates (1*R*,8a*S*,R_P)-**17** and (1*R*,8a*S*,S_P)-**18**. In this regard, bromotrimethylsilane is known as a selective reagent to prepare trimethylsilyl derivatives from phosphinate alkyl esters, thus making the corresponding phosphinic acids readily available *via* hydrolysis with neutral H_2O. Indeed, deprotection of compounds (1*R*,8a*S*,R_P)-**17** and (1*R*,8a*S*,S_P)-**18** with bromotrimethylsilane in dichloromethane followed by the methanolysis and subsequent treatment with propylene oxide in methanol, produced the cyclic α-aminophosphinic acid (1*R*,8a*S*)-**4** in 93% yield and 81:19 diastereoisomeric ratio (Scheme 5).



Scheme 5. Preparation of target compounds (1*R*,8a*S*)-**3** and (1*R*,8a*S*)-**4**.

Conclusions

In conclusion, we have developed the first highly diastereoselective synthesis of cyclic α-aminophosphonic acid (1*R*,8a*S*)-**3** and phosphinic acid (1*R*,8a*S*)-**4** starting from the glycyl-L-proline 2,5-diketopiperazine (*S*)-**6** involving the high diastereoselective addition of trimetyl phosphite and dimethyl phenylphosphonite to the chiral carbenium ion (*S*)-**5a** as the key step. These results show the utility of the 2,5-diketopiperazines as valuable chiral intermediates in the synthesis of organophosphorus compounds with potential application in medicinal and organic chemistry.

Experimental Section

All commercial materials were used as received unless otherwise noted. Flash chromatography was performed with 230-400 mesh Silica Flash 60®. Thin layer chromatography was performed with pre-coated TLC sheets of silica gel (60 F_{254}, Merck) and the plates were visualized with iodine, UV-light and solutions of ninhydrin and $KMnO_4$. Melting points were determined with a Fisher–Johns apparatus and are uncorrected. NMR spectra were recorded on a Bruker Avance III HD instrument (500 MHz for ^1H, 126 MHz for ^{13}C and 202 MHz for ^{31}P) and calibrated using the TMS, $P(O)Ph_3$ and the residual solvent signal as internal standards; chemical shifts (δ) are expressed in parts per million (ppm) and coupling constants (J) in Hertz and an asterisk (*) indicates a duplicate signal corresponding to the minor rotamer. Abbreviations used for NMR characterization: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; bs, unresolved broad signal. High resolution FAB^+ and ESI mass spectra (HRMS) were obtained on a JEOL MStation MS-700. ^1H and ^{13}C NMR data for the compounds (*S*)-**6**[16] and (*S*)-**11**[17] were identical to those described in the literature.

4.1. General procedure for the preparation of *N*-Boc α-aminophosphonate (1*R*,8a*S*)-16 and *N*-Boc α-aminophosphinates (1*R*,8a*S*,R_P)-17 and (1*R*,8a*S*,S_P)-18.

Method A: To a stirred solution of 2,5-diketopiperazine (*S*)-**11** (0.19 mmol) in anhydrous CH_2Cl_2 (2 mL) at -78 °C and under nitrogen was dropwise added 1.0 M solution of Et_3BHLi in THF (0.29 mmol). The reaction mixture was stirred at -78 °C for 1.0 h and then quenched with water (1 mL) and H_2O_2 (1 mL) and warmed at room temperature. The resulting mixture was stirred vigorously for 15 min and then extracted with CH_2Cl_2 (3 x 5 mL). The organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure to obtain the mixture of unstable hemiaminals (1*R*,8a*S*)-**12** and (1*S*,8a*S*)-**13**, which was dissolved in MeOH (2 mL) and catalytic PPTS (0.019 mmol) was added. The mixture was allowed to reach at room temperature and stirred for an additional 12.0 h. The reaction was quenched with Et_3N (0.13 mmol) and the solvent was evaporated under reduced pressure, to give the hemiaminal methyl ethers (1*R*,8a*S*)-**14** and (1*S*,8a*S*)-**15**, which were dissolved in anhydrous CH_2Cl_2 (3 mL) and kept under nitrogen. The corresponding phosphorus nucleophile (trimethyl phosphite or dimethyl phenylphosphonite) (0.38 mmol) was added and the resulting solution was cooled at 0 °C. Boron trifluoride-diethyl ether (0.38 mmol) was added dropwise and the reaction mixture was stirred for 15 min at 0 °C and 3.0 h at room temperature. The reaction was then quenched with water (1 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. Finally, the crude product was purified by flash column chromatography.

Method B: To a stirred solution of 2,5-diketopiperazine (*S*)-**11** (0.19 mmol) in anhydrous CH_2Cl_2 (2 mL) at -78 °C and under nitrogen was dropwise added 1.0 M solution of Et_3BHLi in THF (0.29 mmol). The reaction mixture was stirred at -78 °C for 1.0 h and then quenched with water (1 mL) and H_2O_2 (1 mL) and warmed at room temperature. The resulting mixture was stirred vigorously for 15 min and then extracted with CH_2Cl_2 (3 x 5 mL). The organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure to obtain the mixture of unstable hemiaminals (1*R*,8a*S*)-**12** and (1*S*,8a*S*)-**13**, which was dissolved in anhydrous CH_2Cl_2 (3 mL) and kept under nitrogen. The corresponding phosphorus nucleophile (trimethyl phosphite or dimethyl phenylphosphonite) (0.38 mmol) was added and the resulting solution was cooled at 0 °C. Boron trifluoride-diethyl ether (0.38 mmol) was added dropwise and the reaction mixture was stirred for 15 min at 0 °C and 3.0 h at room temperature. The reaction was then quenched with water (1 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. Finally, the crude product was purified by flash column chromatography.

4.1.1. Dimethyl (1*R*,8a*S*)-*N*-(*tert*-butoxycarbonyl)-4-oxohexahydropyrrolo[1,2-*a*]pyrazine-2-phosphonate 16. White solid, 46% (method A), 40% (method B); m.p. = 116-119 °C. $[\alpha]^{20}$ = -21.06 (*c* 1.0, MeOH). ^1H NMR (DMSO-d_6): δ = 1.43* (s, 9H, $(CH_3)_3C$), 1,46 (s, 9H, $(CH_3)_3C$), 1.69-1.79 (m, 1H, CH_2), 1.89-1.99 (m, 1H, CH_2), 2.07-2.12 (m, 2H, CH_2), 3.35-3.39 (m, 2H, CH_2N), 3.59 (bs, 1H, CHN), 3.65 (d, J = 10.8, 3H, $(CH_3O)_2P$), 3.67 (d, J = 10.7, 3H, $(CH_3O)_2P$), 3.72* (d, J = 10.6, 3H, $(CH_3O)_2P$), 3.73* (d, J = 10.6, 3H, $(CH_3O)_2P$), 3.89-4.01 (m, 1H, CHP), 4.10 (d, J = 17.7, 1H, CH_2CO). ^{13}C NMR (DMSO-d_6): δ = 21.9 (CH_2), 22.0* (CH_2), 27.8 ($(CH_3)_3C$), 28.0 (CH_2), 44.9* (CH_2N), 45.0 (CH_2N), 45.6* (CH_2CO), 46.1 (CH_2CO), 48.0 (d, J = 150.0, CHP), 49.6* (d, J = 149.4, CHP), 52.6* (d, J = 5.1, $(CH_3O)_2P$), 52.7 (d, J = 6.8, $(CH_3O)_2P$), 52.8* (d, J = 6.9, $(CH_3O)_2P$), 56.8 (CHN), 57.1* (CHN), 80.6* ($C(CH_3)_3$), 80.7 ($C(CH_3)_3$), 152.6* (C=O), 153.1 (C=O), 162.7 (C=O), 162.8* (C=O). ^{31}P NMR (DMSO-d_6): δ = 22.9*, 23.1. HRMS (FAB^+): calcd. for $C_{14}H_{26}N_2O_6P$ $[M+H]^+$, *m/z* 349.1528; found for $[M+H]^+$, *m/z* 349.1490.

4.1.2. Methyl (1*R*,8a*S*,R_P)-*N*-(*tert*-butoxycarbonyl)-4-oxohexahydropyrrolo[1,2-*a*]pyrazine-2-phenylphosphinate 17 and (1*R*,8a*S*,S_P)-18. White solid, 33% (method A), 47% (method B). ^1H NMR ($CDCl_3$): δ = 1.04 (s, 9H, $(CH_3)_3C$), 1.15 (s, 9H, $(CH_3)_3C$), 1.20 (s, 9H, $(CH_3)_3C$), 1.22 (s, 9H, $(CH_3)_3C$), 1.29 (s, 9H, $(CH_3)_3C$), 1.71-1.83 (m, 1H, CH_2), 2.05-2.15 (m, 1H, CH_2), 2.14-2.27 (m, 1H, CH_2), 2.42-2.53 (m, 1H, CH_2), 2.52-2.64 (m, 1H, CH_2), 2.68-2.82 (m, 1H, CH_2), 3.52-3.60 (m, 1H, CH_2N), 3.62 (d, J = 11.0, 3H, CH_3OP), 3.66 (d, J = 10.7, 3H, CH_3OP), 3.72 (d, J = 10.8, 3H, CH_3OP), 3.89 (d, J = 18.2, 1H, CH_2CO), 3.92 (d, J = 17.7, 1H, CH_2CO), 3.97-4.06 (m, 1H, CH_2N), 4.03-4.11 (m, 1H, CH_2N), 4.16 (d, J = 18.1, 1H, CH_2CO), 4.26 (d, J = 17.9, 1H, CH_2CO), 4.32 (d, J = 18.4, 1H, CH_2CO), 4.41 (d, J = 18.2, 1H, CH_2CO), 4.71 (dd, J = 8.7, 4.8, 1H, CHP), 4.78 (dd, J = 12.3, 4.6, 1H, CHP), 4.96 (dd, J = 8.2, 4.8, 1H, CHP), 5.04 (dd, J = 11.0, 4.6, 1H, CHP), 7.41-7.65 (m, 5H, H_{arom}), 7.66-7.89 (m, 5H, H_{arom}). ^{31}P NMR ($CDCl_3$): δ = 39.1, 40.0, 40.6, 42.1, 42.4. HRMS (FAB^+): calcd. for $C_{19}H_{28}N_2O_5P$ $[M+H]^+$, *m/z* 395.1736; found for $[M+H]^+$, *m/z* 395.1727.

4.2. ((1*R*,8a*S*)-4-Oxooctahydropyrrolo[1,2-*a*]pyrazin-1-yl)phosphonic acid 3. The cyclic α-aminophosphonate (1*R*,8a*S*)-**16** (0.06 g, 0.17 mmol)

was treated with a 33% solution of hydrogen bromide in acetic acid (3 mL). The reaction mixture was stirred at room temperature for 6.0 h, and the volatiles were evaporated under reduced pressure. The crude product was dissolved in ethanol (2 mL), and the resulting solution was treated with propylene oxide (3 mL) and stirred at room temperature for 12.0 h. The precipitate formed was filtered, washed successively with CH_2Cl_2 and AcOEt and dried under reduced pressure to give 36 mg (>98%) of (1*R*,8a*S*)-**3** in >98:2 d.r. as a white solid; m.p. = 245-248 °C. $[\alpha]^{20}$ = -21.1 (*c* 1.0, H_2O). ^{1}H NMR (D_2O): δ = 1.77-1.96 (m, 1H, CH_2), 2.03-2.36 (m, 3H, CH_2CH_2), 3.46-3.52 (m, 1H, CH_2N), 3.58-3.62 (m, 1H, CH_2N), 3.89 (d, *J* = 17.5, 1H, CH_2CO), 3.94 (d, *J* = 17.5, 1H, CH_2CO), 4.04 (dd, *J* = 14.0, 3.7, 1H, CHP), 4.12 (ddd, *J* = 26.9, 10.3, 4.8, 1H, CHN). ^{13}C NMR (D_2O): δ = 21.7 (CH_2), 28.6 (CH_2), 42.2 (CH_2N), 46.0 (CH_2CO), 50.8 (d, *J* = 139.2, CHP), 55.9 (CHN), 162.7 (C=O). ^{31}P NMR (D_2O): δ = 5.6. HRMS (ESI): calcd. for $C_7H_{14}N_2O_4P$ $[M+H]^+$, *m/z* 221.0691; found for $[M+H]^+$, *m/z* 221.0686.

4.3. ((1*R*,8a*S*)-4-Oxooctahydropyrrolo[1,2-*a*]pyrazin-1-yl)(phenyl) phosphinic acid 4. To a stirred solution of the α-aminophosphinates (1*R*,8a*S*,R_P)-**17** and (1*R*,8a*S*,S_P)-**18** (0.10 g, 0.25 mmol) in dry dichloromethane (7 mL) at room temperature, bromotrimethylsilane (0.4 mL, 3.04 mmol) was added. Stirring was continued for 24.0 h. After evaporation of solvent, the solid residue was washed with dry methanol (5 x 5 mL). Then, propylene oxide (5 mL) was added to the resulting residue and the mixture was kept under stirring for 2.0 h. Then the excess of propylene oxide was removed under reduced pressure, the residue was redissolved in MeOH (2 mL) and precipitated with the addition of Et_2O. The precipitate formed was filtered, washed successively with Et_2O and AcOEt and dried under reduced pressure to give 65 mg (93%) of (1*R*,8a*S*)-**4** in 81:19 d.r. as a light brown solid; m.p. = 162-165 °C. $[\alpha]^{20}$ = -23.6 (*c* 1.0, $CHCl_3$). ^{1}H NMR (D_2O): δ = 1.71-1.86 (m, 1H, CH_2), 1.94-2.13 (m, 2H, CH_2), 2.15-2.31 (m, 1H, CH_2), 2.94-3.16 (m, 1H, CH_2N), 3.34-3.56 (m, 1H, CH_2N), 3.87 (d, *J* = 17.2, 1H, CH_2CO), 3.95 (d, *J* = 17.2, 1H, CH_2CO), 4.02-4.16 (m, 1H, CHN), 4.22 (dd, *J* = 10.5, 4.6, 1H, CHP), 7.48-7.71 (m, 3H, H_{arom}), 7.74-7.97 (m, 2H, H_{arom}). ^{13}C NMR (D_2O): δ = 21.8 (CH_2), 28.5 (CH_2), 30.9* (CH_2), 42.8 (CH_2N), 44.9* (d, *J* = 6.9, CH_2N), 45.6* (CH_2CO), 46.1 (CH_2CO), 53.7 (d, *J* = 91.7, CHP), 56.2 (CHN), 56.6* (CHN), 57.3* (d, *J* = 89.3, CHP), 129.1 (d, *J* = 12.6, C_{arom}), 131.9 (d, *J* = 10.1, C_{arom}), 132.1* (d, *J* = 9.8, C_{arom}), 132.7 (C_{arom}), 132.9* (C_{arom}), 133.4* (C_{arom}), 134.5 (C_{arom}), 162.3 (C=O), 162.5* (C=O). ^{31}P NMR (D_2O): δ = 17.9, 18.2*. HRMS (ESI): calcd. for $C_{13}H_{18}N_2O_3P$ $[M+H]^+$, *m/z* 281.1055; found for $[M+H]^+$, *m/z* 281.1049.

Acknowledgments

The authors thank the Consejo Nacional de Ciencia y Tecnología (CONACYT) for financial support through projects 286614 and 256985. We also thank Victoria Labastida and Jorge Guillermo Domínguez-Chávez for their valuable technical support in obtaining MS spectra and X-ray structure. F.T.H. also wish to thank CONACYT for Graduate Scholarships 626420.

Keywords: Chiral carbenium ions • cyclic α-aminophosphonic acids • cyclic α-aminophosphinic acids • 2,5-diketopiperazines

[1] a) A. Mucha, P. Kafarski, L. Berlicki, *J. Med. Chem.* **2011**, *54*, 5955–5980; b) F. Orsini, G. Sello, M. Sisti, *Curr. Med. Chem.* **2010**, *17*, 264–289; c) E. D. Naydenova, P. T. Todorov, K. D. Troev, *Amino Acids* **2010**, *38*, 23–30; d) B. Lejczak, P. Kafarski, *Top. Heterocycl. Chem.* **2009**, *20*, 31–63; e) A. Yiotakis, D. Georgiadis, M. Matziari, A. Makaritis, V. Dive, *Curr. Org. Chem.* **2004**, *8*, 1135–1158.

[2] K. Gluza, P. Kafarski in *Drug Discovery* (Ed.: H. El-Shemy), InTech, Rijeka, Croatia, **2013**, pp. 325–372.

[3] a) T. Yamagishi, A. Kinbara, N. Okubo, S. Sato, H. Fukaya, *Tetrahedron: Asymmetry* **2012**, *23*, 1633–1639; b) A. Mores, M. Matziari, F. Beau, P. Cuniasse, A. Yiotakis, V. Dive, *J. Med. Chem.* **2008**, *51*, 2216–2226; c) M. Nasopoulou, D. Georgiadis, M. Matziari, V. Dive, A. Yiotakis, *J. Org. Chem.* **2007**, *72*, 7222–7228; d) B. Boduszek, J. Oleksyszyn, C.-M. Kam, J. Selzler, R. E. Smith, J. C. Powers, *J. Med. Chem.* **1994**, *37*, 3969–3976.

[4] a) A. S. Gazizov, A. V. Smolobochkin, R. A. Turmanov, M. A. Pudovik, A. R. Burilov, O. G. Sinyashin, *Synthesis* **2019**, *51*, 3397–3409; b) M. Ordóñez, J. L. Viveros-Ceballos, F. J. Sayago, C. Cativiela, *Synthesis* **2017**, *49*, 987–997; c) J. L. Viveros-Ceballos, M. Ordóñez, F. J. Sayago, C. Cativiela, *Molecules* **2016**, *21*, 1141.

[5] a) R. O. Argüello-Velasco, G. K. Sánchez-Muñoz, J. L. Viveros-Ceballos, M. Ordóñez, P. Kafarski, *J. Heterocycl. Chem.* **2019**, *56*, 2068−2073; b) J. L. Viveros-Ceballos, E. I. Martínez-Toto, C. Eustaquio-Armenta, C. Cativiela, M. Ordóñez, *Eur. J. Org. Chem.* **2017**, 6781−6787; c) M. Ordóñez, A. Arizpe, F. J. Sayago, A. I. Jiménez, C. Cativiela, *Molecules* **2016**, *21*, 1140; d) I. Bonilla-Landa, J. L. Viveros-Ceballos, M. Ordóñez, *Tetrahedron: Asymmetry* **2014**, *25*, 485−487.

[6] J. F. González, I. Ortín, E. de la Cuesta, J. C. Menéndez, *Chem. Soc. Rev.* **2012**, *41*, 6902–6915.

[7] A. D. Borthwick, *Chem. Rev.* **2012**, *112*, 3641−3716.

[8] a) F. Kawagishi, T. Toma, T. Inui, S. Yokoshima, T. Fukuyama, *J. Am. Chem. Soc.* **2013**, *135*, 13684−13687; b) C. Avendaño, E. de la Cuesta, *Curr. Org. Synth.* **2009**, *6*, 143–168.

[9] a) T. Gorewoda, R. Mazurkiewicz, W. G. Mlostoń, G. Schroeder, M. Kubicki, N. Kuźnik, *Tetrahedron: Asymmetry* **2011**, *22*, 823–833; b) S. Jin, P. Wessing, J. Liebscher, *J. Org. Chem.* **2001**, *66*, 3984–3997; c) L. E. Overman, M. D. Rosen, *Angew. Chem. Int. Ed.* **2000**, *39*,4596–4599; d) C. Alcaraz, A. Herrero, J. L. Marco, E. Fernández-Alvarez, M. Bernabé, *Tetrahedron Lett.* **1992**, *33*, 5605–5608; e) A. Lieberknecht, H. Griesser, *Tetrahedron Lett.* **1987**, *28*, 4275–4278.

[10] B. S. Sekhon, *J. Mod. Med. Chem.* **2013**, *1*, 10–36.

[11] S. Hanessian, R. Sharma, *Heterocycles* **2000**, *52*, 1231–1239.

[12] T. Shono, Y. Matsumura, K. Tsubata, *Tetrahedron Lett.* **1981**, *22*, 3249–3252.

[13] CCDC 1957927 [for (1*R*,8a*S*)-**16**] contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

[14] a) M. Butters, C. D. Davies, M. C. Elliott, J. Hill-Cousins, B. M. Kariuki, L. Ooi, J. L. Wood, S. V. Wordingham, *Org. Biomol. Chem.* **2009**, *7*, 5001–5009; b) P. Van der Veken, A. Soroka, I. Brandt, Y. S. Chen, M. B. Maes, A. M. Lambeir, X. Chen, A. Haemers, S. Scharpé, K. Augustyns, I. De Meester, *J. Med. Chem.* **2007**, *50*, 5568–5570; c) R. P. Polniaszek, S. E. Belmont, R. Alvarez, *J. Org. Chem.* **1990**, *55*, 215–223.

[15] a) O. Onomura, P. G. Kirira, T. Tanaka, S. Tsukada, Y. Matsumura, Y. Demizu, *Tetrahedron* **2008**, *64*, 7498–7503; b) T. Shono, T. Fujita, Y. Matsumura, *Chem. Lett.* **1991**, *20*, 81–84.

[16] M. Huisman, M. Rahaman, S. Asad, S. Oehm, S. Novin, A. L. Rheingold, M. M. Hossain, *Org. Lett.* **2019**, *21*, 134–137.

[17] D. Farran, D. Echalier, J. Martinez, G. J. Dewynter, *Pept. Sci.* **2009**, *15*, 474–478.

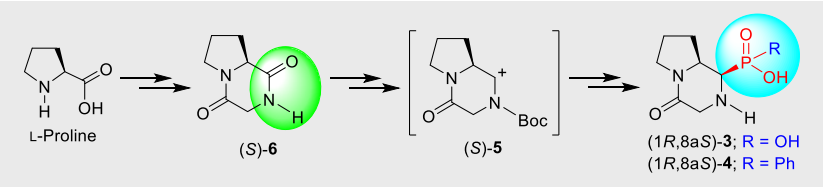
WILEY-VCH

FULL PAPER

Entry for the Table of Contents

Layout 2:

FULL PAPER



This paper describes the first diastereoselective synthesis of cyclic α-aminophosphonic and α-aminophosphinic acids (1*R*,8a*S*)-**3** and (1*R*,8a*S*)-**4** from glycyl-L-proline 2,5-diketopiperazine (*S*)-**6**, through the highly diastereoselective nucleophilic addition of trimethyl phosphite or dimethyl phenylphosphonite to the chiral carbenium ion (*S*)-**5**.

Diastereoselective synthesis

Mario Ordóñez, Fernando Torres-Hernández and José Luis Viveros-Ceballos*

Page No. – Page No.

Highly diastereoselective synthesis of cyclic α-aminophosphonic and α-aminophosphinic acids from glycyl-L-proline 2,5-diketopiperazine