PREPARATION OF EITHER ENANTIOMER OF 1,2-DIAMINOALKANE-2-PHOSPHONIC ACID DERIVATIVES#

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Abstract-Imidazolidine-derived phosphono esters (**1**,**11**) are prepared from *t*-butyl (*R*)-2-*t*-butyl-3-methylimidazolidin-4-one-1-carboxylate (Boc-BMI, **A**) by *Michaelis-Arbuzov* reactions of appropriate intermediates [the 5-bromo-Boc-BMI and the acetoxy derivative (**10**)]. Deprotonation (DBU/LiBr or LTMP/BuLi) and reaction with alkyl halides give *gem.* disubstituted heterocycles (**3**-**7**,**12**-**17**), some of which are converted to the corresponding 2-amino-2-aminomethylalkane-phosphonic acids (**8**,**9**,**18**-**21**). One of the substitution reactions with $P(OMe)_3$ occurs with migration of the heterosubstituent from the α-NBoc to the α-NMe position of the imidazolidine system (*Scheme 4*) A very surprizing reversal of the stereochemical course of alkylation is observed with the dimethyl imidazolidinephosphonate (**11**) upon going from the more reactive (MeI, BnBr, AllylBr) to the less reactive halides (Et-, Pr-, and BuI). The product structures are derived from three X-ray crystal structure analyses, by nmr comparison, and by chemical correlation.

INTRODUCTION

Formally and structurally, an α-aminophosphonic acid results by substitution in an α-aminoacid of the carboxylic acid by a phosphonic acid functional group. Because of the interesting biological activity often observed (the α-aminophosphonic acids are probably the most important substitutes of the corresponding α-amino acids in biological systems[1]) there is an increasing activity in this area, also of research groups devoted to synthetic methodology. In biological systems aminophosphonic acids act as antibiotics,[2] as pharmacological

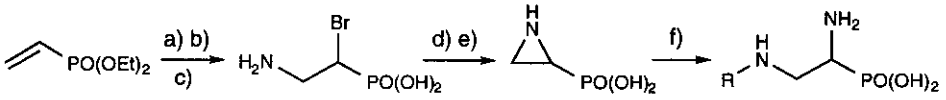
Dedicated to Professor *Rolf Huisgen* at the occasion of his 75th birthday.

≠ Part of the projected Ph.D. thesis of A. S., ETH Zürich.

agents,[3] as enzyme inhibitors,[4] as herbicides and as insecticides.[5] It is well known, that the biological activity of α-aminophosphonic acids depends on their absolute configuration.[6] This has led to the development of a number of different enantioselective syntheses: The most widely used method involves the addition of phosphites to imine and oxonium derivatives (either component being chiral).[7] Anionic or cationic phosphonoglycine equivalents have also been used.[8] We have found only one report on asymmetric hydrogenation of dehydroaminophosphonic acids.[9] Other approaches are the stereoselective ring opening of acetals[10] and the electrophilic amination of phosphorous-stabilized anion derivatives.[11]

In the present paper we report a general method for the synthesis of enantiopure α-branched *N*-methyl-α,β-diaminophosphonic acids. In contrast to the corresponding simple aminophosphonic acids, and also to the analogous α,β-diaminocarboxylic acids, not much is known about this class of compounds. We retrieved only one example from a *Chemical Abstract* search as of April 1994: Racemic diaminophosphonic acids with various substituents on the β-nitrogen were synthesized by nucleophilic ring opening of aziridine phosphonic acid as outlined in *Scheme 1*.[12] The products thus obtained have been found to be biologically active as inhibitors of the leucine aminopeptidase.[13]

Scheme 1

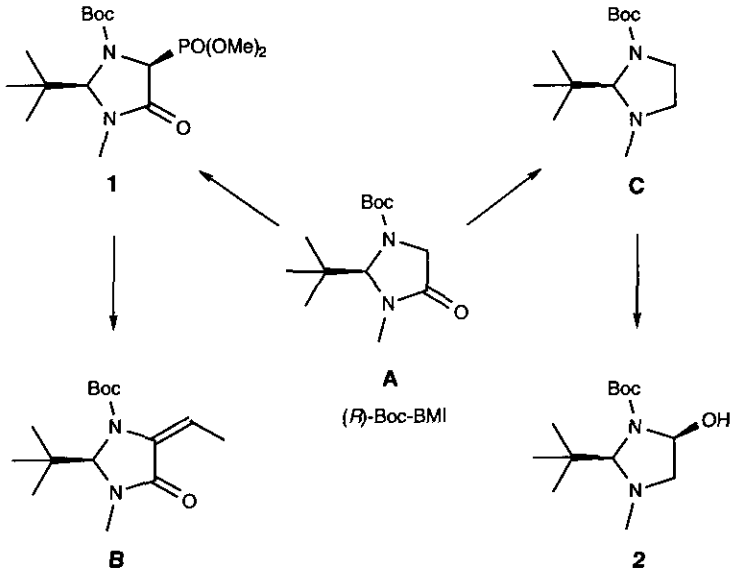


a) Br_2 , b) NH_3/ H_2O, c) H^+/ H_2O, d) OH^-, e) ion-exchange chromatography, f) RNH_2.

We have previously published the preparation of the phosphorylated glycine derivative (**1**)[14] by bromination of the chiral amino acid building block Boc-BMI (**A**)[14-22] and *Michaelis-Arbuzov* reaction without isolation of the intermediate bromide. *Wittig-Horner* olefination of aldehydes with the heterocyclic phosphonate (**1**), using the base system 1,8-diazabicyclo[5.4.0]undec-7-en (DBU) / lithium bromide in THF,[23-29] was found to yield 5-alkylideneimidazolidinones (**B**) of *E* configuration, which react with cuprates highly diastereoselectively to eventually give β-branched α-amino acids (see *Scheme 2*).[14b] The heterocyclic phosphonate ester (**1**) and another enantiomerically pure intermediate (**2**) available from Boc-BMI through the 4,5-unfunctionalized imidazolidine (**C**)[17] were now used for the preparation of α,β-diaminophosphonic acids.

It is important at this point to mention that both enantiomers of the starting material Boc-BMI are readily available, because BMI is prepared in enantiopure form by resolution with mandelic acid.[15] Thus while the work described herein was carried out with (*R*)-Boc-BMI, all enantiomers of the products shown in *Schemes 2-6* and *8* are equally well accessible.

Scheme 2



RESULTS AND DISCUSSION

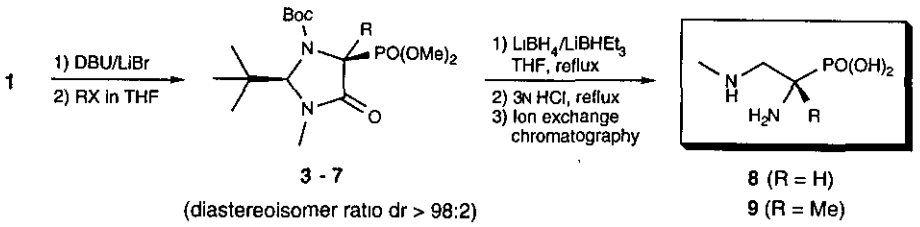
Attempts to prepare 2-amino-1-methylaminoalkane-2-phosphonic acids from **1**: We have found that the phosphonate ester (**1**) can be alkylated with 1-iodoalkanes and allyl or benzyl bromide under exactly the same conditions under which it undergoes olefination reactions with aldehydes (*Scheme 3*). The yields of purified products are high, and a single diastereoisomer is formed exclusively (by ^{1}H-nmr analysis of the crude product in DMSO-d_6 at 100 °C), characterized by a 7-8 Hz coupling in the nmr spectrum between the hydrogen on the acetal carbon C(2) and the phosphorous. The configurational assignment of the products (**3-7**) rests upon the X-ray crystal structure analysis of the allyl substituted phosphonoester (**6**), see *Figure 1*, and their similar nmr spectra. As expected, the electrophiles enter from that face of the phosphono-enolate intermediate which is remote from the sterically demanding *t*-butyl group pushing the phosphonoester group into the *cis* position; an overall alkylation of **1** with retention of configuration results.

Following a procedure applied successfully for the deoxygenation of **A** to give **C**[17], the non-alkylated derivative (**1**), and its enantiomer *ent*-(**1**), as well as the product (**3**) of methylation were reduced with $LiBH_4$/$LiBHEt_3$ in THF and the crude products subsequently hydrolyzed to the corresponding diaminophosphonic acid hydrochloride salts. The free amino acids (**8**), *ent*-(**8**) and (**9**) thus formed were purified by ion exchange chromatography (*Dowex 50 X 8*) and isolated in reasonable yields (44-53% over two steps) (*Scheme 3*).

The dimethyl phosphonate esters (**4-7**) with larger substituents between the carbonyl and the phosphono group we were not able to reduce under the conditions mentioned above. Inspection of the crystal structure of compound (**6**) is probably telling us why: both sides of the amide carbonyl group in the ring are sterically protected from nucleophilic attack (the *t*-butyl and the phosphonate groups on one side and the allyl-substituent on the other side, see *Figure 1*). Thus, the products (**4-7**) look like they are a dead end *en route* to

diaminophosphonic acids, the target molecules of the present study. We therefore looked for another approach, turning around the sequence of events, as described in the following section.

Scheme 3

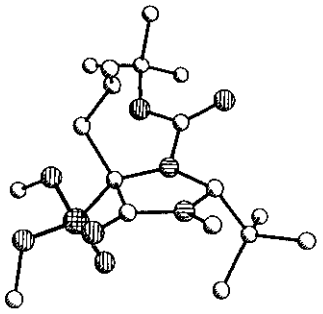


3 - 7
(diastereoisomer ratio dr > 98:2)

8 (R = H)
9 (R = Me)

Compound	**1**	**3**	**4**	**5**	**6**	**7**
R	H	Me	Et	Bu	Allyl	Bn
Yield [%]	-	83	72	77	74	78
$J_{H\text{-}C(2)/P}$ [Hz]	7.0	6.7	8.0	8.0	7.0	7.8

Bn = benzyl



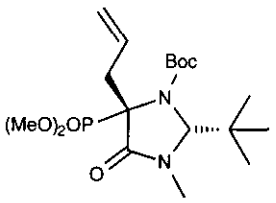
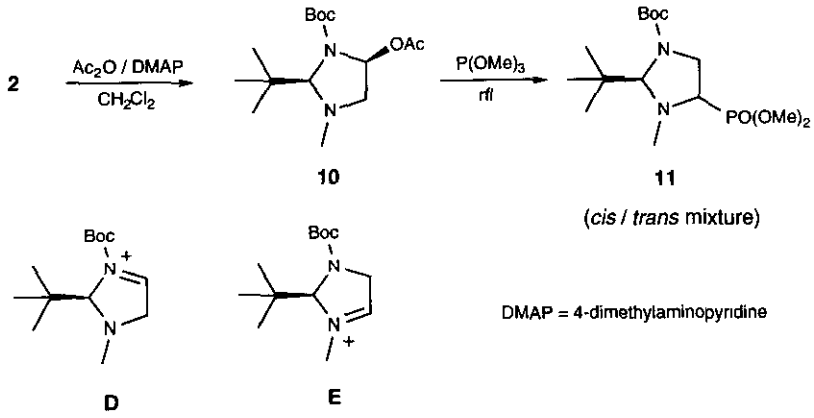


Figure 1. *Crystal Structure of the Allylimidazolidinone Phosphonate* (**6**). PLUTO presentation and *formula* of **6**; the absolute configuration follows from that of the (R)-(+)-Boc-BMI[15] used for the preparation of **6** - The structure was determined, as part of the requirements for a crystallographic laboratory course by *B. Rheiner*, under the direction of *PD Dr. V. Gramlich*. Their contribution as well as the help we received from *F. N. Kühnle* for producing this and the other PLUTO plots in this paper are gratefully acknowledged. The data set will be deposited with the Cambridge Crystallographic Data Base.

Preparation of 1-amino-2-methylamino-2-alkane-2-phosphonic acids: The product (**C**) of deoxygenation of Boc-BMI (**A**) was now used as a starting material. It had been shown[17] that lithiation of **C** occurs on CH_2 next to the Boc group, and among the electrophiles tested was oxygen. The surprisingly stable hydroxy compound (**2**) shown in *Scheme 2* could be isolated and purified by chromatography, and it was a single isomer to which we had assigned the *trans* configuration in our previous paper.[17] A more careful nmr analysis using nuclear Overhauser effect (NOE) measurements, as well as an independent synthesis of **2**[30] have now established that our assignment had been wrong, and that the *cis* isomer (**2**) was actually formed in both cases.[31] Acetylation of this hydroxy derivative (→ **10**) and *Michaelis-Arbuzov* reaction in refluxing neat trimethyl phosphite[32] gave in 70% yield a phosphonate ester (**11**) as a *ca.* 1:1 mixture of diastereoisomers (separable, but not configurationally assigned), see *Scheme 4*. The structure of **11** could be unambiguously proved by crystal structure analysis of derivatives prepared from it, *vide infra*. Surprizingly at first sight, the phosphonate group in **11** is in the 4- and not in the 5-position of the imidazolidine ring. In hindsight, it was not so astonishing that an acyliminium ion (**D**) rearranged to a more stable iminiumion (**E**) (*Scheme 4*) under the drastic conditions (112 °C) used for the phosphonation.[33]

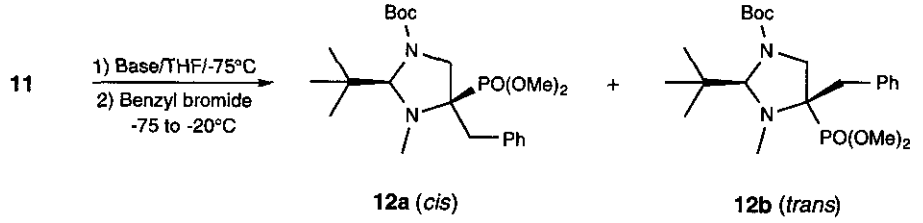
Scheme 4



The readily available phosphonate ester (**11**) was now used for alkylations; it turned out that the results of such alkylations were the same with either diastereoisomer of **11**, and therefore we used the mixture as obtained from the *Arbuzov* reaction. We first tried the benzylation of the phosphonate (**11**) with different bases (see Table in *Scheme 5*). With DBU/LiBr and with lithium bis(trimethylsilyl)amide (LHMDS) (Entries 1 and 2) we observed no product formation. The use of lithium diisopropylamide (LDA) led to the desired products (**12a**) and (**12b**) in a ratio of 1.6 : 1 in 52% yield. A better yield (62%) and higher selectivity were obtained with lithium tetramethylpiperidide (LTMP)/BuLi (Entry 5). The addition of an equivalent BuLi is important for good yields (compare Entries 4 and 5, *Scheme 5*); the necessity to remove HNR_2 from Li nucleophiles in order to get good

yields of reactions with electrophiles has been recognized some time ago, and was explained by hydrogen-bond formation between the amine and the Li nucleophile (for instance a Li enolate).[34,35]

Scheme 5



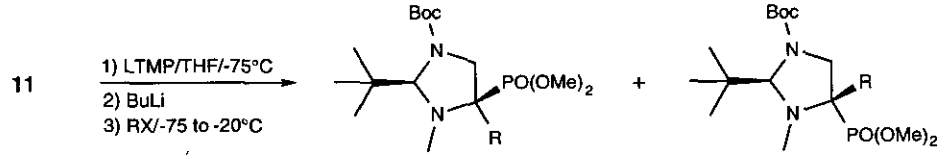
12a (*cis*) **12b** (*trans*)

Entry	Base	Ratio (**12a** : **12b**)	Yield [%]
1	DBU/LiBr	-	-
2	LHMDS	-	-
3	LDA	1.6 : 1	52
4	LTMP[1]	> 98 : 2	7
5	LTMP/BuLi	2.4 : 1	62
6	*t*-BuLi	1.8 : 1	55

[1] 60% of starting material was isolated besides **12a**.

Under the thus optimized conditions we next tested various other electrophiles for alkylation of the phosphonoester (**11**). The results are summarized in *Scheme 6*. Besides benzyl bromide, allyl bromide and iodomethane, the higher iodo alkanes could also be employed successfully in these alkylation reactions, see products (**13-17**) (yields ranging from 45 to 67%). The secondary iodoalkane 2-iodopropane, however, did not give rise to the desired product.

Scheme 6

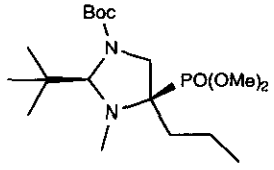


12a-17a (*cis*) **12b-17b** (*trans*)

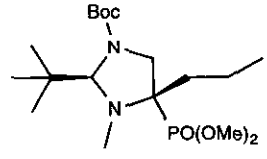
RX	Prod.-No.	Yield [%][1]		Ratio (**a** : **b**)[2]
		a	**b**	
$PhCH_2Br$	**12**	44	18	2.4 : 1
MeI	**13**	53	14	3.8 : 1
AllylBr	**14**	33	25	1.3 : 1
EtI	**15**	3	52	1 : 17
PrI	**16**	-	60	< 1 : 50
BuI	**17**	-	45	< 1 : 50

[1] The missing material is not starting phosphonate (**11**), but unidentified products of decomposition are formed.

[2] The ratio was determined from the weight of the chromatographically separated pure samples.



16a (by hydrogenation of **14a**)



16b (by hydrogenation of **14b**)

Surprizingly, only one stereoisomer was formed with iodopropane and -butane, while the other alkylating reagents gave mixtures of epimers which were all separated chromatographically. The configurations of the allyl and propyl derivatives were correlated by catalytic hydrogenation of the former to the latter ones: thus, the major allylation product (**14a**) gave a propyl derivative (**16a**) which we did not detect in the crude product mixture from the propylation, and the epimer (**14b**) gave (**16b**) identical with the propylation product (*Scheme 6*). The diastereoisomers of series **b** to which we assign *trans* configuration show a *very* characteristic pattern of signals in the ^{1}H-nmr spectra for the CH_2 protons in position (5): due to the presence of rotamers (*ca.* 1:1, room temperature, in DMSO or $CDCl_3$) each of the diastereotopic hydrogens gives rise to two signals split to a doublet

of doublets by coupling with its *gem.* neighbor and with phosphorous; this leads to two sharp sets of multiplets around $\delta = 3.0$ and $\delta = 4.3$ ppm; the H-C(2) appears as two signals around 4.1 ppm. In contrast, all epimers **a** of the *cis* series show the H-C(2) at lower field than the H-C(5) protons. The corresponding parts of the ^{1}H-nmr spectra of a *cis/trans* pair are shown in *Figure 2*.- Furthermore, it is characteristic that all isomers of the **a** series run faster in the chromatography on silica gel than their **b** epimers.

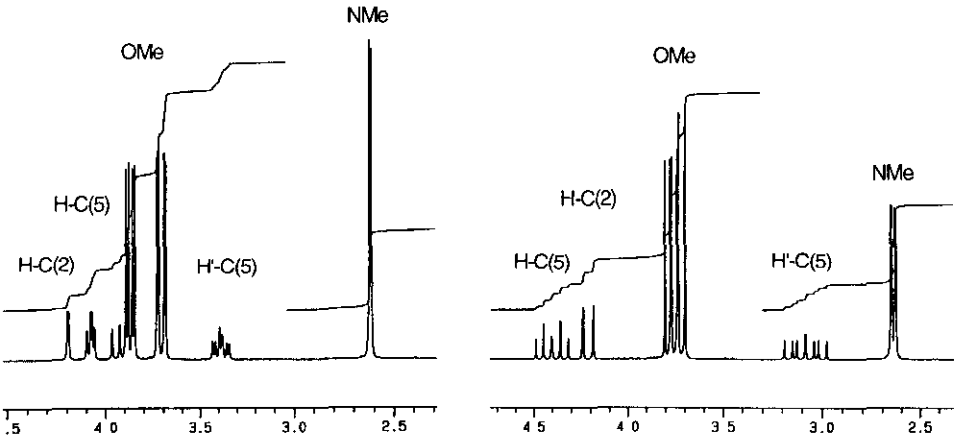


Figure 2. *Section of the 300 MHz ^{1}H-Nmr Spectra of the* cis *and* trans *Propyl Derivatives (16a) and (16b).* As typical for the entire **b** series of compounds, the signal from the acetal hydrogen H-C(2) appears between the two multiplets from the diastereotopic H-C(5) hydrogens (spectrum on the right), while it appears at lower field than both H-C(5) hydrogens in the **a** series (spectrum on the left).

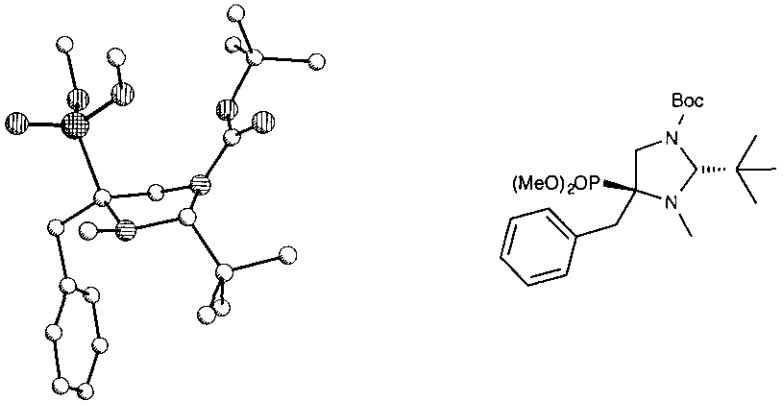


Figure 3 *Crystal Structure of the* trans *Benzyl-imidazolidine Phosphonate (12b)* PLUTO presentation and formula of **12b**, the absolute configuration follows from that of the (R)-(+)-Boc-BMI[15] used for the preparation of **12b**.-The X-ray analysis was carried out by *V. Gramlich, D. Frank, R. Schönbachler,* and *M. Sieber* during the crystallographic laboratory course, ETH Zurich, winter term 1993/94. The coordinates will be deposited with the Cambridge Crystallographic Data Base.

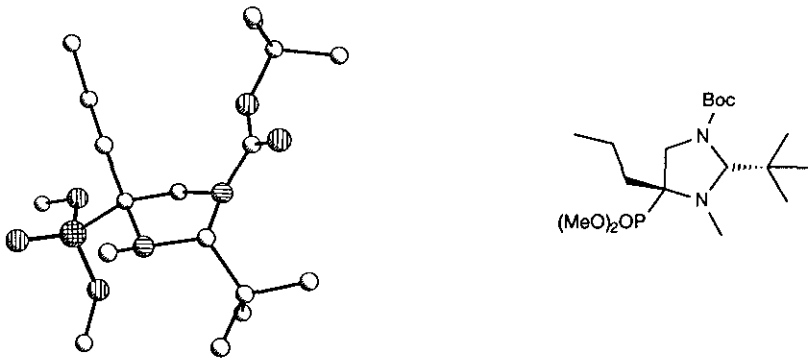


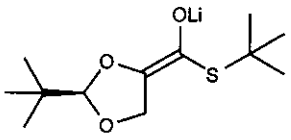
Figure 4. *PLUTO Plot and* Formula *of the* cis *Propyl-imidazolidine-phosphonate (16a).* For further information and acknowledgements see *Figures 1* and *3*.

The assignment of *cis* or (*R,R*)-configuration to the **a** series and *trans* or (2*R*,4*S*)-configuration to the **b** series is based on the X-ray crystal structures of the *cis* propyl (**16a**) and of the *trans* benzyl derivative (**12b**), see *Figures 3* and *4*; together with the characteristic nmr spectra in the two series this gives an unambiguous assignment to all compounds (**12a-17a**) and (**12b-17b**) isolated.

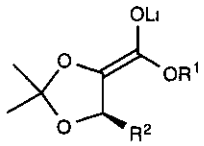
By the structure determination of the alkylation products obtained from the phosphono ester (**11**) we have established a *very* surprizing fact: the reversal of the stereochemical outcome of these alkylations on going from the more reactive electrophiles (BnBr, MeI, AllylBr) to the less reactive ones (EtI, PrI, BuI). The highest selectivity for the expected attack *trans* to the bulky *t*-butyl group was observed with MeI (→ **13a** + **13b**, ratio 3.8 : 1). With benzyl and allyl bromide the selectivity decreased and with iodoethane it reversed (→ **15a** + **15b**, ratio 1 : 17); finally we did not detect any of the expected product with iodopropane and -butane: only the *trans* isomers (**16b**) and (**17b**), resulting from attack on the *t*-butyl substituted face of the heterocyclic ring, were formed!

While we and others have encountered *cis*-selectivity of reactions of enolate and iminium ion intermediates derived from five-ring heterocycles (see the discussion in a review article[31] and *Scheme 7*), and while reversals of the stereochemical course of reactions involving enolates and *Michael* acceptors of cyclic acetal structures upon change of the chemical nature of the reagent (alkyl halide *vs.* carbonyl compound[36] or alkyl cuprate *vs.* benzyl cuprate[37]) have been observed before, we are not aware of a precedent for the results shown in *Scheme 6*. We may assume that at least the reactions with iodo methane, ethane, propane and butane, occuring at temperatures below -20 °C in the non-polar solvent THF, take place by an S_N2 mechanism, and we do not see how and why the more reactive iodo methane should approach preferentlially from the one face and the less reactive higher iodoalkanes almost exclusively from the other face of the trigonal nucleophilic center.

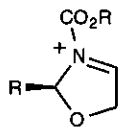
Scheme 7.



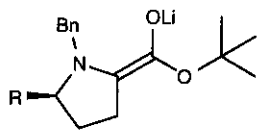
cis-attack[36] (4:1 to 50:1)



cis-attack in alkylation[36,38] (2:1 to 50:1)
trans-attack in carbonyl addition[36] (4:1)



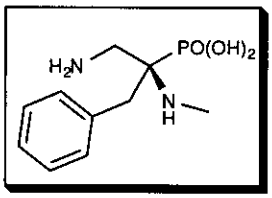
cis-attack by nucleophiles[33,39] (4:1 to 9:1)



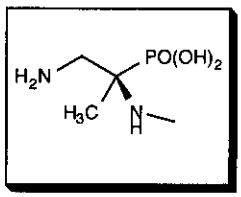
cis-attack[40,41] (8:1)

The diastereoisomerically pure heterocyclic phosphono esters (**12a**, **13a**, **15b**) and (**17b**) were readily hydrolyzed in refluxing 6N HCl to the corresponding diaminophosphonic acid hydrochloride salts. Purification by ion-exchange chromatography (*Dowex 50 X 8*) afforded the free 1-amino-2-methylamino-alkane-2-phosphonic acids (**18-21**) (70-82% yield) (*Scheme 8*).

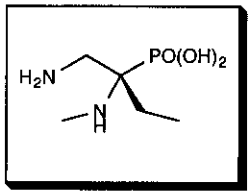
Scheme 8.



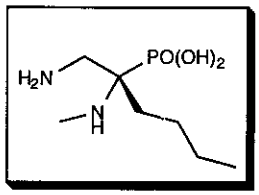
18 (from **12a**)



19 (from **13a**)



20 (from **15b**)



21 (from **17b**)

EXPERIMENTAL PART

Melting points were determined on a *Büchi-510* apparatus in open capillary tubes, and are uncorrected. Infrared spectra were recorded on a *Perkin-Elmer FT-IR 1600* spectrophotometer. ^{1}H- and ^{13}C-Nmr spectra were recorded in *Varian-Gemini-200* spectrometers, in $CDCl_3$ or DMSO-d_6 solution with tetramethylsilane (TMS) as an internal standard. Chemical shifts are given in δ values (ppm) and coupling constants J are given in Hz. Optical rotations $[\alpha]_D$ were measured at room temperature in a *Perkin-Elmer 241* polarimeter, in 1 dm cells; concentration c in g/100 ml. THF was initially distilled over KOH and then heated to reflux over Na/benzophenone (under argon) until the blue color of the benzophenone ketyl persisted; at this point the THF was distilled and handled by means of syringes and cannulae. The BuLi employed (*ca.* 1.6 M in hexane) was titrated prior to its use. Tlc: *Merck-DC-F254* plates; detection by uv light. Flash column chromatography: *Fluka silica gel 60 40-63 mm*, and a pressure of 0.2-0.6 bar. Microanalyses were performed by the microanalytical laboratories at ETH-Zürich.

General Procedure for the Alkylation of the Phosphono ester (**1**) (G.P.1). To a solution of 300 mg (0.824 mmol) phosphono ester (**1**) in 8 ml THF, 0.85 ml of 1M LiBr in THF were added. The mixture was cooled to -78 °C and 0.127 ml (0.85 mmol) DBU (1,8-Diazabicyclo[5.4.0]undec-7-en) were added. The resulting suspension was stirred at -78 °C. After 30 min 4 equivalents of the electrophile were added. The reaction mixture was allowed to warm to -20 °C within 4 h (the conversion was followed by tlc). The reaction was quenched by the addition of saturated NH_4Cl solution and extracted with four portions of Et_2O. The combined etheral extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated in a rotatory evaporator.

t-*Butyl (2R,5S)-2-t-butyl-5-dimethoxyphosphoryl-3,5-dimethyl-4-oxo-1-imidazolidine-1-carboxylate* (**3**). Alkylation according to G.P.1 with 300 mg (0.824 mmol) phosphono ester (**1**) in 8 ml THF, 0.85 ml of the LiBr solution and 0.127 ml (0.85 mmol) DBU. After 30 min 0.213 ml (3.296 mmol) iodomethane were added. After work up the crude product was purified by flash chromatography (ether) giving 259 mg (83%) of the diastereoisomerically pure compound (**3**). mp 122 °C. $[\alpha]_D$ = +69.3° (*c* = 1.0, $CHCl_3$). Ir ($CHCl_3$): 3000*s*, 2980*w*, 2960*w*, 2850*w*, 1605*s*, 1480*m*, 1455*m*, 1400*s*, 1370*s*, 1355*s*, 1305*m*, 1260*s*, 1160*s*, 1110*w*, 1060*s*, 1040*s*, 985*w*, 910*w*, 865*m*, 850*m*, 835*w*. ^{1}H-Nmr (300 MHz, $CDCl_3$): 1.09 (*s*, *t*-butyl); 1.51 (*s*, *t*-butyl); 1.80 (*d*, *J* = 14.3, CH_3-C(5)); 3.03, 3.81, 3.86 (3*s*, CH_3-N(3), rotamers); 3.83 (*d*, *J* = 10.8, $2CH_3O$); 5.10 (*d*, *J* = 6.7, H-C(2)). ^{13}C-Nmr (75 MHz, $CDCl_3$): 26.98 (CH_3); 28.20 (CH_3); 31.41 (CH_3); 38.16 (C); 53.54 (CH_3); 53.61 (CH_3); 64.61 (*d*, *J* = 156.8, (C-P)); 81.07 (CH); 81.77 (C); 169.34 (C). FAB-ms: 379.2 (14.39), 323.1 (40.95), 321.1 (30.37), 277.1 (10.10), 222.1 (14.21), 221.1 (100), 169.2 (46.38), 113.0 (10.89), 111.0 (15.69), 56.9 (46.55). Anal. Calcd for $C_{16}H_{31}N_2O_6P$: C 50.79, H 8.26, N 7.40. Found C 51.06, H 8.04, N 7.40.

t-*Butyl (2R,5S)-2-t-butyl-5-dimethoxyphosphoryl-5-ethyl-3-methyl-4-oxo-1-imidazolidine-1-carboxylate* (**4**). Alkylation according to G.P.1 with 2 g (5.49 mmol) phosphono ester (**1**) in 30 ml THF, 5.6 ml of the LiBr solution and 0.837 ml (5.60 mmol) DBU. After 30 min 3.54 ml (43.92 mmol) ethyl iodide were added. After work up the crude product was purified by flash chromatography (ethyl acetate/hexane, 10:1) giving 1.552 g (72%) of the diastereoisomerically pure compound (**4**). mp 159 °C. $[\alpha]_D$ = +78.5° (*c* = 1.235, $CHCl_3$). Ir ($CHCl_3$): 2900*m*, 2870*m*, 1655*s*, 1430*w*, 1405*w*, 1355*w*, 1320*m*, 1310*m*, 1255*m*, 1205*m*, 1010*m*, 985*m*, 900*w*, 805*w*, 785*w*. ^{1}H-Nmr (300 MHz, DMSO-d_6, 100 °C): 0.50 (*t*, *J* = 7.3, CH_2-CH_3); 1.03 (*s*, *t*-butyl); 1.45 (*s*, *t*-butyl); 1.90-2.10 (*m*, C*H*-CH_3); 2.50-2.80 (*m*, C*H*-CH_3); 2.92 (*s*, CH_3-N); 3.68 (*d*, *J* = 10.8, $2CH_3O$); 5.01 (d, J = 8.0, H-C(2)). ^{13}C-Nmr (75 MHz, DMSO-d_6) : 6.73, 6.90 (CH_3, rotamers); 26.42, 26.71 (CH_2, rotamers); 27.29 (CH_3); 27.56 (CH_3); 30.53 (CH_3); 37.78 (C); 53.02 (CH_3); 53.12 (CH_3); 68.37 (*d*, *J* = 164.7, (C-P)); 80.41, 80.64 (CH, rotamers); 80.77 (C); 167.06 (C). FAB-ms: 393.2 (17.45), 337.1 (48.09), 335.1 (12.59), 236.1 (10.66), 235.1 (100), 183.2 (22.50), 56.9 (42.91). Anal. Calcd for $C_{17}H_{33}N_2O_6P$: C 52.03, H 8.48, N 7.14. Found C 52.57, H 8.24, N 7.10.

t-*Butyl (2R,5S)-2-t-butyl-5-dimethoxyphosphoryl-5-butyl-3-methyl-4-oxo-1-imidazolidine-1-carboxylate* (**5**). Alkylation according to G.P.1 with 0.5 g (1.37 mmol) phosphono ester (**1**) in 8 ml THF, 1.5 ml of the LiBr solution and 0.224 ml (1.50 mmol) DBU. After 30 min 1.37 ml (12.00 mmol) butyl iodide were added. After

work up the crude product was purified by flash chromatography (ethyl acetate/hexane, 10:1) giving 440 mg (77%) of the diastereoisomerically pure compound (**5**). mp 95-96 °C. $[\alpha]_D$ = +56.1° (*c* = 1.05, $CHCl_3$). Ir ($CHCl_3$): 3000*w*, 2950*s*, 2925*m*, 2870*w*, 1700*s*, 1480*w*, 1470*w*, 1455*w*, 1400*m*, 1370*s*, 1355*m*, 1310*m*, 1060*m*, 1040*s*, 850*w*, 835*m*. ^{1}H-Nmr (300 MHz, DMSO-d_6, 100 °C): 0.70-0.90 (*m*, CH_2-CH_3); 0.82 (*t*, *J* = 7.3, CH_3-Butyl); 1.03 (*s*, *t*-butyl); 1.19-1.27 (*m*, CH_2-CH_2CH_3); 1.45 (*s*, *t*-butyl); 1.90-2.00 (*m*, CH-$CH_2CH_2CH_3$); 2.40-2.50 (*m*, CH-$CH_2CH_2CH_3$); 2.91, 2.92 (2*s*, CH_3-N, rotamers); 3.68 (*d*, *J* = 10.8, CH_3O); 3.684 (*d*, *J* = 10.7, CH_3O); 4.99 (*d*, *J* = 8.0, H-C(2)). ^{13}C-Nmr (75 MHz, DMSO-d_6, 100 °C): 13.59 (CH_3); 21.72 (CH_2); 24.34 (CH_2); 24.51 (CH_2); 26.99 (CH_3); 27.77 (CH_3); 30.62 (CH_3); 37.89 (C); 52.98, 53.06 (CH_3, rotamers); 53.15 (CH_3); 68.20 (*d*, *J* = 163.3, (C-P)); 80.90 (CH); 81.01 (C); 153.31 (C); 167.45 (C). FAB-ms: 364.9 (6.20), 263.0 (46.84), 211.1 (18.38), 110.9 (5.33), 56.8 (100). Anal. Calcd for $C_{19}H_{37}N_2O_6P$: C 54.27, H 8.87, N 6.66. Found C 53.98, H 9.11, N 6.71.

t-*Butyl (2*R,*5*S*)-5-allyl-2-*t*-butyl-5-dimethoxyphosphoryl-3-methyl-4-oxo-1-imidazolidine-1-carboxylate* (**6**). Alkylation according to G.P.1 with 1.0 g (2.74 mmol) phosphono ester (**1**) in 15 ml THF, 3.0 ml of the LiBr solution and 0.448 ml (3.00 mmol) DBU. After 30 min 1.85 ml (21.92 mmol) allyl bromide were added. After work up the crude product was purified by flash chromatography (ethyl acetate/hexane, 10:1) giving 818 mg (74%) of the diastereoisomerically pure compound (**6**). mp 169 °C. $[\alpha]_D$ = +52.8° (*c* = 1.0, $CHCl_3$). Ir ($CHCl_3$): 3025*m*, 3000*w*, 2975*w*, 1715*s*, 1490*w*, 1410*m*, 1380*m*, 1365*m*, 1305*w*, 1135*w*, 1075*m*, 1050*m*, 940*w*, 900*w*, 860*w*, 840*w*. ^{1}H-Nmr (300 MHz, DMSO-d_6, 100 °C): 1.01, 1.02 (2*s*, *t*-butyl, rotamers); 1.44, 1.45 (2*s*, *t*-butyl, rotamers); 2.63-2.71 (*m*, CH-$CHCH_2$); 2.89 (*s*, CH_3-N); 3.35-3.40 (*m*, CH-$CHCH_2$); 3.69 (*d*, *J* = 10.9, CH_3O); 3.70 (*d*, *J* = 10.8, CH_3O); 4.91 (*d*, *J* = 7.8, H-C(2)); 5.05 (*d*, *J* = 7.1, CH_2CH=C*H*); 5.09 (s, CH_2CH=C*H*); 5.20-5.23 (m, CH_2C*H*=CH2). ^{13}C-Nmr (75 MHz, DMSO-d_6, 100 °C): 29.49 (CH_3); 27.30 (CH_3); 30.21 (CH_3); 37.42 (C); 52.62 (CH_3); 52.73 (CH_3); 67.36 (*d*, *J* = 165.5, (C-P)); 80.60 (CH, C); 119.97 (CH_2); 129.89 (CH); 130.07 (CH_2); 166.66 (C). FAB-ms: 405.1 (20.27), 350.1 (13.15), 349.1 (59.66), 347.0 (26.47), 248.1 (19.30), 247.0 (100), 207.0 (17.75), 195.1 (47.72), 139.1 (15.62), 111.0 (13.42), 56.9 (59.41). Anal. Calcd for $C_{18}H_{33}N_2O_6P$: C 53.46, H 8.22, N 6.93. Found C 53.88, H 7.88, N 6.93.

t-*Butyl (2*R,*5*S*)-5-benzyl-2-*t*-butyl-5-dimethoxyphosphoryl-3-methyl-4-oxo-1-imidazolidine-1-carboxylate* (**7**). Alkylation according to G.P.1 with 1.0 g (2.74 mmol) phosphono ester (**1**) in 15 ml THF, 3.0 ml of the LiBr solution and 0.448 ml (3.00 mmol) DBU. After 30 min 2.60 ml (21.92 mmol) benzyl bromide were added. After work up the crude product was purified by flash chromatography (ethyl acetate/hexane, 8:1) giving 970 mg (78%) of the diastereoisomerically pure compound (**7**). mp 69 °C. $[\alpha]_D$ = +8.1° (*c* = 1.045, $CHCl_3$). Ir ($CHCl_3$): 2950*s*, 2910*s*, 2875*w*, 2800*w*, 1685*s*, 1580*w*, 1475*w*, 1460*m*, 1435*m*, 1390*m*, 1350*s*, 1280*m*, 1145*s*, 1110*s*, 1045*s*, 1020*s*, 975*m*, 930*w*, 865*w*, 830*m*, 815*m*. ^{1}H-Nmr (300 MHz, DMSO-d_6, 100 °C): 0.96 (*s*, *t*-butyl); 1.47 (*s*, *t*-butyl); 2.60 (*s*, CH_3-N); 3.10-3.30 (*dd*, J_1 = 14.1, J_2 = 13.9, CH-Phenyl); 3.77 (*d*, *J* = 10.8, $2CH_3O$); 3.80-4.00 (*m*, CH-Phenyl, rotamers); 4.35 (*d*, *J* = 7.8, H-C(2)); 7.00-7.04 (*m*, aromat.); 7.18-7.23 (*m*, aromat.). ^{13}C-Nmr (75 MHz, DMSO-d_6): 26.71, 26.98, 27.64 (CH_3, rotamers); 30.69 (CH_3); 36.42, 37.83 (CH_2, rotamers); 53.20, 53.29 (CH_3, rotamers); 53.64 (CH_3); 68.77 (*d*, *J* = 162.0, (C-P)); 80.41 (CH);

81.11, 81.35 (C, rotamers); 127.11 (CH); 127.85 (CH); 129.56, 129.98 (CH, rotamers); 133.99, 134.18 (C, rotamers); 151.78, 153.12 (C, rotamers); 166.50 (C). FAB-ms: 455.1 (12.52), 400.1 (17.31), 399.1 (50.35), 397.1 (21.35), 298.1 (27.22), 297.1 (100), 246.2 (13.32), 245.1 (43.79), 207.1 (22.86), 189.1 (25.88), 188.1 (11.48), 187.1 (10.65), 111.0 (21.54), 100.1 (10.66), 91.0 (27.08), 56.9 (71.25). Anal. Calcd for $C_{22}H_{35}N_2O_6P$: C 58.14, H 7.76, N 6.16. Found C 58.33, H 7.50, N 6.16.

General Procedure for Isolation of the Free Aminophosphonic Acids (G.P.2). The ion-exchange resin (*Dowex 50 X 8*, 20-50 mesh) was activated with 1N HCl and washed with EtOH and H_2O until neutral. The amino acid was put on the column as its hydrochloride salt and was eluted with 1% aq. NH_3 solution. Ninhydrin-positive fractions were combined and concentrated *in vacuo*.

(S)-2-Amino-1-methylaminoethane-2-phosphonic acid (**8**). A suspension of 0.6 g (1.644 mmol) phosphono ester (**1**) and 40.5 mg (1.74 mmol) $LiBH_4$ in 7.5 ml THF was stirred at room temperature under argon for 30 min. The suspension was heated to reflux and 0.42 ml (0.42 mmol) of a 1M solution of $LiBH(Et)_3$ in THF (*Aldrich*) were added and stirring was continued for 3 h at refluxing temperature. After evaporating of the solvent, the mixture was flash chromatographed (ethanol/ethyl acetate, 4:1). The resulting colorless foam was dissolved in 4 ml 3N HCl and heated to reflux for 3 h. The solvent was removed under reduced pressure. The free phosphono amino acid (**8**) was isolated according to G.P.2 yielding 133 mg (53%) of the acid **8**. For analytical purposes the acid was recrystallised from MeOH/H_2O. mp >250 °C.$[\alpha]_D$ = +3.4° (*c* = 1.1, 1N HCl). Ir (KBr): 3425*s*, 3400-2500*s*, 1620*s*, 1570*s*, 1535*m*, 1465*m*, 1340*w*, 1270*m*, 1215*w*, 1200-1000*s*, 1000*w*, 990*w*, 975*s*, 760*s*, 580*s*, 550*s*, 505*m*, 495*m*, 470*m*, 415*m*. ^{1}H-Nmr (300 MHz, 20% DCl): 2.70 (*s*, CH_3-N); 3.20-3.50 (*m*, CH_2-C(1)); 3.50-3.60 (*m*, H-C(2)). ^{13}C-Nmr (75 MHz, 20% DCl): 36.41 (CH_3); 47.65 (*d*, *J* = 137.3, CH); 50.04 (CH_2). FAB-ms : 309.1 (15.97), 277.1 (22.87), 186.1 (11.00), 185.1 (100), 155.0 (37.10), 93.0 (94.89), 75.0 (32.74), 56.9 (22.49).

(R)-2-Amino-1-methylaminoethane-2-phosphonic acid (*ent*-**8**). $[\alpha]_D$ = -4.3° (*c* = 1.15, 1N HCl)

(S)-2-Amino-1-methylaminopropane-2-phosphonic acid (**9**). A suspension of 0.6 g (1.587 mmol) methylated phosphono ester (**3**) and 38.1 mg (1.638 mmol) $LiBH_4$ in 10 ml THF was stirred at room temperature under argon for 30 min. The suspension was heated to reflux and 0.397 ml (0.397 mmol) of 1M $LiBH(Et)_3$ in THF (*Aldrich*) were added and stirring was continued for 3 h at refluxing temperature. After evaporation of the solvent, the mixture was flash chromatographed (ethanol/ethyl acetate, 4:1). The resulting colorless foam (576 mg) was dissolved in 10 ml 6N HCl and heated to reflux for 5 h. The solvent was removed under reduced pressure. The free phosphono amino acid (**9**) was isolated according to G.P.2 yielding 115 mg (44%) of the acid (**9**). For analytical purposes the diamino acid (**9**) was transformed to its hydrochloride salt and recrystallised from MeOH/H_2O. mp >250 °C. $[\alpha]_D$ = -2.7° (*c* = 2.54, 1N HCl). Ir (KBr): 3520*s*, 3500-2000*s*, 2050*w*, 1615*m*, 1545*m*, 1460*m*, 1320*m*, 1160*m*, 1095*w*, 1045*w*, 1010*w*, 940*s*, 830*w*, 785*s*, 700*s*, 550*s*, 500*m*. ^{1}H-Nmr (300 MHz, D_2O): 1.58 (*d*, *J* = 12.6, CH_3-C(1)); 2.84 (*s*, CH_3-N); 3.30-3.50 (*m*, CH_2-C(1)). ^{13}C-Nmr (75 MHz, D_2O): 20.62 (CH_3); 37.16 (CH_3); 54.52 (*d*, *J* = 139.1, C). FAB-ms: 505.2 (14.08), 337.1

(55.49), 169.1 (100), 93.0 (15.32), 87.0 (61.52), 56.9 (18.39). Anal. Calcd for $C_4H_{13}N_2O_3P \cdot HCl \cdot 1/2H_2O$ (213.6): C 22.49, H 7.08, N 13.11. Found C 22.76, H 7.20, N 13.25.

t-*Butyl (2*R,*5*R)*-5-acetoxy-2-*t*-butyl-3-methyl-1,3-imidazolidine-1-carboxylate* (**10**). A solution of 3.60 g (13.95 mmol) hydroxyderivative (**2**), 3.59 ml (20.93 mmol) *i*-Pr_2NEt (*Hünig*-Base), 1.97 ml (20.93 mmol) $(CH_3CO)_2O$ and a catalytic amount of DMAP in 30 ml CH_2Cl_2 was stirred for 16 h at r.t. The solvent was removed *in vacuo* and the resulting oil was purified by flash chromatography (ether/pentane, 1:2) yielding 3.82 g (91%) of the acetoxy compound (**10**) as a colorless oil. $[\alpha]_D$ = +5.0° (*c* = 1.0, $CHCl_3$). Ir ($CHCl_3$): 2980, 2870, 2800, 1760, 1700, 1480, 1460, 1370, 1340, 1320, 1170, 1140, 1120, 1010, 970, 890, 860. ^{1}H-Nmr (300 MHz, $CDCl_3$): 0.97 (*s*, *t*-butyl); 1.47 (*s*, *t*-butyl); 2.06 (*s*, CH_3O); 2.42 (*s*, CH_3-N); 3.08-3.14 (*dd*, J_1 = 5.3, J_2 = 13.6, H-C(4)); 3.20-3.23 (*dd*, J_2= 13.5, J_3 = 7.0, H-C(4)); 4.19 (*s*, H-C(2)); 6.51-6.56 (*dd*, J_1= 5.3, J_3 = 7.0, H-C(5)). ^{13}C-Nmr (75 MHz, $CDCl_3$): 21.13 (CH_3); 26.64 (CH_3); 28.20 (CH_3); 37.64 (C); 47.64 (CH_3); 61.77 (CH_2); 80.93 (C); 83.51 (CH); 90.99 (CH); 154.82 (C); 170.31 (C). Ms: 301 (5.5), 243 (64.7), 241 (67.7), 227 (35.8), 187 (52.8), 185 (53.4), 141 (55.5), 125 (38.7), 83 (100.0), 57 (78.4), 43 (56.9), 41 (59.5), 29 (48.6), 18 (17.9) Anal. Calcd for $C_{15}H_{28}N_2O_4$: C 58.98, H 9.39, N 9.33. Found C 59.89, H 9.58, N 9.22.

t-*Butyl (2*R,*4*R)*- and (2*R,*4*S)*-2-*t*-butyl-4-dimethoxyphosphoryl-3-methyl-1,3-imidazolidine-1-carboxylate* (**11**). A solution of 2.0 g (6.66 mmol) acetoxy derivative (**10**) in 8 ml (66 mmol) $P(OMe)_3$ was heated to reflux for 24 h. The solvent was evaporated *in vacuo* to yield a clear oil. The two epimers formed were separated by flash column chromatography (ethyl acetate/ hexane, 1:1) yielding 848 mg (36%) of **11a** (first eluted isomer) as a colorless oil and 736 mg (32%) of **11b** as a colorless solid. The configuration of the two isomers was not determined.

Isomer (**11a**): $[\alpha]_D$ = -14.9° (*c* = 1.0, $CHCl_3$). Ir ($CHCl_3$): 2972*s*, 2870*w*, 1693*s*, 1500*m*, 1456*m*, 1394*s*, 1368*s*, 1321*m*, 1164*s*, 1125*w*, 1112*w*, 1039*s*, 904*m*.^{1}H-Nmr (300 MHz, DMSO-d_6, 100 °C): 0.83, 0.88, 0.94 (*t*-butyl, rotamers); 1.41, 1.43, 1.44 (*t*-butyl, rotamers); 2.53 (*s*, CH_3-N); 2.85-2.91 (*m*, H-C(5)); 3.16-3.20 (*m*, H-C(5)); 3.70 (*d*, *J* = 10.4, CH_3O); 3.71 (*d*, *J* = 10.3, CH_3O); 4.04, 4.08 (2*s*, H-C(2), rotamers); 4.10-4.14 (m, H-C(4)). ^{13}C-Nmr (75 MHz, DMSO-d_6): 25.38, 25.57, 25.89 (CH_3, rotamers); 27.68, 27.84, 28.07 (CH_3, rotamers); 38.15 (C); 45.36 (CH_3); 46.94 (CH_2); 52.44, 52.53 (CH_3, rotamers); 52.96, 53.05 (CH_3, rotamers); 61.29 (*d*, *J* = 174.7, CH-P); 79.58 (C); 87.91, 87.73 (CH, rotamers); 153.83 (C). Ms: 293.1 (16.89), 237.0 (28.17), 194.1 (6.87), 193.0 (100.00), 84.0 (5.33), 83.0 (94.36), 57.0 (38.80), 42.0 (10.23), 41.0 (15.62), 29.0 (9.08).

Isomer (**11b**): mp 44 °C. $[\alpha]_D$ = -21.7° (*c* = 1.5, $CHCl_3$). Ir ($CHCl_3$): 3007*s*, 2978*s*, 1693*s*, 1463*w*, 1393*s*, 1365*m*, 1310*w*, 1166*s*, 1108*w*, 1035*s*, 978*w*, 944*w*, 890*m*, 830*m*. ^{1}H-Nmr (300 MHz, DMSO-d_6, 100 °C): 0.86, 1.02, 1.12 (*t*-butyl, rotamers); 1.39, 1.41, 1.45 (*t*-butyl, rotamers); 3.30-3.44 (*m*, H-C(5)); 3.54-3.58 (*m*, H-C(5)); 3.67 (*d*, *J* = 10.0, 2CH_3O); 4.03-4.13 (*m*, H-C(4)); 4.15 (*s*, H-C(2)). ^{13}C-Nmr (75 MHz, DMSO-d_6): 26.65, 26.87, 26.93 (CH_3, rotamers); 27.87, 28.08 (CH_3, rotamers); 46.41 (CH_2); 51.86 (CH_3); 51.96, 52.11 (CH_3, rotamers); 57.81 (*d*, *J* = 132.9, HC-P); 78.98 (C); 85.78 (CH); 154.28 (C). Ms: 293.2 (27.03), 277.2 (10.81), 237.1 (40.91), 193.1 (100.00), 127.1 (7.10), 83.1 (84.83), 57.1 (23.73), 41.0 (7.38). Anal.

Calcd for $C_{15}H_{31}N_2O_5P$: C 51.42, H 8.92, N 7.99. Found C 51.62, H 8.62, N 7.82.

General Procedure for the Alkylation for the Phosphono ester (**11**) (G.P.3). A solution of 315 mg phosphono ester (**11**) in 2 ml THF was cooled to - 78 °C. A precooled solution (-78 °C) of 0.99 mmol LTMP in 2 ml THF (prepared by adding 0.99 mmol of a *t*-BuLi-solution to 0.99 mmol TMP in 2 ml THF at -78 °C; the LTMP solution was stirred for 30 min at -78 °C before use) was slowly added. The yellow solution was stirred for 30 min and 0.99 mmol BuLi (solution in hexane) were slowly added and stirring was continued for additional 30 min at -78 °C. Two equivalents of the electrophile were added and the reaction mixture was allowed to warm to -20 °C within 6 h (the raction was followed by tlc). Work up according to G.P.1.

t-*Butyl* (2R,*4*R)- *and* (2R,*4S*)-*4-benzyl-2*-t-*butyl-4-dimethoxyphosphoryl-3-methyl-1,3-imidazolidine-1-carboxylate* (**12a**, **12b**). Alkylation according to G.P.3 with 227 mg (0.648 mmol) phosphono ester (**11**) in 2 ml THF, 0.713 mmol LTMP in 2 ml THF, 0.713 mmol BuLi and 0.30 ml (2.557 mmol) benzyl bromide. The two isomers (**12a**) and (**12b**) formed, were separated by flash column chromatography (ethyl acetate/hexane, 1:1) giving 124 mg (44%) of the isomer (**12a**) (running faster during chromatography) as a colorless solid and 50 mg (18%) of the isomer (**12b**) as a colorless solid.

(2R,*4*R)-*Isomer* (**12a**). mp 117 °C. $[\alpha]_D$ = +20.8° (*c* = 1.0, $CHCl_3$). Ir ($CHCl_3$): 2961*s*, 1689*s*, 1602w, 1487*w*, 1455*w*, 1394*s*, 1368s, 1308*m*, 1166*s*, 1127*m*, 1064*s*, 1038*s*, 972*w*, 917*w*, 865*w*, 830m. ^{1}H-Nmr (300 MHz, DMSO-d_6, 95 °C): 0.93 (*s*, *t*-butyl); 1.47 (*s*, *t*-butyl); 2.20-2.50 (*m*, C*H*-Ph, rotamers); 2.72 (*s*, CH_3-N); 3.10-3.20 (*m*, C*H*-Ph); 3.19 (*d*, *J* = 10.9, CH_3O); 3.29 (*dd*, J_{gem} =13.6, J_{HP} = 6.5, H'-C(5)); 3.74 (*d*, *J* = 10.3, CH_3O); 4.00-4.10 (*m*, H''-C(5)); 4.18 (*s*, H-C(2)); 7.15-7.40 (*m*, aromat.). ^{13}C-Nmr (75 MHz, DMSO-d_6): 26.47 (CH_3); 27.81 (CH_3); 33.19, 33.34, 33.53 (CH_2, rotamers); 37.62, 37.71 (CH_3, rotamers); 48.41, 48.80 (CH_2, rotamers); 50.13, 50.23 (CH_3, rotamers); 54.39, 54.48 (CH_3, rotamers); 67.28, 67.71 (2*d*, *J* = 173.1, C-P, rotamers); 79.80, 79.97 (C, rotamers); 85.10, 85.27, 85.94, 86.13 (CH, rotamers); 126.26, 126.42 (CH, rotamers); 127.54 (CH); 130.58, 130.73 (CH, rotamers), 136.11 (C), 153.79, 154.47 (C, rotamers). Ms: 441.3 (1.37), 384.2 (6.13), 383.2 (30.10), 327.2 (10.19), 284.2 (15.25), 283.2 (100.00), 273.2 (10.51), 218.1 (11.53), 217.1 (79.67), 191.1 (8.38), 174.1 (11.89), 173.1 (94.20), 91.0 (29.19), 57.1 (24.07). Anal. Calcd for $C_{22}H_{37}N_2O_5P$: C 59.98, H 8.47, N 6.36. Found C 59.84, H 8.52, N 6.06.

(2R,*4S*)-*Isomer* (**12b**). mp 126 °C. $[\alpha]_D$ = -13.8° (*c* = 0.92, $CHCl_3$). Ir ($CHCl_3$): 2977*s*, 1693*s*, 1486*w*, 1454*w*, 1397*s*, 1367*m*, 1346*w*, 1311*w*, 1168*m*, 1126*m*, 1042*s*, 917*w*, 879*w*, 824*m*. ^{1}H-Nmr (300 MHz, DMSO-d_6): 0.44, 0.47, 0.86, 0.98 (*t*-butyl, rotamers); 1.37, 1.38 (*t*-butyl, rotamers); 2.69, 2.70 (CH_3-N, rotamers); 2.70-3.15 (*m*, C*H*-Ph, H'-C(5)); 3.60-3.80 (*m*, 2CH_3O, C*H*-Ph, rotamers); 4.02, 4.06 (H-C(2), rotamers); 4.22, 4.29 (2*dd*, $J_{gem} = J_{HP}$ = 12.5, H''-C(5), rotamers); 7.10-7.30 (*m*, aromat.). ^{13}C-Nmr (75 MHz, DMSO-d_6): 26.12, 26.25 (CH_3, rotamers); 27.87, 28.07 (CH_3, rotamers); 34.70, 34.88 (CH_2, rotamers); 37.57, 37.66 (CH_3, rotamers); 48.65, 49.38 (CH_2, rotamers); 51.62, 51.70, 52.21, 52.31, 52.76 (2CH_3, rotamers); 66.73, 66.99 (2*d*, J_1 = 129.4, J_2 = 129.1, C-P, rotamers); 78.43, 78.98 (C, rotamers); 84.37, 84.89 (CH, rotamers); 126.38, 126.39 (CH, rotamers); 127.39 (CH); 131.43, 131.49 (CH, rotamers); 134.46, 134.53, 134.63 (C, rotamers); 153.89 (C). Ms: 440.3 (<1.00), 273.1 (12.57), 218.1 (13.99), 217.1 (100.00), 173.1 (29.79), 172.1 (11.44), 95.0 (4.32), 91.0 (4.66), 57.0 (4.77), 32.0 (10.10), 28.0 (42.48).

t-*Butyl (2R,4R)- and (2R,4S)-2-t-butyl-3,4-dimethyl-4-dimethoxyphosphoryl-1,3-imidazolidine-1-carboxylate* (**13a,13b**). Alkylation according to G.P.3 with 0.5 g (1.428 mmol) phosphono ester (**11**) in 4 ml THF, 1.571 mmol LTMP in 4 ml THF, 1.571 mmol BuLi and 0.352 ml (5.712 mmol) MeI. The two isomers (**13a**) and (**13b**) formed, were separated by flash column chromatography (ethyl acetate/hexane, 1:1) giving 278 mg (53%) of the isomer (**13a**) (running faster during chromatography) and 72 mg (14%) of the isomer (**13b**) both as colorless oils.

(2R,4R)-Isomer (**13a**). $[\alpha]_D$ = -18.0° (*c* = 0.96, $CHCl_3$). Ir ($CHCl_3$): 2980*s*, 2870*w*, 2811*w*, 1690*s*, 1488*m*, 1464*m*, 1393*s*, 1368*s*, 1347*w*, 1313*m*, 1164*s*, 1130*s*, 1108*w*, 1057*s*, 1035*s*, 997*w*, 916*w*, 887*m*, 916*w*, 887*m*, 865*m*, 865*w*, 830*m*. ^{1}H-Nmr (300 MHz, DMSO-d_6, 94 °C): 0.89, 0.91, 1.00 (*t*-butyl, rotamers); 1.12 (*d*, *J* = 15.1, CH_3-C(4)); 1.40, 1.42 (*t*-butyl, rotamers); 2.48 (*s*, CH_3-N); 3.32-3.38 (*m*, H-C(5)); 3.60-3.70 (*m*, H-C(5)); 3.69 (*d*, *J* = 23.4, CH_3O); 3.72 (*d*, *J* = 23.3, CH_3O); 4.07 (*s*, H-C(2)). ^{13}C-Nmr (75 MHz, DMSO-d_6): 14.22 (CH_3); 25.90, 26.19, 26.53 (CH_3, rotamers); 27.77, 28.07 (CH_3, rotamers); 38.14, 38.28 (CH_3, rotamers); 52.96 (*d*, *J* = 145.2, CH_3); 53.14, 54.16 (CH_2, rotamers); 62.04, 62.50 (*2d*, J_1 = 173.9, J_2 = 175.8, C-P, rotamers); 79.53, 79.68, 79.76 (C, rotamers); 85.66, 85.85, 86.58, 86.78 (CH, rotamers); 154.83, 154.96 (C, rotamers). Ms: 365.2 (<1.00), 307.1 (8.68), 251.0 (10.40), 207.0 (39.41), 183.0 (11.91), 141.0 (48.59), 137.0 (5.25), 130.0 (4.90), 110.0 (4.81)98.0 (6.99), 97.0 (100.00), 96.0 (16.63), 95.0 (11.28), 78.9 (24.61), 78.9 (22.47), 57.0 (33.53), 56.0 (24.75), 44.0 (13.82), 41.0 (33.65), 39.0 (11.45), 28.0 (21.89). Anal. Calcd for $C_{16}H_{33}N_2O_5P$: C 52.73, H 9.13, 7.69. Found C 52.95, H 9.30, N 7.39.

(2R,4S)-Isomer (**13b**). $[\alpha]_D$ = -29.6° (*c* = 1.01, $CHCl_3$). Ir ($CHCl_3$): 2979*s*, 2814*w*, 1692*s*, 1486*m*, 1456*m*, 1385*s*, 1367*s*, 1345*m*, 1309*m*, 1171*s*, 1149*s*, 1106*w*, 1052*s*, 1030*s*, 973*w*, 916*w*, 880*w*, 859*w*, 825*m*. 1H-Nmr (300 MHz, DMSO-d_6): 0.84, 0.86 (*t*-butyl, rotamers); 1.21, 1.22 (*2d*, *J* = 13.5, CH_3-C(4), rotamers); 1.40, 1.41 (*t*-butyl, rotamers); 2.53, 2.57 (CH_3-N, rotamers); 2.82, 2.92 (*2dd*, J_{gem} = 12.5, J_{HP} = 21.4, H'-C(5)); 3.60-3.70 (*m*, $2CH_3O$); 4.11, 4.12 (H-C(2), rotamers); 4.31, 4.39 (*2dd*, J_{gem} =J_{HP} = 12.5, H''-C(5), rotamers); ^{13}C-Nmr (75 MHz, DMSO-d_6): 19.36, 19.58 (CH_3, rotamers); 26.54, 26.67 (CH_3, rotamers); 27.77, 27.89 (CH_3, rotamers); 37.43, 38.40 (CH_3, rotamers); 51.53, 51.69, 51.79, 52.15, 52.24, 52.54, 52.63 ($2CH_3$, rotamers); 53.38, 54.25 (CH_2, rotamers); 62.95, 63.27 (*2d*, J_1 = 129.4, J_2 = 129.7, C-P, rotamers); 78.54, 79.08 (C, rotamers); 84.92, 85.44 (CH, rotamers); 153.79, 153.86 (C, rotamers). Ms: 307.1 (5.80), 251.0 (6.43), 207.0 (17.02), 152.1 (4.50), 141.0 (22.02), 137.0 (17.46), 110.0 (8.05), 108.9 (4.67), 97.0 (52.09), 96.0 (49.55), 95.0 (37.37), 80.0 (55.52), 78.9 (49.26), 68.0 (10.51), 57.0 (18.38), 56.0 (66.66), 55.0 (20.94), 54.0 (10.41), 46.9 (17.59), 44.0 (39.18), 42.0 (22.15), 41.0 (100.00), 39.0 (42.58), 31.0 (13.46).

t-*Butyl (2R,4R)- and (2R,4S)-4-allyl-2-t-butyl-4-dimethoxyphosphoryl-3-methyl-1,3-imidazolidine-1-carboxylate* (**14a, 14b**). Alkylation according to G.P.3 with 330 mg (0.943 mmol) phosphono ester (**11**) in 3 ml THF, 1.036 mmol LTMP in 3 ml THF, 1.036 mmol BuLi and 0.32 ml (3.77 mmol) allyl bromide. The two isomers (**14a**) and (**14b**) formed, were separated by flash column chromatography (ethyl acetate/hexane, 1:1) giving 122 mg (33%) of the isomer (**14a**) (running faster during chromatography) as a colorless solid and 92 mg (25%) of the isomer (**14b**) as a colorless oil.

(2R,4R)-Isomer (**14a**). mp 68 °C. $[\alpha]_D$ = -2.2° (*c* = 1.05, $CHCl_3$). Ir ($CHCl_3$): 2958*s*,1690*s*, 1464*s*, 1395*s*,

1368*m*, 1319*w*, 1258*m*, 1164*s*, 1128*s*, 1035*s*, 923*m*, 872*w*, 828*m*. ^{1}H-Nmr (300 MHz, DMSO-d_6, 93 °C): 0.90 (*s*, *t*-butyl); 1.41 (*s*, *t*-butyl); 2.30-2.50 (*m*, $CH_2CH=CH_2$); 2.59 (*s*, CH_3-N); 3.30 (*dd*, $J_{gem} = J_{HP}$ = 11.0, H'-C(5)); 3.64 (*d*, *J* =12.5, CH_3O); 3.74 (*d*, *J* =12.3, CH_3O); 3.85-3.90 (*m*, H''-C(5)); 4.10 (*s*, H-C(2)); 5.04 (*d*, J_{cis} = 10.2, $CH_2CH=CH$); 5.12 (*d*, J_{trans} = 16.1, $CH_2CH=CH$); 5.60-5.72 (*m*, $CH_2CH=CH2$). ^{13}C-Nmr (75 MHz, DMSO-d_6): 26.38 (CH_3); 27.82 (CH_3); 33.57, 33.70, 33.87, 34.02 (CH_2, rotamers); 37.39 (CH_3); 49.91, 50.27 (CH_2, rotamers); 51.60, 51.69, 51.77 (CH_3, rotamers); 53.90, 53.98 (CH_3, rotamers); 65.60, 66.00 (2*d*, *J* = 172.6, C-P, rotamers); 79.25, 79.45 (C, rotamers); 85.75, 85.92, 86.46, 86.65 (CH, rotamers); 118.51, 118.91 (CH_2, rotamers); 132.27, 132.40, 132.80, 132.91 (CH, rotamers); 153.34, 153.60 (C, rotamers). Ms: 391.1 (<1.00), 333.2 (5.85), 233.1 (28.18), 207.2 (6.76), 168.1 (9.27), 167.1 (85.66), 123.1 (100.00), 95.1 (5.90), 80.0 (18.46), 79.0 (14.72), 57.1 (38.94), 41.1 (15.93). Anal. Calcd for $C_{18}H_{35}N_2O_5P$: C 55.37, H 9.03, N 7.17. Found C 55.55, H 8.77, N 7.21.

(2R,4S)-Isomer (**14b**). $[\alpha]_D$ = -13.0° (*c* = 1.08, $CHCl_3$). Ir ($CHCl_3$): 3436*m*, 2974*s*, 2861*w*, 1703*s*, 1697*s*, 1497*s*, 1456*m*, 1395*s*, 1369*s*, 1308*m*, 1159*s*, 1031*s*, 918*w*, 877*w*, 821*m*. ^{1}H-Nmr (300 MHz, DMSO-d_6): 0.84, 0.86 (*t*-butyl, rotamers); 1.39, 1.41 (*t*-butyl, rotamers); 2.42-2.49 (m, CH_2-CH=CH_2); 2.58, 2.59 (CH_3-N, rotamers); 2.96, 3.07 (2*dd*, J_{gem} = 12.2, J_{HP} = 23.9, H'-C(5), rotamers); 3.60-3.78 (*m*, $2CH_3O$, rotamers); 4.10, 4.14 (H-C(2), rotamers); 4.21, 4.29 (2*dd*, $J_{gem} = J_{HP}$ = 12.5, H''-C(5), rotamers); 5.09, 5.12, 5.15 (CH_2-CH=CH_2, rotamers); 5.82-5.91 (*m*, CH_2-CH=CH_2, rotamers). ^{13}C-Nmr (75 MHz, DMSO-d_6): 26.80, 26.93 (CH_3, rotamers); 27.89 (CH_3); 35.89, 36.03, 36.19, 36.38 (CH_3, rotamers); 37.22, 37.31, 37.41 (CH_3, rotamers); 50.11, 50.85 (CH_2, rotamers); 51.48, 51.62, 52.06, 52.15, 52.51, 52.61 ($2CH_3$, rotamers); 66.05, 66.34 (2*d*, *J* = 129.4, C-P, rotamers); 78.53, 79.11 (C, rotamers); 84.67, 85.20 (C, rotamers); 118.31, 118.40 (CH_2, rotamers); 132.46, 132.55 (CH, rotamers), 153,96, 154.02 (C, rotamers). Ms: 391.3 (<1.00); 333.2 (13.41), 281.3 (5.81), 277.2 (15.26), 233.2 (44.72), 223.2 (13.52), 207.2 (10.11), 193.1 (11.63), 186.2 (9.54), 183.1 (61.30), 167.1 (79.15), 130.1 (23.20), 123.1 (100.00), 110.1 (14.53), 95.1 (6.23), 86.2 (28.56), 83.1 (10.34), 79.0 (13.93), 57.1 (62.37), 41.1 (22.32).

t-*Butyl (2R,4S)-2-t-butyl-4-dimethoxyphosphoryl-4-ethyl-3-methyl-1,3-imidazolidine-1-carboxylate* (**15b**). Alkylation according to G.P.3 with 1.0 g (2.857 mmol) phosphono ester (**11**) in 8 ml THF, 3.142 mmol LTMP in 8 ml THF, 3.142 mmol BuLi and 0.92 ml (11.44 mmol) EtI. The two isomers (**15a**) and (**15b**) formed, were separated by flash column chromatography (ether/pentane, 1:1) giving 34 mg (3%) of the isomer (**15a**) (running faster during chromatography) and 558 mg (52%) of the isomer (**15b**) both as colorless oils. **15b**: $[\alpha]_D$ = -10.8° (*c* = 1.0, $CHCl_3$). Ir ($CHCl_3$): 2982*s*, 1693*s*, 1463*w*, 1394*s*, 1367*m*, 1345*w*, 1307*w*, 1260*m*, 1169*s*, 1053*s*, 1032*s*, 916*w*, 878*w*, 821*m*. ^{1}H-Nmr (300 MHz, DMSO-d_6): 0.85, 0.87, 0.98 (*t*-butyl, rotamers); 0.90, 0.91 (2*t*, *J* = 7.5, CH_3-CH_2, rotamers); 1.40, 1.41 (*t*-butyl, rotamers); 1.60-1.74 (*m*, CH_3-CH_2); 2.52, 2.55 (CH_3-N, rotamers); 2.96, 3.05 (2*dd*, J_{gem} = 12.3, J_{HP} = 31.5, H'-C(5), rotamers); 3.58-3.74 (*m*, $2CH_3O$, rotamers); 4.10, 4.15 (H-C(2), rotamers); 4.22, 4.31 (2*dd*, $J_{gem} = J_{HP} \approx$ 12.6, H''-C(5), rotamers). ^{13}C-Nmr (75 MHz, DMSO-d_6): 7.58, 7.66, 7.80, 7.87 (CH_3, rotamers); 24.57, 24.76, 25.08, 25.24 (CH_2, rotamers); 25.90 (CH_3); 26.80, 26.93, 27.01 (CH_3, rotamers); 27.16, 27.90, 28.07 (CH_3, rotamers); 37.26, 37.35, 37.43 (CH_3, rotamers); 50.05, 50.66 (CH_2, rotamers); 51.32, 51.46, 51.99, 52.08, 52.46, 52.56 ($2CH_3$, rotamers); 66.75, 66.91 (2*d*, *J* = 127.3, C-P); 78.47, 79.05 (C, rotamers); 84.78, 85.30 (CH, rotamers); 153.99, 154.06 (C,

rotamers). Ms: 379.1 (<1.00), 321.2 (5.62), 221.1 (18.15), 211.2 (16.46), 193.1 (14.73), 155.1 (100.00), 111.1 (92.71), 83.1 (13.19), 80.0 (15.49), 79.0 (15.26), 57.1 (32.1), 41.0 (10.63). Anal. Calcd for $C_{17}H_{35}N_2O_5P$: C 53.95, H 9.32, N 7.40. Found C 54.07, H 9.47, N 7.32.

t-*Butyl (2*R,*4*R*)-2-*t*-butyl-4-dimethoxyphosphoryl-3-methyl-4-propyl-1,3-imidazolidine-1-carboxylate* (**16a**). To a solution of 100 mg (0.256 mmol) allyl derivative (**14a**) in 10 ml EtOH, 10 mg 10% palladium-on-charcoal were added under argon atmosphere. The argon atmosphere was replaced by hydrogen. The suspension was stirred for 14 h. The catalysts was removed by filtration over celite and the solvent removed *in vacuo*; 93 mg (93%) of **16a** as a colorless solid was obtained. mp 86 °C. $[\alpha]_D$ = -9.4° (*c* = 1.0, $CHCl_3$). Ir ($CHCl_3$): 2950*s*, 1687*s*, 1457*w*, 1394*s*, 1368*m*, 1309*w*, 1166*m*, 1130*m*, 1062*s*, 1032*s*, 929*w*, 911*w*, 855*w*, 826*m*. ^{1}H-Nmr (300 MHz, $CDCl_3$): 0.89 (*t*, *J* = 7.2, CH_3); 0.93, 0.94 (*t*-butyl, rotamers); 1.00-1.50 (*m*, $CH_2CH_2CH_3$, rotamers); 1.50-1.80 (*m*, $CH_2CH_2CH_3$); 1.46 (*s*, *t*-butyl); 2.61, 2.62 (CH_3-N, rotamers); 3.34-3.48 (*m*, H'-C(5)); 3.71, 3.72 (2*d*, *J* = 10.6, CH_3O, rotamers); 3.86, 3.88 (2*d*, *J* = 10.2, CH_3O, rotamers); 3.95, 4.08 (2*d*, *J* = 12.1, H"-C(5), rotamers); 4.08, 4.20 (2*d*, *J* = 2.7, H-C(2), rotamers). ^{13}C-Nmr (75 MHz, $CDCl_3$): 14.48, 14.62 (CH_3, rotamers); 17.63, 17.77, 18.16, 18.26 (CH_2, rotamers); 26.67, 26.76 (CH_3, rotamers); 28.37 (CH_3); 31.47, 31.60, 32.02, 32.15 (CH_2, rotamers); 37.87, 37.96 (CH_3, rotamers); 39.33, 39.43 (C, rotamers); 50.61, 50.80 (CH_2, rotamers); 51.60, 51.68 (CH_3, rotamers); 54.42, 54.50 (CH_3, rotamers); 65.91, 66.59 (2*d*, J_1 = 170.4, J_2 = 171.2, C-P, rotamers); 79.96, 80.42 (C, rotamers); 86.59, 86.78, 87.53, 87.71 (CH, rotamers). Ms: 393.3 (<1.00), 335.2 (13.42), 279.1 (15.25), 235.1 (49.68), 169.1 (43.56), 126.1 (9.51), 125.1 (100.00), 80.0 (6.58), 79.0 (6.58), 57.1 (22.06). Anal. Calcd for $C_{18}H_{37}N_2O_5P$: C 55.09, H 9.50, N 7.14. Found C 55.27, H 9.29, N 7.14.

t-*Butyl (2*R,*4*S*)-2-*t*-butyl-4-dimethoxyphosphoryl-3-methyl-4-propyl-1,3-imidazolidine-1-carboxylate* (**16b**). Alkylation according to G.P.3 with 500 mg (1.430 mmol) phosphono ester (**11**) in 5 ml THF, 1.571 mmol LTMP in 5 ml THF, 1.571 mmol BuLi and 0.56 ml (5.720 mmol) propyl iodide. Purification by flash column chromatography (ethyl acetate/hexane, 1:1) yielded 336 mg (60%) of the isomer (**16b**) as a colorless oil. $[\alpha]_D$ = -4.7° (*c* = 1.165, $CHCl_3$). Ir ($CHCl_3$): 2964*s*, 2874*m*, 1693*s*, 1486*w*, 1464*w*, 1394*s*, 1367*m*, 1345*w*, 1308*w*, 1260s, 1169*s*, 1097m, 1034*s*, 908*m*, 877*w*, 820*s*. ^{1}H-Nmr (300 MHz, $CDCl_3$): 0.91 (*s*, *t*-butyl); 0.94 (*t*, *J* = 7.3, $CH_2CH_2CH_3$, rotamers); 1.46, 1.49 (*t*-butyl, rotamers); 2.63, 2.64, 2.65, 2.66 (CH_3-N, rotamers); 3.03, 3.14 (2*dd*, J_1 =18.8, J_2 = 12.4, H'-C(5), rotamers); 3.72 (*d*, *J* = 10.6, CH_3O); 3.76, 3.79 8 (2*d*, *J* = 10.6, CH_3O, rotamers); 4.19, 4.24 (H-C(2), rotamers); 4.36, 4.45 (2*dd*, $J_1 = J_2$ = 12.5, H"-C(5)). ^{13}C-Nmr (75 MHz, $CDCl_3$): 14.75 (CH_3); 16.73, 16.80, 16.95, 17.02 (CH_2, rotamers); 27.06, 27.25 (CH_3, rotamers); 28.39, 29.72 (CH_3, rotamers); 34.80, 34.96, 35.57, 35.73 (CH_2, rotamers); 37.71, 37.88, 37.97 (CH_3, rotamers); 39.27 (C); 51.08, 51.74 (CH_2, rotamers); 51.61, 52.32, 52.42, 52.77, 52.88 ($2CH_3$, rotamers); 67.48, 67.73 (2*d*, *J* = 125.6, C-P, rotamers); 79.28, 80.07 (C, rotamers); 85.38, 85.93 (C, rotamers); 154.87, 155.19 (C, rotamers).Ms: 393.3 (<1.00), 335.2 (12.64), 279.1 (13.05), 235.1 (47.01), 225.2 (11.12), 183.0 (13.38), 170.1 (10.51), 169.1 (87.34), 126.1 (11.76), 125.1 (100.00), 95.0 (8.54), 80.0 (13.27), 79.0 (13.55), 57.1 (36.86), 41.0 (12.87).

t-*Butyl (2R,4S)-4-butyl-2-*t*-butyl-4-dimethoxyphosphoryl-3-methyl-1,3-imidazolidine-1-carboxylate* (**17b**). Alkylation according to G.P.3 with 800 mg (2.286 mmol) phosphono ester (**11**) in 6.5 ml THF, 2.515 mmol LTMP in 6.5 ml THF, 2.515 mmol BuLi and 1.64 ml (9.144 mmol) butyl iodide. Purification by flash column chromatography (ethyl acetate/hexane, 1:1) yielded 420 mg (45%) of the isomer (**17b**) as a colorless oil. $[\alpha]_D$ = -6.7° (*c* = 1.50, $CHCl_3$). Ir ($CHCl_3$): 2959*s*, 2872*m*, 1693*s*, 1486*m*, 1466*m*, 1395*s*, 1367*m*, 1345*w*, 1307w, 1169*s*, 1033*s*, 915*w*, 880*w*, 822*m*. ^{1}H-Nmr (300 MHz, DMSO-d_6): 0.85, 0.87, 0.89, 0.98 (*m*, *t*-butyl, CH_3, rotamers); 1.20-1.40 (*m*, $2CH_2$); 1.40, 1.41 (*t*-butyl, rotamers); 1.40-1.60 (*m*, CH_2); 2.55, 2.56 (CH_3-N, rotamers); 2.96, 3.05 (2*dd*, J_{gem} = 12.4, J_{HP} = 31.6, H'-C(5), rotamers); 3.30-3.70 (*m*, $2CH_3O$); 4.10, 4.14 (H-C(2), rotamers); 4.24, 4.32 (2*dd*, J_{gem} = J_{HP} = 12.4, H"-C(5), rotamers). ^{13}C-Nmr (75 MHz, DMSO-d_6): 13.79 (CH_3); 22.68 (CH_2); 24.89, 24.96 (CH_2, rotamers); 26.82, 26.93 (CH_3, rotamers); 27.91, 28.10 (CH_3, rotamers); 32.37, 32.53 (CH_2, rotamers); 37.35, 37.42 (CH_3, rotamers); 50.56, 51.23 (CH_2, rotamers); 51.35, 51.45, 52.02, 52.11, 52.51, 52.60 ($2CH_3$, rotamers); 66.53, 66.76 (2*d*, *J* = 126.1, C-P, rotamers); 78.50, 79.07 (c, rotamers); 84.78, 85.29 (CH, rotamers); 153.96, 154.05 (C, rotamers). Ms: 407.3 (<1.00), 249.2 (6.06), 249.1 (19.39), 239.12 (12.18), 184.1 (10.44), 183.1 (100.00), 140.1 (8.11), 139.1 (86.32), 95.0 (8.01), 80.0 (9.36), 57.0 (23.57). Anal. Calcd for $C_{19}H_{39}N_2O_5P$: C 56.14, H 9.67, N 6.89. Found C 55.86, H 9.57, N 6.71.

(R)-1-Amino-2-methylamino-3-phenylpropane-2-phosphonic acid (**18**). A suspension of 300 mg (0.680 mmol) phosphono ester (**12a**) in 10 ml 6N HCl was heated to reflux for 6 h. Isolation according to G.P.2 gave 109 mg (82%) of the diamino acid (**18**) as a colorless solid. For analytical purposes the acid (**18**) was recrystallized from EtOH/ether. mp 216-217 °C. $[\alpha]_D$ = +21.3° (*c* = 0.94, H_2O). Ir (KBr): 3500-2000*s*, *br.*, 1590*m*, 1497*w*, 1456*w*, 1087*s*, *br.*, 964*w*, 923*w*, 754*m*, 697*m*. ^{1}H-Nmr (400 MHz, D_2O): 2.88 (*s*, CH_3-N); 3.18-3.72 (*m*, CH_2Ph or CH_2-C(2)); 3.38-3.44 (*m*, CH_2Ph or CH_2-C(2)); 7.40-7.50 (*m*, aromat.). ^{13}C-Nmr (75 MHz, D_2O): 32.22 (CH_3); 38.04 (CH_2); 43.68 (CH_2); 62.79 (*d*, *J* = 121.3, C-P); 130.79 (CH); 131.88 (CH); 133.37 (CH); 135.38 (C). FAB-ms: 489.1 (20.78, $(2M+1)^+$), 255.0 (12.41), 245.1 (25.15, $(M+1)^+$), 235.1 (39.22), 219.1 (11.70), 205.1 (40.85), 185.1 (18.55), 175.1 (28.29), 173.1 (15.49), 164.1 (19.51), 163.1 (100.00), 146.1 (24.86), 132.0 (20.76), 122.0 (19.12), 115.0 (10.01), 105.0 (23.67), 74.9 (15.62), 71.9 (13.20), 56.9 (15.21).

(R)-1-Amino-2-methylaminopropane-2-phosphonic acid (**19**). A suspension of 600 mg (1.648 mmol) phosphono ester (**13a**) in 20 ml 6N HCl was heated to reflux for 6 h. Isolation according to G.P.2 gave 200 mg (72%) of the diamino acid (**19**) as a colorless solid. For analytical purposes the acid was recrystallized as its hydrochloride salt from MeOH. mp 219-232 °C. $[\alpha]_D$ = -1.1° (*c* = 1.04, H_2O). Ir. (KBr): 3500-2000*s*, *br.*, 1215*s*, 1074*s*, 928*s*, 660*s*. ^{1}H-Nmr (300 MHz, D_2O): 1.46 (*d*, *J* = 12.7, CH3-C(1)); 2.71 (*s*, CH_3-N); 3.20-3.50 (*m*, CH_2-C(1)). ^{13}C-Nmr (75 MHz, D_2O): 17.77 (CH_3); 30.52 (CH_3); 43.94 (CH_2); 59.17 (*d*, *J* = 137.6, C-P). FAB-ms: 505.2 (9.61, $(3M+1)^+$), 337.1 (60.61, $(2M+1)^+$), 261.1 (30.61), 235.2 (14.41), 209.1 (13.50), 195.1 (10.63), 169.1 (93.73, $(M+1)^+$)155.1 (10.42), 149.1 (17.83), 138.0 (15.55), 110.0 (14.37), 87.0 (96.54), 74.9 (49.31), 72.9 (31.45), 56.9 (38.92).

(S)-1-Amino-2-methylaminobutane-2-phosphonic acid (**20**). A suspension of 813 mg (2.190 mmol) phosphonoester (**15b**) in 25 ml 6N HCl solution was heated to reflux for 6 h. Isolation according to G.P.2 gave 279 mg (70%) of the diamino acid (**18**) as a colorless solid. For analytical purposes the acid (**20**) was recrystallized from EtOH/ether. mp 228-230 °C. $[\alpha]_D$ = -7.5° (*c* = 1.20, H_2O). Ir (KBr): 3500-2000*s, br.*, 1620*m*, 1466*w*, 1220*w*, 1074*s, br.*, 958*s* 804*w*, 645*m*. ^{1}H-Nmr (300 MHz, D_2O): 0.89 (*t*, *J* = 7.56, CH_3); 1.60-1.80 (*m*, C*H*-CH_3); 1.90-2.10 (*m*, C*H*-CH_3); 2.70 (*s*, CH_3); 3.15, 3.20, 3.23 (CH_3-N, rotamers). ^{13}C-Nmr (75 MHz, D_2O): 8.87, 8.96 (CH_3); 23.74 (CH_2); 30.81 (CH_3); 42.36, 42.52 (CH_2); 62.70 (*d*, *J* = 122.4, C-P). FAB-ms: 364.7 (21.81, $(2M+1)^+$), 276.9 (39.74), 207.9 (44.35), 192.8 (13.24), 182.9 (27.47, $(M+1)^+$), 172.9 (24.01), 151.9 (13.60), 142.9 (34.45), 138.9 (31.61), 137.9 (14.95), 136.9 (13.15), 124.9 (12.16), 112.9 (27.20), 110.9 (20.20), 101.9 (10.50), 100.9 (100.00), 92.9 (23.12), 85.9 (22.43), 83.9 (22.65), 69.8 (32.12), 55.8 (14.45). Anal. Calcd for $C_5H_{15}N_2O_3P$: C 32.97, H 8.30, N 15.38. Found C 32.73, H 7.98, N 14.78.

(S)-1-Amino-2-methylaminohexane-2-phosphonic acid (**21**). A suspension of 440 mg (1.084 mmol) phosphono ester (**17b**) in 13 ml 6N HCl was heated to reflux for 6 h. Isolation according to G.P.2 gave 170 mg (75%) of the diamino acid (**21**) as a colorless solid. For analytical purposes the acid (**21**) was recrystallized from EtOH/ether. mp 219-221 °C. $[\alpha]_D$ = -0.3° (*c* = 0.98, H_2O). Ir (KBr): 3500-2000*s, br.*, 1618*m*, 1468*w*, 1086*s, br.*, 949*s*, 800*w*, 645*m*. ^{1}H-Nmr (300 MHz, D_2O): 0.81 (*t*, *J* = 7.1, CH_3); 1.10-1.40 (*m*, $2CH_2$); 1.59-1.71 (*m*, CH-C(2)); 1.87-1.97 (*m*, CH-C(2)); 2.69 (*s*, CH_3-N); 3.18 (*d*, *J* = 14.1, CH_2-N). ^{13}C-Nmr (75 MHz, D_2O): 15.73 (CH_3); 24.95 (CH_2); 26.53, 26.61 (CH_2); 30.40 (CH_2); 30.85 (CH_3); 43.01 (CH_2); 62.54 (*d*, *J* = 123.2, C-P). FAB-ms: 421.2 (23.25, $(2M+1)^+$), 221.1 (12.16), 211.2 (11.57, $(M+1)^+$), 201.2 (31.58), 185.2 (10.62), 171.2 (39.57), 141.2 (23.25), 139.1 (21.29), 130.1 (12.10), 129.1 (100.00), 112.1 (14.95), 98.0 (15.67), 71.0 (19.03), 55.9 (15.81).

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