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Synthesis of (*1S, 2S*)-Phosphothreonine *via N*-Trimethylsilylimine of (*S*)-Lactic Aldehyde.

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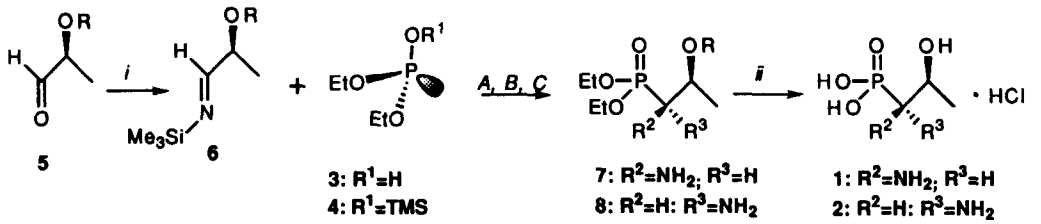
Abstract: The title compound is obtained in high diastereomeric purity based on the stereoselective addition of trimethylsilylphosphite to *N*-trimethylsilylimine of (*S*) lactic aldehyde.

Over the years, the synthesis of α-alkyl phosphonic acids and their related phosphonopeptides has been an important area of research, particularly in connection with the search for biologically active surrogates for the corresponding carboxylic acids.[1,2] Presently a number of methods are available for the synthesis of optically pure and enriched α-alkyl phosphonic acids,[3] *via* resolution, enzymatic techniques, or utilising some aspect of asymmetric bond formation. Recently we have been involved in a general program directed towards the use of *N*-metallo imines in general and *N*-trimethylsilylimines in particular as useful tools for introducing nitrogen functionality for the synthesis of biologically significant molecules.[4]

We now extend our work in this area by describing the asymmetric synthesis of (*1S, 2S*)-1-amino-2-hydroxy-propane-phosphonic acid[5] **1** based on the stereoselective addition of diethylphosphite **3** or its trimethylsilylderivative[6] **4** to *N*-trimethylsilylimine **6** of the (*S*)-lactic aldehyde[4c] **5**. (Scheme 1)

Scheme 1



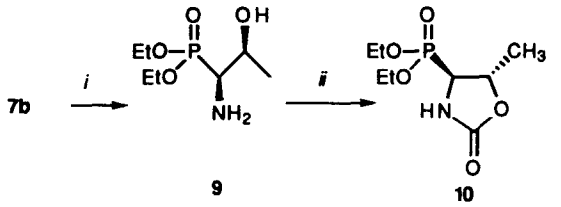
a: R= $SiBu^tMe_2$; **b**: R=$SiPr^i_3$; **c**: R=$SiEt_3$

i : LiHMDSA/THF/-78°C;
Method A: **3**/ THF/-78°C/then r.t. 5hrs; Method B: **3**/ BF_3/THF/-78°C/then r.t. 5hrs; Method C: **4**/THF/-78°C then r.t. 5 hrs;
ii: HCl 6N/H_2O, 6 hrs

Several attempts (Table 1) have been made in order to achieve the best diastereomeric ratio working on the hydroxy protecting group of the imine and on the nature of the phosphorylating reagent. The best yield (85%) and diastereomeric ratio (*syn/anti* >98/2) have been obtained using as phosphorylating agent the trimethylsilyldiethoxyphosphite (TMSDEP) **4** and as protecting group of the hydroxy functionality the triisopropyl silyl group (Table 1).

The stereochemistry of the final aminophosphonic esters was attributed by means of a combinative ^{1}H, ^{13}C- and ^{31}P-NMR of the esters **7** and **8**, of the acids **1** and **2**, obtained from the diastereomeric mixture of esters by acidic hydrolysis (HCl 6N in H_2O at 80°C for 6 hrs; Scheme 1), and of the corresponding oxazolidin-2-one **10** obtained from the ester **7b** following the sequential reactions[7] depicted in Scheme 2.

Scheme 2



Reagents and conditions: *i* TBAF/THF/r.t./3 hrs, 68% *ii* Carbonylimidazole/THF/Hunig base/r.t./15 hrs, (20%)

Table 1: Aminophoshonic esters from DEP or TMSDEP and silylimines.

Entry	R	Phosph. Agent	Products[8]	Yields %*	Ratio *syn/anti*[§]
1	TBDMS	DEP	**7a, 8a**	30	50/50
2	TBDMS	DEP/BF_3	**7a, 8a**	53	55/45
3	TBDMS	TMSDEP	**7a, 8a**	67	96/4
4	TIPS	DEP/BF_3	**7b, 8b**	50	80/20
5	TIPS	TMSDEP	**7b, 8b**	85	>98/2
6	TES	TMSDEP	**7c, 8c**	59	90/10

TBDMS=*tert*-Butyldimethylsilyl; TIPS=Triisopropylsilyl; TES=triethylsilyl. *The yields were calculated on the pure isolated products. §The diastereomeric ratio was determined by ^{1}H NMR on the crude reaction mixture.

As anticipated above careful analysis of the NMR spectra of the products allowed us to attribute the configuration *syn* to the diastereoisomer **7** and the configuration *anti* to the diastereomer **8** on the basis of the following reasons: **A**: In Tables 2 and 3 of Scheme 3 are reported the values of the J_{HCCH} between H_1-H_2, J_{PCCH} between P and H_2 and J_{PCCC} between P and the C_3 in the corresponding acids **1** and **2**.

Scheme 3

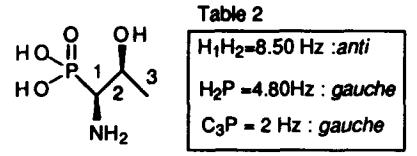


Table 2

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

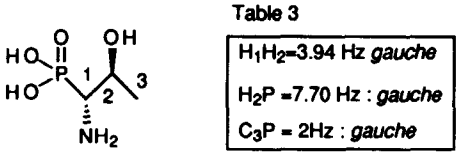
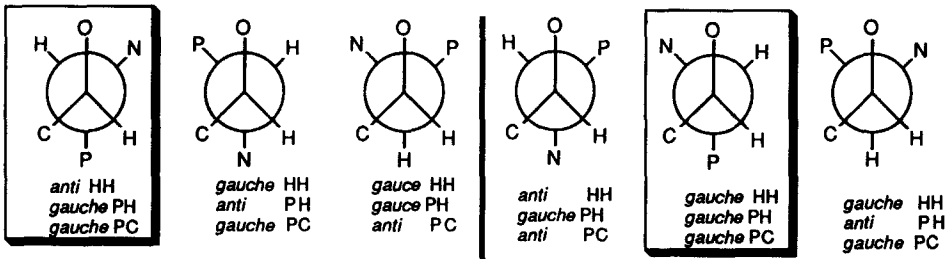


Table 3

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



S, S *SYN* S,R *ANTI*

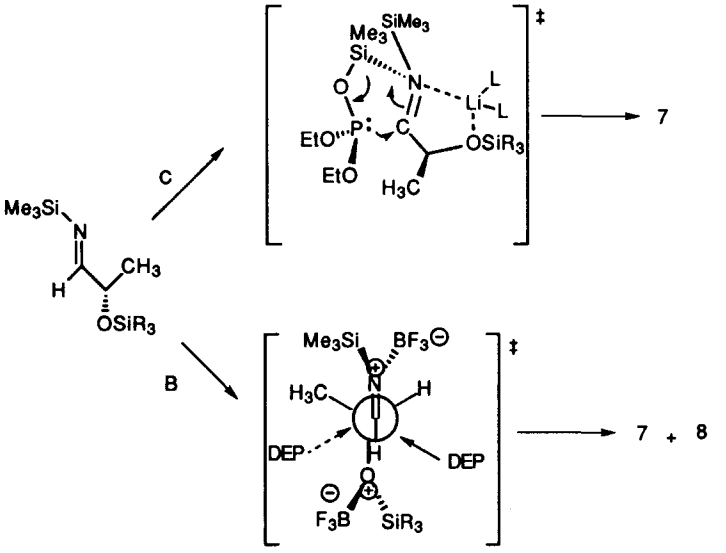
These values allow to assign to each dihedric angle corresponding to the coupling constant a neat preferential conformation respectively *anti-gauche-gauche* for one of compounds and *gauche-gauche-gauche*

for the second compound[9]. The analysis of all the conformations for *S,S* and *S,R* configurations as reported in Scheme 3 shows that *agg* conformation is possible only for the *syn* configuration and a *ggg* conformation is possible only for the *anti* configuration. As consequence to the isomer **1** should be attributed the *syn* configuration and to the isomer **2** should be attributed the *anti* configuration. **B**: Analysis of the data arising from the cyclic structure **10**, prepared from the open-chain compound **7b**, confirms the attribution we have made. In this case we used the NOE technique (steady state experiment). Irradiating the methyl group of the cyclic compound **10** with a saturation time of 5 sec, an increment of 13% on both vicinal and geminal hydrogens is observed. This behaviour is a clear evidence that the vicinal proton is *cis* to the methyl group. In fact it is well known that in similar compounds the *trans* hydrogen gives, if any, very inferior increment[10].

Having, by this way, assigned the correct stereochemistry, we can tentatively sketch a mechanistic picture of the overall process. In fact the knowledge, even if approximate, of the reaction mechanism would be very useful in extending its synthetic scope and providing a better understanding of the addition of P-nucleophiles to sp^2 carbon centres[11].

The formation of the *syn* diastereomer **7a** as major product in the addition of the *N*-(α-silyloxy)-trimethylsilylimine can be rationalized on the basis of our previous studies and observations in alkylations with C-nucleophiles (alkyllithium or lithium ester enolates) in the same series.[4]

Scheme 4



Method B: DEP/BF_3 Method C: TMSDEP

The different diastereomeric ratio obtained using as nucleophile DEP, DEP/BF_3, or TMSDEP suggests two different pathways:

A) The spontaneous tautomerism of diethylphosphites was shown[12] to lie overwhelmingly on the side of tetra-coordinated 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 for aldehydes[13]. Attack takes place from the "pro *S* " side of a *quasi* planar cyclic pentamembered structure, due to the presence of the lithium cations, arising from the formation of imine, present in the reaction medium. In this case the nucleophile is forced to attack from the less hindered face of the diastereotopic plane of the five-membered cyclic structure so that a *syn* addition product is obtained predominantly or exclusively (entries 3, 5, 6 of Table 1).

B) The electronic demand of the imine bond suggests that the rate determining step in the path B (Scheme 4) incorporates nucleophilic attack by the iminic nitrogen on an electrophilic species, presumably BF_3 or the DEP itself, to form an open-chain iminic cation. Addition to this cation of the nucleophilic P (III) species, accompanied by valency expansion at phosphorus, *via* an open chain transition state (Cornforth's dipolar model[14]) gives a mixture of *anti* and *syn* addition products. Of course the proposed mechanisms are to be considered an oversimplification and we are fully aware that more accurate studies must be performed and, in fact, they are currently being conducted.

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5 At our knowledge no report has been published up-to-now on the preparation of the reported and other diastereomers of phosphothreonine. ***Preparation of (1S, 2S)-1-amino-2-hydroxy-propane phoshonic acid*** **1**: The imine **6b**, (2 mmol), prepared according lit. 4a was slowly added to equimolar amount of TMSDEP under argon atmosphere at -78°C. After two hours, the temperature was slowly brought to room temperature and the reaction was stirred an additional 5 h. until the reaction was complete [TLC ethyl acetate/cyclohexane 7/3]. The reaction mixture was quenched with ammonium chloride/water at 0°C and extracted with methylene chloride. The organic phase was dried on anhydrous $MgSO_4$ and the solvent removed by reduced pressure. Flash chromatography of the crude mixture (ethyl acetate-cyclohexane 7/3) gives **7b** $[\alpha]_D$ +8.9 (c=1.73, $CHCl_3$) in 85% yield. Three mmoles of **7b** were mixed with 5 ml HCl 6N and the mixture was heated at 80°C for 6 h. The solution was poured into 20 ml of ethyl acetate. The aqueous phase lyophilised at reduced pressure to give the target **1** (*hygroscopic*) in 98% yield. $[\alpha]_D$ +5.1 (c=1.67, H_2O).

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7 Because the oxazolidin-2-one was needed only for diagnostic reasons, no optimisation of yields was performed.

8 All the product gave consistent I.R., ^1H, ^{13}C and ^{31}P- NMR spectra and satisfactory elemental analysis as well.

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