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Efficient Synthesis of the four Diastereomers of Phosphothreonine from Lactaldehyde.

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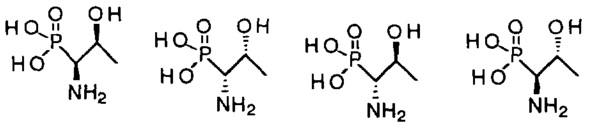
***Abstract*:** The four stereoisomers of phosphothreonine are obtained in high diastereomeric purity based on the stereoselective addition of trimethylsilyldiethylphosphite (TMSDEP) to scalemic *N*-trimethylsilyl-lacticimine and addition of TMSDEP to lactaldehyde followed by Mitsunobu inversion of the corresponding α-hydroxy-β-silyloxy phosphonate.

α-Amino phosphonic acids have been recognised as biologically active surrogates for the corresponding carboxylic acids.[1,2] In recent years, this class of amino acids has attracted substantial synthetic interest[3] because of their importance as enzyme inhibitors[4] and as conformational modifiers in physiologically active peptides.[5] Among these amino acids, their β-hydroxy congeners [6] can be viewed as the analogous amino acids of threonine or serine, which should have marked effects on phosphono peptides as well as presumably show biological activity. Most synthetic routes to enantiomerically enriched phosphoamino acids are based on resolution, enzymatic techniques, or utilising some aspect of asymmetric bond formation. We wish to describe here a new method for the synthesis of each optically active *P* -threonine[7] (**1a-1d**) (Fig. 1) starting from α-silyloxy-lactaldehyde and its *N*-trimethylsilylimine[8] derivative[9].

Figure 1.



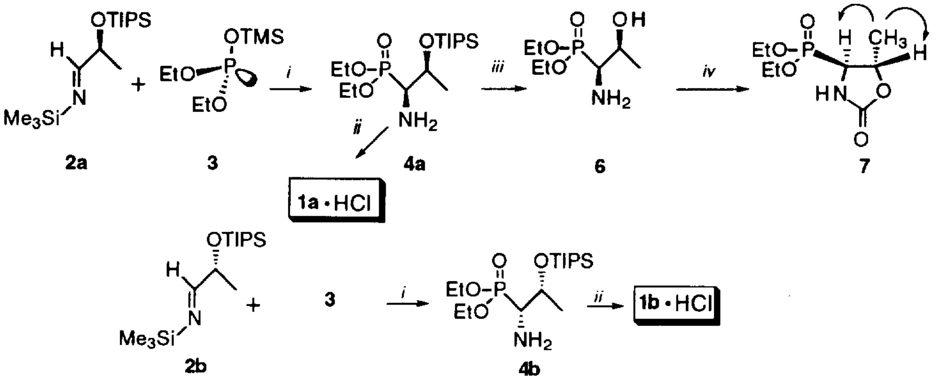
1a **1b** **1c** **1d**

Initially formed Schiff base (*N*-trimethylsilylimine) **2a**, obtained from the (*S*)-2-triisopropylsilyoxy lactaldehyde[10] **5a**, underwent selective phosphonylation with trimethylsilyldiethyl phosphite[11] **3** to give β-silyloxy-α-amino-phosphonic ethyl ester **4a** in 85% yield and >98:2 *syn/anti* diastereomeric ratio (Scheme 1); subsequent desilylation and hydrolysis (HCl, reflux) yielded optically active β-hydroxy α-amino propane phosphonic acid **1a**. The structure of **1a** possessing the (1*S*, 2*S*) configuration[12] was determined by means of a combined ^{1}H, ^{13}C and ^{31}P-NMR spectroscopic analysis of the ester **4a**, of the acid **1a**, and of the corresponding oxazolidin-2-one **7** obtained from **4a** upon desilylation followed by ring closure with 1,1'-carbonyldiimidazole in the presence of Hünig's base. (Scheme 1)

(1*R*, 2*R*) -Phosphothreonine **1b** was obtained from **2b** in the same manner following the protocol described above. The ^{1}H, ^{13}C and ^{31}P NMR spectra of **4b** and **1b** were superimposable upon those of **4a** and

1a. Moreover the value of specific rotation for **1b** was very close but opposite to that of **1a** thus confirming the structure assigned. In this way two enantiomers of phospho-threonine were prepared in two steps.

Scheme 1

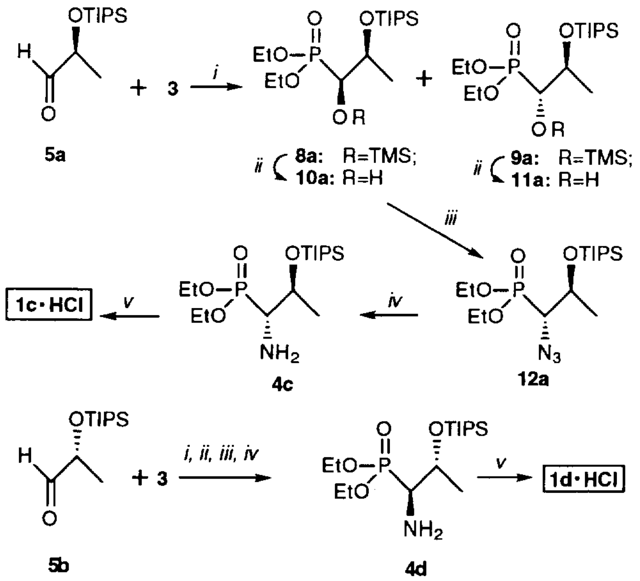


i: THF/CH_2Cl_2, -78°C, then r.t. 5hrs.*ii*: HCl 6N, 6 hrs⇅ ; *iii* TBAF/THF/r.t./3 hrs; *iv* : CDI/DIPEA/CH_2Cl_2

The synthesis of the other two enantiomers was next examined. At the present time, since all attempts to obtain directly the *anti* products **4c** or **4d** *in high diastereomeric excess*, following the addition reaction of TMSDEP to the imine **2**, were unsuccessful[9], we decided to explore a new approach.

Recent studies[13] from our laboratory have shown that a very high *syn* diastereoselectivity could be achieved in the phosphonylation of α-hydroxy aldehydes, using as the protecting group of the hydroxy functionality the very bulky triisopropylsilyl group[14] (TIPS). Taking into account these results we decided to prepare the other two phosphothreonine enantiomers, namely the enantiomers (*1R,2S*) and (*1S, 2R*), according to Scheme 2.

Scheme 2

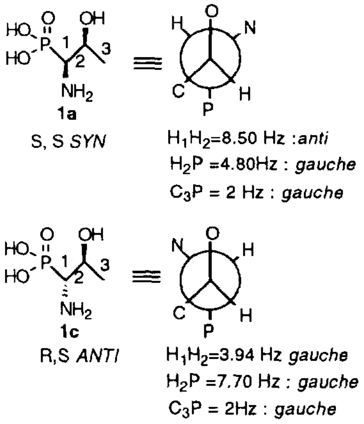


i : CH_2Cl_2, -78°C, then r.t. 5hrs. *ii* : citric acid/ MeOH, 3 hrs;
iii: HN_3, Ph_3P, $(EtO_2CN{=})_2$; *iv*: H_2/PtO_2; *v*: 6N HCl, ⇅ .

Reaction of the (*S*) -triisopropylsilyloxy lactaldehyde **5a** with one equivalent of TMSDEP **3** in CH_2Cl_2 at -78°C for three hrs furnished the trimethylsilyloxy phosphonic esters **8a** and **9a** which, upon treatment with citric acid in methanol, were converted to alcohols **10a** and **11a** in 62% overall yield and 92/8 diastereomeric ratio. Next, the elaboration of **10a** with introduction of the amine moiety and concomitant inversion of configuration was realised by a Mitsunobu reaction[15]. Two procedures, which differ in the source of N_3 group, were adopted to gain this goal: use of HN_3 , PPh_3 and diethylazodicarboxylate[16] and alternatively use of commercially available diphenyl phosphoryl azide, PPh_3 and diethylazodicarboxylate[17]. Since the former procedure proved a cleaner and higher yielding reaction this was the choice procedure despite the dangerous use of hydrazoic acid. (Scheme 2).

Complete inversion of configuration occurred giving rise to the corresponding azide **12a** (67%) contaminated by 20% of starting material[18]. Reductive work-up of this intermediate furnished the phosphoamino ester **4c**. By the same procedure the phosphoamino ester **4d** was obtained starting from the unnatural (*R*)-triisopropylsilyloxy lactaldehyde **5b**. The esters **4c** and **4d** were converted to the target phosphoaminoacids by hydrolysis with 6N HCl at reflux (Scheme 2). Pure phosphoaminoacids **1a**, **1b**, **1c**, and **1d** were obtained according to the literature procedure.[7]

Scheme 3



1a
S, S *SYN*

H_1H_2=8.50 Hz :*anti*
H_2P =4.80Hz : *gauche*
C_3P = 2 Hz : *gauche*

1c
R,S *ANTI*

H_1H_2=3.94 Hz *gauche*
H_2P =7.70 Hz : *gauche*
C_3P = 2Hz : *gauche*

As anticipated above analysis of the NMR spectra of the products allowed assignment of *syn* -configuration to the diastereoisomers **4a** and **4b**, and *anti* -configuration to the diastereomers **4c** and **4d**. The coupling constants between H_1-H_2, P-H_2 and P-C_3 in the acids **1a** and **1c**, are compatible with two conformations *anti, gauche, gauche* and *gauche, gauche, gauche* . Since the former is possible only for to the diastereoisomer **1a** and latter for the diastereoisomer **1c**[19] the configuration of these two compounds is thus established. Moreover analysis of the data arising from the cyclic structure **7**, prepared from the open-chain compound **4a**, confirms the assignments we have made. In this case a NOE technique (steady state experiment) was used. Irradiating the methyl group of the cyclic compound **7** with a saturation time of 5 sec, an increment of 13% on both vicinal and geminal hydrogens is observed. (Scheme 1).

This behaviour is conclusive evidence that the two vicinal protons are at the same distance (2.8 Å) from the methyl group and therefore the vicinal proton is *cis* to the methyl group.[20] Finally the specific rotations of the corresponding aminophosphonic acids are in agreement with the values reported in literature.[8]

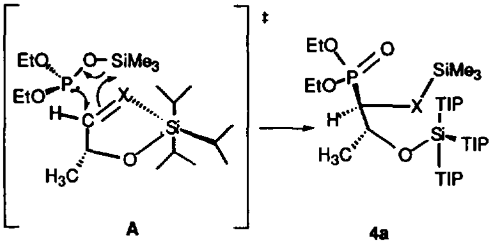
Mechanistic considerations.

The present nucleophilic addition of TMSDEP to prochiral sp^2 system[21] of α-trialkylsilyloxy imines is characterised by two important features: (i) the α-silyloxy group induces a high degree of *syn* diastereoselectivity, without chelating Lewis acids; (ii) with increasing bulkiness of the silicon protecting group, an increase of the *syn*- diastereoselectivity is observed[9]. This remarkable observation of high *syn* diastereoselectivity on increasing the bulkiness of the silicon protecting group stands in contrast to the normal, steric hindrance dependent, *anti* selectivity seen for these species[22].

The high *syn* selectivity observed requires that a Cram cyclic model should be invoked[23]. In the preliminary report[9] we attributed the high syn diastereoselectivity to the chelating effect of lithium cations arising from the preparation of the *N*-trimethylsilylimine (prepared *in situ* from aldehyde and lithium hexamethyldisilylamide). After that preliminary letter, we checked the reaction diastereoselectivity in absence of lithium cations[24]. This goal has been attained using as the source of iminic nitrogen sodium hexamethyldisilylamide. Although a large reduction of the yields occurred, nevertheless, from steric point of view, a ***high syn diastereoselectivity*** was, once again, observed.

Denmark[25], Kobayashi[26], Myers[27] and Sakurai[28] have recently reported the role of a hypercoordinate silicon atom[29] in determining the diastereoselectivity in certain types of reactions. This knowledge leads to postulate a silicon dependent diastereoselectivity through a coherent mechanistic pathway involving a bicyclic transition-state due to the chelating effect of a trigonal bipyramidal organosilicon (Chart 1).

Chart 1



X=N-SiMe₃

In this bicyclic transition state A one of the isopropyl group of the silicon is, inevitably, going to match the effect of the methyl group of the imine, increasing the *syn* diastereoselectivity since the already disfavoured *pro-anti* face becomes even more encumbered.

Computational Studies. In order to evaluate the possible formation of a chelated imine presenting a hypercoordinate silicon atom, we performed *ab initio* computations on the model compound $HN=CH-CH_2OSiH_3$. All calculations were performed at SCF/3-21G* level using the Gaussian 92 program[30] on a Microvax 3500. All possible linear and bent input geometries were analysed and fully optimised by gradient techniques. The final minima were checked by frequency analysis and only one geometry was found to be a real minimum corresponding to the cyclic structure (**B**). Electronic features are reported in Table 1. This structure is more stable than a linear form (which represents a rotational transition state) by 17.9 KJ/m. The calculated H-Si-O angles are consistent with a cyclic structure possessing a distorted trigonal bipyramidal geometry for the silicon. (see geometry in Fig. 2)

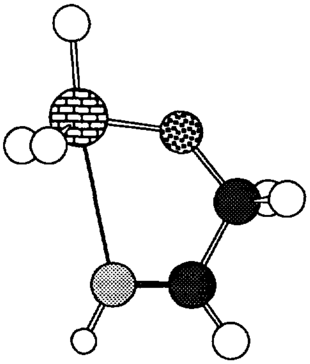


Fig. 2 - Structure B: $H_3SiOCH_2CH=NH$

Bond lengths (Å): N-C, 1.252; C-C, 1.506; C-O, 1.410; O-Si, 1.647; Si-N, 2.688. Bond Angles (deg): N-C-C, 118.7; C-C-O, 111.9; C-O-Si, 137.1; O-Si-N, 70.5; Si-N-C, 101.8; H_a-Si-O, 102.2; H_g-Si-O, 115.4.

The calculated Si-N bond-length allows to exclude the formation of a strong σ bond between the silicon and the nitrogen atoms. In fact the calculated value of 2.68 Å lies between a valence bond (1.8 Å) and the sum of the Van der Waals radii (3.4 Å). Therefore the Si-N bond is a weak bond with some degree of covalence (calculated bond order 0.154 e^-) but mainly electrostatic in agreement with previous calculations on neutral pentacoordinated silicon compounds[31]. A particular importance has to be given to the stabilisation of the LUMO orbitals found in the cyclic complex (0.42 eV), as the more the LUMO energy is lowered the more the imine bond is favoured towards the nucleophilic attack of the phosphono derivative.

The computational studies provide several clues to the origin of the diastereoselectivity for our Abramov reaction. a) The geometry of the structure (**B**) is fully consistent with our hypothesis that a Cram cyclic model, presenting a pentacoordinate silicon atom, should be involved in our reaction mechanism: the structure of the complex, in fact, has the geometry and energetic features necessary for the easy formation of the above mentioned transition state. b) The stabilisation of the cyclic structure (**A**) should depend from the substituent on the nitrogen atom, since, insofar as the N-Si bond is electrostatic, any substituent capable to increase the negative charge on the nitrogen will increase the stability of the complex. Recently we have found, by computational and ^{13}C NMR studies[32], that the polarisation of the imine bond increases on the increasing of the metallic character of the substituent. In our case the presence of the trimethylsilyl group directly attacked to the imine nitrogen increases the electrophilic character of the imine carbon.

Conclusion

By our studies we have been able to perform a highly diastereoselective synthesis of the four enantiomers of the phosphothreonine. From computational studies it has been shown that a pentacoordinate silicon group may be involved in determining the sense of the diastereoselection in the reaction of TMSDEP with α-silyloxy imines and α-silyloxy aldehydes[33]. Last but not least the use of the trimethylsilyl derivative of DEP plays an important role in the Abramov reaction both from yields and diastereoselectivity point of view. In fact, as it has been shown by other authors[34], the spontaneous tautomerism of diethylphosphite lies overwhelmingly on the side of tetracoordinated electrophilic species, $(EtO)_2P(O)H$ rather than on the tri-coordinated nucleophilic species $(EtO)_2P(OH)$. Freezing out the latter by means of *O*-silylation is thus expected to promote nucleophilic reactivity strongly *via* a concerted [2+3] cycloaddition reaction as suggested by Evans[35]. Finally the dependence of the diastereoselectivity by the steric bulkiness of the *O*-protecting group of the imine or of the aldehyde is quite surprising in the light of the literature data[22]. At the moment the experimental results and the theoretical calculations support the proposed bicyclic transition state with two pentacoordinate silicon atoms. Nevertheless we are fully aware that much more work is needed and, in fact, it is being undertaken.

Table 1 Calculated total energy, charge distributions and bond orders of **A**

E_t	Q Si	Q N	Q C	b.o.C=N	b.o. N-Si
-495.46226	+ 0.932	-0.629	+0.092	0.990	0.154

E_t in atomic units; Q=charge in electrons; b.o.: bond order in electrons.

Experimental Section

General: Melting points are uncorrected. All reactions were conducted under an argon atmosphere. THF was distilled from Na/benzophenone ketyl and CH_2Cl_2 was distilled from P_2O_5. ^{1}H- and ^{13}C-NMR spectra were recorded at 300 and 75 MHz in $CDCl_3$ using TMS or residual $CHCl_3$ as internal reference or in D_2O using dioxane as external reference. ^{31}P-NMR (121.5 MHz) was taken in $CDCl_3$ or D_2O using 85% H_3PO_4 as an external standard with broad-band ^1H-NMR decoupling.

General Procedure for the Synthesis of Phosphoaminoesters (4a and 4b).

The imine[10] **2a** (1mmol) in THF (2 mL) was slowly added at -78°C to the silylphoshonic ester (TMSDEP), prepared *in situ* in methylene chloride (20 mL) from DEP (1.2 mmol), TEA (1.2 mmol), TMSCl (1.2 mmol) under argon atmosphere at 0°C (30 min). After two hours, the temperature was left to reach r.t. spontaneously and the reaction was stirred overnight. Next, the reaction mixture was poured into a buffered (pH 4/5 HCl/NH_4Cl) ice-water solution. Organic compounds were extracted with CH_2Cl_2, combined organic phases were dried on anhydrous $MgSO_4$, and the solvent was removed by reduced pressure. Purification by flash chromatography (SiO_2, ethyl acetate) gave pure **4a** (85%). The enantiomer **4b** was obtained in 70% following the same procedure.

(1S, 2S) **Diethyl-1-Amino-2-(Triisopropylsilyloxy)-Propanephosphonate 4a**:

an oil; $[\alpha]_D^{20}$= +8.9 (1.73, $CHCl_3$); ^1H-NMR ($CDCl_3$) δ 1.05 (21H, m), 1.28 (3H, d, J=6.8), 1.30 (9H, m), 1.75 (2H, bs), 2.92 (1H, dd, J=13.4 and 5.6), 4.15 (4H, m), 4.25 (1H, m). ^{13}C-NMR ($CDCl_3$) 12.30, 12.84, 16.40, 18.00, 55.68 (d, J=149.3), 61.38 (d, J=6.75), 68.27. ^{31}P-NMR ($CDCl_3$) 26.27. IR (film) 3.500-3250, 2950, 2870, 1465, 1390, 1245, 1100. *m/e* (368, M+1), 323, 230, 186, 167, 157, 138, 116, 100. Anal. Calcd for $C_{16}H_{38}NO_4SiP$: C, 52.29; H, 10.42, N, 3.81. Found: C, 52.08 ; H, 10.38; N, 3.83.

(1R, 2R) **Diethyl-1-Amino-2-(Triisopropylsilyloxy)-Propanephosphonate 4b:**

an oil; $[\alpha]_D^{20}$= -9.15 (1.52, $CHCl_3$). Anal. Calcd for $C_{16}H_{38}NO_4SiP$: C, 52.29; H, 10.42; N, 3.81. Found: C, 52.40; H, 10..44; N, 3.80.

General Procedure for the Hydroxy-phosphonylation of α-Triisopropylsilyloxy Lactaldehyde: Synthesis of 10a and 10b.

To a stirred solution of silylphosphonic ester (TMSDEP) (1.1 mmol) in CH_2Cl_2 (20 mL) under argon atmosphere (*S*)-lactaldehyde (1 mmol) in 4 mL of CH_2Cl_2 was slowly added at -78°C and the reaction mixture was stirred at the same temperature for 3 hr. Water was added to quench the reaction and the mixture was warmed to 0°C. The mixture was extracted with methylene chloride and the organic extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo to give the crude adducts **8a** and **9a**. Exposure of the crude mixture to citric acid (2 eq) in methanol (30 mL) at room temperature for 6 hr gave, after column chromatography on silica gel (cyclohexane: acetone: methylene chloride=40:20:40) the hydroxyphosphonic esters **10a** and **11a** in 62% (92/8 ratio). The enantiomers **10b** and **11b** were obtained in 70% yield (92/8 ratio) following the same protocol.

(1S, 2S) **Diethyl-1-hydroxy-2-(Triisopropylsilyloxy)-Propanephosphonate syn-10a**:

an oil; $[\alpha]_D^{20}$= +7.3 (1.2, $CHCl_3$); ^1H-NMR ($CDCl_3$) δ 4.31 (1H, m); 4.15 (4 H, m); 3.61 (1 H, dt, J=4.90, 6.44); 3.00 (1 H, dd, J=4.90, 16.1); 1.30 (9 H, m); 1.05 (21 H, m). ^{13}C-NMR ($CDCl_3$) 12.43, 16.15, 16.26, 17.86, 21.08, (d, J=5.5), 62.08 (d, J=6); 62.17 (d, J=6); 68.22 (d, J=5.5), 72.56 (d, J=161.5). ^{31}P-NMR ($CDCl_3$) 23.1. IR (film) 3260, 2910, 2860, 1460, 1380, 1230. *m/e* 201 (M^+- 167), 187, 157, 145, 117, 87. HRMS *m/e* 369.2226 (MH^+) calcd for $C_{16}H_{37}O_5SiP$ found. 369.22499 Anal. Calcd for $C_{16}H_{37}O_5SiP$: C, 52.15; H, 10.12. Found: C, 52.30 ; H, 10.16.

(1R, 2R) **Diethyl-1-hydroxy-2-(Triisopropylsilyloxy)-Propanephosphonate syn-10b**

an oil; $[\alpha]_D^{20}$= -7.3 (1.46, $CHCl_3$). Anal. Calcd for $C_{16}H_{37}O_5SiP$: C, 52.15; H, 10.12. Found: C, 52.25 ; H, 10.14.

General Procedure for the Synthesis of α-Azido Phosphonates (12a and 12b)

To a stirred solution of alcohol **10a** (1 mmol) and triphenylphosphine (1.2 mmol) in THF (1.5 mL) HN_3 (3 ml 1 M sol. in benzene)[36] and diethylazodicarboxylate (1.2 mmol) at -5°C were added successively during 30 min. Then the mixture was stirred overnight at r.t.. The reaction was quenched with water, filtered to remove triphenylphosphine oxide, dried on Na_2SO_4 and chromatographed on silica gel (cyclohexane /ethyl acetate 6/4) to give the azido phosphonate **12a** in 67% yield.

(1R ,2S) **Diethyl-1-azido-2-(Triisopropylsilyloxy)-Propanephosphonate 12a**

an oil; $[\alpha]_D^{20}$=-10.5 (*c* 0.93, $CHCl_3$); ^1H-NMR ($CDCl_3$) δ 1.1 (21H, m), 1.3 (9H, m), 3.91 (1H, dd, J=2.2 and 17.1), 4.16 (4H, m), 4.46 (1H, m). ^{13}C-NMR ($CDCl_3$) 12.15, 16.25, 16.35, 17.88, 18.68, 62.72 (d, J=6.5), 63.05 (d, J=6.5), 65.23 (d, J=156.5), 68.39 (d, J=9.5). ^{31}P-NMR ($CDCl_3$) 19.22. IR (film) 2920, 2860, 2120, 1260. *m/e* 394 (M+1), 365, 350, 322, 294, 248, 222, 184, 157, 109, 81. HRMS calcd for $C_{16}H_{36}N_3O_4PSi$

(MH$^+$):394.229099. Found 394.22900. Anal. Calcd for $C_{16}H_{36}N_3O_4PSi$: C, 48.83; H, 9.22; N, 10.68. Found C, 48.65 ; H, 9.19 ; N, 10.72.

(*1S, 2R*) Diethyl-1-azido-2-(Triisopropylsilyloxy)-Propanephosphonate 12b

Y% 79 ; an oil; $[\alpha]_D^{20}$= +11.3 (*c* 0.91, $CHCl_3$); Anal. Calcd for $C_{16}H_{36}N_3O_4PSi$: C, 48.83; H, 9.22; N, 10.68. Found C, 48.70 ; H, 9.21 ; N, 10.69.

General Procedure for Hydrogenation of Azido Phosphonates

A solution of azide **12a** in EtOAc was hydrogenated at room temperature for 30 min over PtO_2 (0.2 eq) under atmospheric pressure. The catalyst was removed by filtration through Celite, and the filtrate was concentrated in vacuo to give the phosphoamino ester **4c**. Y%=quantitative. The enantiomer **4d** was obtained following the same protocol in quantitative yield.

(*1R ,2S*) Diethyl-1-amino-2-(Triisopropylsilyloxy)-Propanephosphonate 4c.

an oil; $[\alpha]_D^{20}$= -0.35 (*c* 1.44, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 1.05 (21H, m), 1.25 (3H, d, J=6.3), 1.33 (6 H, t, J=6.0), 1.65 (2 H, bs), 3.25 (1H, dd, J=3.03 and 19.5), 4.15 (4H, m), 4.31 (1H, m). ^{13}C-NMR ($CDCl_3$) 12.18, 16.28, 16.33, 17.75, 17.94, 55.60 (d, J=149.0), 61.86 (d, J=6.5), 62.19 (d, J=6.5), 67.59 (d, J=11.0). ^{31}P-NMR ($CDCl_3$) 26.08. IR (film) 2940, 2860, 1510, 1380, 1240. *m/e* 368 (M+1), 324, 230, 201, 186, 167, 138, 116, 100, 75, 59. Anal. Calcd for $C_{16}H_{38}NO_4PSi$: C, 52.29; H, 10.42; N, 3.81. Found C, 52.43 ; H, 10.45 ; N, 3.79.

(*1S ,2R*) Diethyl-1-amino-2-(Triisopropylsilyloxy)-Propanephosphonate 4d.

an oil; $[\alpha]_D^{20}$= +0.68 (*c* 1.6, $CHCl_3$). Anal. Calcd for $C_{16}H_{38}NO_4PSi$: C, 52.29; H, 10.42; N, 3.81. Found C, 52.20 ; H, 10.46; N, 3.82.

General Procedure for the Synthesis of Phosphoaminoacids hydrochlorids.

3 mmol of the aminophosphonic ester were mixed with 5 ml 6N hydrochloric acid and the mixture was refluxed for 6h. Ethyl acetate was added. The aqueous phase was lyophilised to give phosphoamino acids **1a**, **1b**, **1c** and **1d** respectively in almost quantitative yield.

(*1S ,2S*) -1-amino-2-hydroxy-Propanephosphonic acid x HCl 1a

hygroscopic; $[\alpha]_D^{20}$= +5.1 (*c* 1.67, H_2O);

^{1}H-NMR (D_2O) δ 1.13 (3H, d, J=6.3), 2.91 (1H, dd, J_{H1-H2}=8.50, J_{H1-P}=13.8), 3.82 (1 H, ddq, J_{H1-H2}=8.5; J_{H2-P}=4.80; J_{H2-CH3}=6.3)

^{13}C-NMR (D_2O) 21.5 (d, J=2.0); 55.68 (d, J=140.2); 65.86 . ^{31}P-NMR (D_2O) 14.55.

(*1R ,2R* -1-amino-2-hydroxy-Propanephosphonic acid x HCl 1b

hygroscopic; $[\alpha]_D^{20}$= -5.88 (*c* 2.89, H_2O);

^{1}H-NMR (D_2O) δ 1.13 (3H, d, J=6.3), 2.91 (1H, dd, J_{H1-H2}=8.50, J_{H1-P}=13.8), 3.82 (1 H, ddq, J_{H1-H2}=8.5; J_{H2-P}=4.80; J_{H2-CH3}=6.3)

^{13}C-NMR (D_2O) 21.5 (d, J=2.0); 55.68 (d, J=140.2); 65.86 . ^{31}P-NMR (D_2O) 14.55.

(*1R ,2S*) -1-amino-2-hydroxy-Propanephosphonic acid x HCl 1c.

hygroscopic; $[\alpha]_D^{20}$= -6.9 (*c* 0.67, D_2O);

^{1}H-NMR (D_2O) δ 1.31 (3H, d, J=6.6), 3.39 (1H, dd, J_{H1-H2}=3.9, J_{H1-P}=15.4), 4..31 (1 H, ddq, J_{H1-H2}=3.9; J_{H2-P}=7.7; J_{H2-CH3}=6.6). ^{13}C-NMR (D_2O) 18.36 (d, J=2.0); 55.00 (d, J=141.0); 65.60 . ^{31}P-NMR (D_2O) 14.48.

(*1S ,2R* -1-amino-2-hydroxy-Propanephosphonic acid x HCl 1d.

an oil; $[\alpha]_D^{20}$= +7.4 (*c* 0.61, D_2O).

^{1}H-NMR (D_2O) δ 1.31 (3H, d, J=6.6), 3.39 (1H, dd, J_{H1-H2}=3.9, J_{H1-P}=15.4), 4..31 (1 H, ddq, J_{H1-H2}=3.9; J_{H2-P}=7.7; J_{H2-CH3}=6.6). ^{13}C-NMR (D_2O) 18.36 (d, J=2.0); 55.00 (d, J=141.0); 65.60 . ^{31}P-NMR (D_2O) 14.48.

Purification by column chromatography on ion-exchange resin *Dowex 50 W x 8* (eluting H_2O)[8] gave pure phosphoaminoacids **1a, 1b, 1c** and **1d.**

1a Y% 78 m.p.=230-233°C; $[\alpha]_D^{20}$= +8.5 (*c* 0.28, H_2O) (lit[8a]. m.p. 231-232; $[\alpha]_D^{20}$= +8.9 (*c* 1.0, H_2O)

1b Y% 80 m.p. 228-230°C $[\alpha]_D^{20}$= -8.9 (*c* 0.208, H_2O) (lit[8b]. m.p. 234-236; $[\alpha]_D^{20}$=-9.4 (*c* 1.8, H_2O)

1c Y% 84 m.p. 217-219°C $[\alpha]_D^{20}$= -8.9 (*c* 0.294, H_2O). ^{1}H-NMR (D_2O) δ 1.27 (3H, d, J=6.7), 3.33 (1H, dd, J_{H1-H2}=3.7, J_{H1-P}=15.4), 4.26 (1H, m). ^{13}C-NMR (D_2O) 18.14 ; 55.50 (d, J=136.5); 65.77 . ^{31}P-NMR (D_2O) 13.02. Anal. Calcd for $C_3H_{10}NO_4P$: C, 23.23; H, 6.50; N, 9.03. Found C, 23.15 ; H, 6.48; N, 9.05.

1d Y% 85 m.p. 218-220°C $[\alpha]_D^{20}$=+8.8 (*c* 0.218, H_2O) (lit[8b]. m.p. 220-221; $[\alpha]_D^{20}$=+9.6 (*c* 1.5, H_2O)

(*1S,2S*) Diethyl-1-amino-2-hydroxy-propanephosphonate 6

3 mmol (0.98g) of the *O*-protected phosphoamino ester **4a** were dissolved in 10 ml anhydrous THF at 0°C under argon atmosphere. In one portion 3 ml of 1N solution of tetrabutylammonium fluoride (TBAF) in THF was added and the reaction was stirred for 3 h. The reaction mixture was poured into a saturated solution of $MgSO_4$ in H_2O, organic compounds were extracted with ethyl acetate, dried by anhydrous Na_2SO_4, after which the solvent was removed by reduced pressure. The product was purified by flash chromatography to give **6** (68%).

^1H NMR ($CDCl_3$) 1.35 (9H, m); 2.65 (3 H, bs); 2.83 (1H, dd, J=3.9 and 13.5); 4.1 (1 H, m); 4.18 (4 H, m). ^{13}C NMR ($CDCl_3$) 16.36, 19.2 (d, J=13.8), 52.0 (d, J=156.0), 62.40 (d, J=75), 65.5. ^{31}P-NMR ($CDCl_3$) 28.41. I.R. (film): 3300, 2980, 2940, 2915, 1490, 1460, 1380, 1235, 1150. .*m/e* 193 (M-$H_2$0) 179, 166, 138, 111, 100. Anal. Calcd for $C_7H_{18}NO_4P$: C, 39.81; H, 8.59; N, 6.63. Found C, 39.94 ; H, 8.61 ; N, 6.60.

(4*S*, 5*S*)-5-methyl-2-oxo-oxazolidin-4-yl-phosphonic acid diethyl ester 7.

2 mmol (0.42 gr) of **6** and 0.2 mmol (0.03 gr) of ethyldiisopropyl amine were mixed in 100 ml anhydrous THF at 0°C under argon atmosphere. Slowly 2 mmol (0.32 gr) of *N,N*-carbonyldiimidazole were added, and the reaction mixture was stirred for 15 h. The solvent was removed by reduced pressure and the residue was poured into a 10% HCl_{aq} sol. Organic compounds were extracted with CH_2Cl_2, dried with anhydrous $MgSO_4$, after which the solvent was removed by reduced pressure. The product was purified by flash chromatography ($CHCl_3/CH_3OH/NH_4OH$ 23:3:1) to give the cyclic product **7** in 25% yield.

an oil ^1H-NMR ($CDCl_3$) δ 1.37 (6 H, t, J=7); 1.52 (3 H, d, J=6.2); 3.63 (1 H, bd, J=6.63); 4.2 (4 H, m). ^{13}C-NMR ($CDCl_3$) 16.32, 20.95 (d, J=8.5), 56.5 (d, J=166.3), 63.2 (d, J=52.7), 73.8, 158.5 (d, J=7.6). ^{31}P-NMR ($CDCl_3$) 18.63. IR (film) 3400, 2990, 1770, 1385, 1230, 1180. *m/e* 237 (M^+), 222, 193, 179, 165, 138, 111, 100, 82, 56. Anal. Calcd for $C_8H_{16}NO_5P$: C, 40.51 ; H, 6.8 , N, 5.91 . Found: C, 40.40 ; H, 6.6; N, 5.92.

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