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THE ASYMMETRIC SYNTHESIS OF α-SUBSTITUTED α-METHYL AND α-PHENYL PHOSPHONIC ACIDS: DESIGN, CARBANION GEOMETRY, REACTIVITY AND PREPARATIVE ASPECTS OF CHIRAL ALKYL BICYCLIC PHOSPHONAMIDES

Youssef L. Bennani† and Stephen Hanessian*

Department of Chemistry, Université de Montréal, P.O. Box 6128, Station Centre-ville, Montréal, P.Q., H3C 3J7 (Canada).

Abstract: The design, preparation, structural and spectroscopic analyses of topologically unique and enantiomerically pure alkyl phosphonamides are described. In the case of α-ethyl and α-benzyl phosphonamides, the geometry of both the secondary and tertiary carbanions was determined to be planar through deprotonation/deuteration/alkylation experiments. Stereoselective alkylations of such systems proceeded in good yields and with high diastereoselectivities. The resulting α,α-alkylated phosphonamides were hydrolyzed to give the corresponding α,α-alkyl phosphonic acids with high degrees of enantiomeric purity.

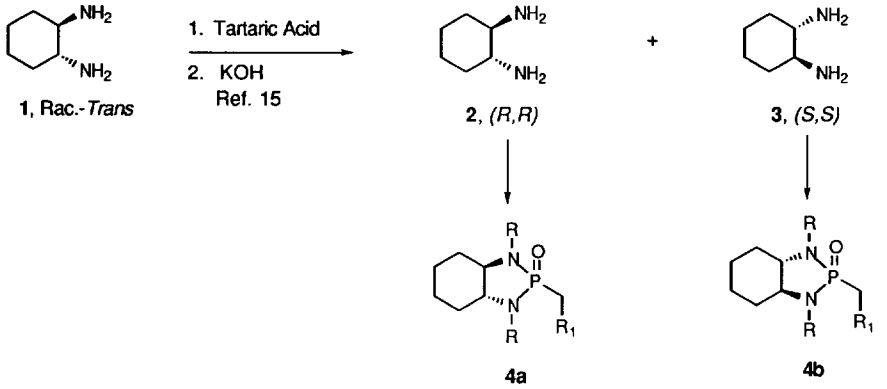
Stereoselective C–C bond formation is one of the pivotal reactions in organic synthesis. Chiral auxiliaries, used in a stoichiometric[1] or catalytic[2] amount, allow for these reactions to occur in a highly efficient and enantio- or diastereoselective manner. Applications in carbonyl chemistry are now well established and routinely used in modern synthetic schemes. Extensions to other functionalities, such as sulfonyl[3] or phosphoryl[4] have also been active areas of research. Over a decade ago, we reported our preliminary results on the design and reactivity of anions derived from topologically unique chiral bicyclic phosphonamides with applications in the asymmetric olefination of cyclohexanones[5] and in alkylations.[6] We subsequently described the asymmetric synthesis of α-alkyl, α-halo,[7] α- and β-amino-phosphonic acids,[8-10] as well as the synthesis of enantiomerically pure ethylidene, allylidene and benzylidene cyclohexanes utilizing the same phosphonamide carbanion technology.[11] 1,4-Conjugate addition reactions of related allylic phosphonamide anions to enones,[12a] sequential Michael reactions[12b] and cyclopropanations have also been highly successful.[13] Herein we report a detailed account of our studies pertaining to the design, topology, carbanion geometry, and reactivity of α-alkyl phosphonamides in conjunction with the asymmetric synthesis of α-methyl and α-phenyl α-alkyl phosphonic acids of high enantiomeric purity. Since our original disclosure,[5] other chiral cyclic phosphoryl based reagents have been described and studied in alkylation, amination, olefination, and addition reactions.[14]

† Abbott Laboratories, One Abbott Park, North Chicago, IL 60064, USA

Design and Hypothesis

Paramount in the design of our alkyl phosphonamides systems was the choice of a chiral scaffold. Our deliberations to find a readily available, easily derivatizable bidentate chiral molecule having C_2 symmetry resulted in the selection of *trans*-1,2-diaminocyclohexane **1**, (*trans*-DACH), which was easily resolved through its tartrate[5,6] to give diamines (*R,R*)-**2** or (*S,S*)-**3** in enantiomerically pure forms, Scheme 1.

Scheme 1

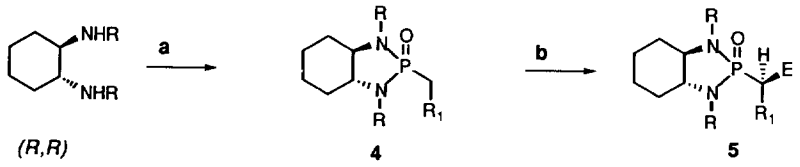


It was anticipated that the attachment of a derivative of this diamine to an alkyl phosphoryl group would result in the formation of an *enantiomerically pure* bicyclic phosphonamide of type **4a** or **4b**. The diazaphosphorinane system was expected to impart some rigidity that would dictate a number of structural, functional and reactivity features (*vide infra*). Because of the stereoelectronic requirements on the two nitrogens, it was also expected that the corresponding stabilized α-carbanions would exhibit diastereofacial bias in their reaction with electrophiles as shown for **4** in Scheme 2. It was hypothesized that, for steric and stereoelectronic reasons, the electrophile would approach the α-carbanion derived from an (*R,R*)-alkyl bicyclic phosphonamide of type A, preferentially from the "left cleft" as depicted in **5**, while phosphonamides derived from the (*S,S*)-diamine (type B) would react from the "right cleft".

Preparation and conformational analysis

Enantiomerically pure (*R,R*)-1,2-diaminocyclohexane[15] **2** was converted into its *N,N'*-dimethyl analogs of type **6** by reaction with ethyl chloroformate in the presence of sodium hydroxide, followed by LAH reduction[16] in THF (80-85% yields). The *N,N'*-diethyl analog **7** was prepared from the corresponding *N,N'*-diacetyl compound by reduction with LAH in THF also. The *N,N'*-dibenzyl analog **8** was prepared through reductive amination with benzaldehyde (Scheme 3). Although many other derivatives were prepared and screened in a variety of transformations, most of the results described herein were obtained from the (*R,R*)- and (*S,S*)-*N,N'*-dimethyl-1,2-diaminocyclohexane derivatives. The *N,N'*-dibenzyl and *N,N'*-dineopentyl analogs showed superior results in a different context.[17]

Scheme 2



a. $Cl_2P(O)CH_2R_1$; b. Base, electrophile $E^{(+)}$
R= Alkyl Groups

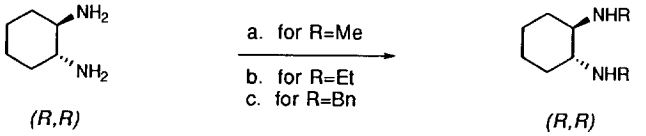
(R,R)

Favored , "left cleft"
diastereofacial approach
A

(S,S)

Favored , "right cleft"
diastereofacial approach
B

Scheme 3



(R,R)

2

(R,R)

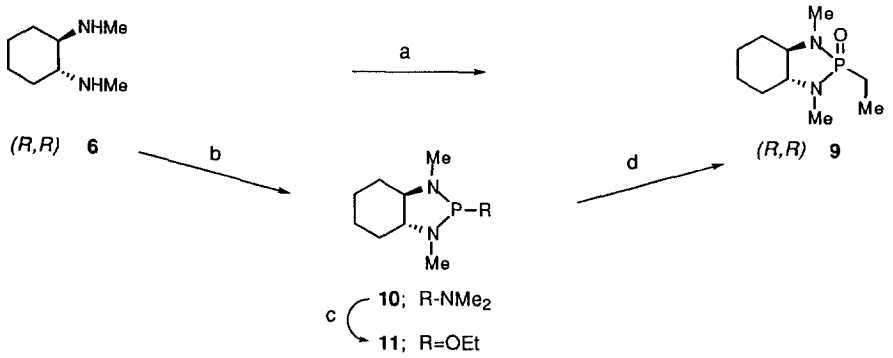
6 (R=Me)
7 (R=Et)
8 (R=Bn)

a. i.$ClCO_2Et$, NaOH, C_6H_6; ii.LAH, THF; b. i.AcO_2, MeOH; ii.LAH, THF;
c. i.PhCHO, MeOH; ii.$NaBH_4$, MeOH

Two methods for the preparation of alkyl phosphonamides were routinely used. In method A, treatment of (*R,R*)-*N,N'*-dimethyl-1,2-diaminocyclohexane **6** with ethyl phosphonic dichloride in benzene in the presence of two mole equivalents of triethylamine resulted in the formation of the corresponding bicyclic ethyl phosphonamide **9** in 70-76% isolated yields (Scheme 4).

A second method[18] consisted in heating the *N,N'*-dimethyldiamine **6** at 110°C with one mole equivalent of hexamethylphosphorus triamide to give the distillable phospholane **10**, which was further treated, in a one-pot sequence, with ethanol in benzene to give **11**. Treatment with ethyl iodide in an Arbuzov type of reaction gave the desired ethyl phosphonamide **9** in 70-75% yield (Scheme 4). Recently, Spilling and coworkers[19] reported the preparation of these same alkyl phosphonamides through the alkylation of bicyclic phosphite anions.

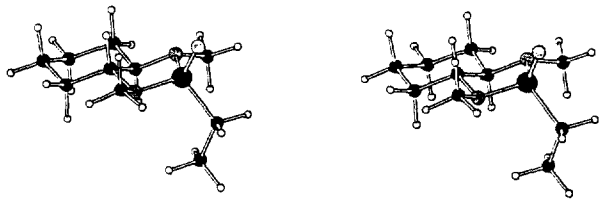
Scheme 4



a. $Cl_2P(O)Et$, Et_3N, C_6H_6 ; b. HMPT, neat, 100°C under N_2; c. EtOH, C_6H_6 , 80°C; d. EtI, C_6H_6 , 80°C

Molecular modeling experiments using MODEL (version 2.95)[20] revealed the relative minimum energy conformation shown in Figure 1 for ethyl phosphonamide **9** at 17.36 Kcal/mol. The cyclohexane ring is *trans*-fused to the 1,3-diaza-2-ethyl phosphoryl group in a chair conformation. The average of the six angles about the phosphorus atom is 129.3° indicating its tetrahedral nature.

Figure 1



Insights from ^1H NMR studies into the preferred conformations of phosphorus containing saturated five-membered heterocyclic rings such as 1,3,2-dioxaphospholanes,[21] 1,3,2-oxazaphospholanes[22] and 1,3,2-diazaphospholanes[23] and analogy to computed energies of heteroatom containing five-membered rings,[24] were consistent with a conformation close to a half-chair C_2 (as compared to C_s) for the diazaphosphoryl system.[25] Two contributing factors to the inherent rigidity of this bicyclic system are: *firstly* , the presence of heteroatoms in a five-membered ring which affects the equilibrium due to torsional and rotational energies about the atomic bonds. This introduces steric and electronic factors that create a higher rotation energy barrier, thus minimizing the pseudorotation about the ring.[26] *Secondly*, by analogy to the *trans*-perhydrindane system,[27] the presence of the cyclohexane ring held exclusively in a *trans* conformation "locks" the system in the preferred rigid conformation shown in Figure 2. This was confirmed in the case of over two dozen X-ray structures.[28] We believe that the rigidity of this system is important in dictating the levels of asymmetric induction observed *(vide infra)*.

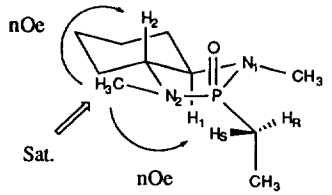
One general and consistent trend in these alkyl bicyclic phosphonamides is the presence of the *N*-alkyl groups in a *trans*-pseudo-equatorial relationship. In the case of phosphonamide **9**, the average sum of angles

obtained from molecular modeling as well as from over a dozen X-ray structures obtained in our laboratory, is ΣN_1=335° and ΣN_2=336° which implies a non-planar geometry about the nitrogen atoms. Energy calculations on various invertomers about the nitrogen atom substituents revealed that indeed the preferred conformation was that indicated in Figure 1. This non-planar geometry about the N atoms (*vide infra*) and the *trans*-pseudo-equatorial relationship between the *N*-Me groups was also studied by IR. Indeed, analysis of the IR spectrum in CCl_4 of ethyl phosphonamide **9** revealed two distinct bands at 2725 and 2685 cm^{-1} which we assigned as being Bohlmann bands.[29] These bands are characteristic of the presence of a *trans*-diaxial relation of an α-hydrogen atom to the lone pair of electrons on nitrogen. That these absorptions were not due to the stretching of *N*-CH_3 substituents was ascertained by examining the IR spectrum of the *bis*-*N*-CD_3 analog of **9** which still showed these characteristic bands along with two additional ones at 2225 and 2065 cm^{-1} for C-D stretching. The spectroscopic data, presented hereafter, are important in understanding and probing the geometry of the carbanions involved in these highly stereospecific olefination and alkylation reactions, using these enantiomerically pure chiral bicyclic alkyl phosphonamides. In the case of ethyl phosphonamide **9**, ^1H, ^{13}C and ^{31}P in $CDCl_3$, acetone$_{d\text{-}6}$, CD_2Cl_2, C_6D_6, and THF$_{d\text{-}8}$, in the absence or presence of non-chiral resolving lanthanide complexes such as Resolve-Al Pr-FOD® or Eu-FOD® at various concentrations and at temperatures ranging from –115°C to 25°C (THF$_{d\text{-}8}$), all showed the presence of one single chemical entity with no detectable signals for any invertomers or enantiomers. The ^{13}C NMR spectrum of **9** displayed two chemical shifts at 27.9 and 29.6 ppm for the two *N*-Me groups, confirming their different chemical environments. From the ^1H NMR spectrum of phosphonamide **9**, we assigned the chemical shift at 2.69 ppm to H_2 (*syn* to P=O) and that at 2.50 ppm to H_1 based on a variety of similar 1,3,2-dioxa-[30]; 1,3,2-oxaza-[31] and 1,3,2-diazaphospholanes[32] most of which have been confirmed by X-ray analysis. For H_1 and H_2 (Figure 2) the coupling pattern and coupling constants of these hydrogens at the ring junctions by two-dimensional J-Resolve technique[33] (ddd; $^3J_{H2\text{-}H1}$ =11.5, $^3J_{H2\text{-}H3a}$=9.3, $^3J_{H2\text{-}H3c}$=3.3 Hz) excluded any $^3J_{P\text{-}C\text{-}N\text{-}H2}$ coupling. This was more easily displayed in the ^1H and J-Resolve NMR's of *N,N'*-bis-trideutriomethyl analog of **9**. The calculated (from MM2 and X-ray) dihedral angle ϕ(P-H_2) was 78.6°while vicinal coupling ^3J(PNCH) value according to the Karplus rule should be close to zero.[34] These analytical data indicated the existence of a relatively rigid bicyclic core, where pseudorotation about the five-membered ring was minimized by the overall topology and inherent stereoelectronic features of such a system.

At this point, it was critical to assign an exact ^1H NMR chemical shift to each of the *N*-Me groups as well as to the P–C(H_S; H_R) protons, since this would provide valuable information regarding the sense of asymmetric induction in the various experiments detailed below. The *N*-Me groups displayed two distinct doublets at δ 2.60 and 2.56 ppm. Having assigned the further downfield chemical shift at 2.69 ppm to H_2,[30-32] irradiation of the doublet at 2.56 ppm resulted in an nOe enhancement of 5.1% at H_2 and at one of the P-CH_2 protons (Figure 2).

We assigned the doublet at 2.56 ppm to N(2)-Me. The diastereotopic P–C(H_S; H_R) protons displayed very close chemical shifts at 1.80 ppm in a 2 x ddq pattern, which was further complicated by overlapping with some of the cyclohexanyl protons. Using the J-Resolve technique, these two diastereotopic protons were distinguished and their corresponding coupling constants measured to be $^2J_{P\text{-}H}$=15.5 Hz for both. This implied their existence

Figure 2



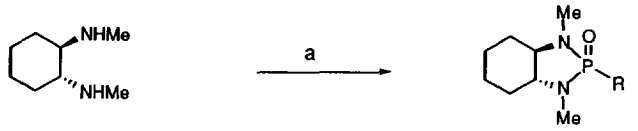
at similar angles to the phosphoryl (P=O) group[34]. The methyl group of the P-ethyl (P–CH_2-CH_3) displayed a set of two triplets at 1.04 ppm ($^3J_{P-H}$=18.5 Hz). From a combination of relative energy minimization experiments,[32] the equal coupling constants of the two diastereotopic protons H_S; and H_R and the correlation of the Karplus equation for the variation of $^3J_{P-C-C-H}$ to our system, it was concluded that, in solution, the ethyl group existed in an *anti* relationship to the phosphoryl group (Figure 2).

Stereoelectronic factors and nature of the P–N bond

The geometry about the nitrogen atoms and therefore the positioning of the *N*-alkyl groups played an important role in the degree of asymmetric induction obtained from these bicyclic phosphonamides. Three-dimensional molecular models, minimum energy considerations, and X-ray structures reflected an inherent enantiofacial bias (*vide supra*) which was most likely an important contributing factor to the observed high levels of enantioselectivity. In systems containing P(III)–N or P(V)–N groups, the P–N distance depends on the hybridization state of the nitrogen atom[35] which usually varies between 1.62 and 1.77Å. The average distance deduced from 75 X-ray structures containing the N–P(O)–N is 1.65Å.[36] As compared to P–C and P–P distances (1.82Å and 2.21Å respectively), this average P–N value is suggestive of a geometry about the nitrogen atoms that is intermediate between planar and pyramidal. Among the factors affecting the nitrogen atom to be in a planar hybridization state (sp^2) is the ability of phosphorus to attract the lone pair on nitrogen, and the back-donation of electrons from phosphorus to nitrogen in its antibonding σ^* orbital. Cowley and coworkers[37] and Huchins and coworkers[38] reported from their studies on a series of dialkylamino-phospholanes that the nitrogen hybridization varies from sp^3 to sp^2 as a function of the electron withdrawing ability of the P–substituent. This lowers the phosphorus *3d* orbital energy and facilitates an interaction of type $\pi(2p\text{-}3d)$ in the P–N bond which increases the 2s character in the nitrogen orbitals. These changes are expressed in the ^{1}H NMR spectra by the increase of $^3J_{P-N-C-H}$.

In the case of ethyl phosphonamide **9**, the two *N*-Me groups have different chemical shifts and coupling constants (ΔJ=1.6 Hz). This is certainly due to their different chemical environments and possibly to a slight difference in the sp^3-sp^2 character of the nitrogen atoms. In order to evaluate the relationship between the geometry about the nitrogen atoms and the nature of the phosphorus substituents we prepared a series of bicyclic phosphonamides and analyzed their ^{1}H NMR parameters. The chloro- **12**, phenyl **13**, and benzyloxy **14** phosponamides which were prepared in good yields from (*R,R*)-*N,N'*-dimethyl-1,2-diaminocyclohexane **2** and the corresponding phosphoryl dichlorides represent compounds having a gradation of electron withdrawing to electron donating groups on the phosphorus (Scheme 5; Table 1).

Scheme 5



(R,R)

6

a. $Cl_2P(O)R$, Et_3N, C_6H_6

(R,R)

12, R = Cl
13, R = Ph
14, R = OBn

Table 1

R	δ (N_1CH_3)	δ (N_2CH_3)	$^3J_{P-H}$ [a]	$^3J_{P-H}$ [b]	Δ^3J_{P-H} [c]	δ (H_1)[d]	δ (H_2)[d]	δ ^{31}P
C_2H_5	2.60	2.56 [e]	10.0	11.5	1.5	2.48	2.60	46.73
Cl	2.57	2.46 [h]	12.0	15.9	3.9	2.48	2.84	33.29
Ph	2.41	2.53 [f]	11.0	11.6	0.6	2.61	2.92	31.08
OBn	2.48	2.42 [g]	11.4	11.4	0	2.61	2.61	26.78

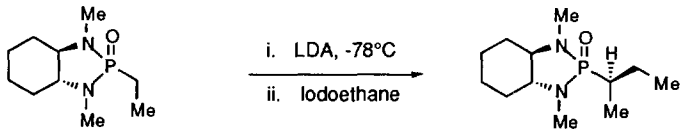
Chemical shifts assignments: ^1H and ^{31}P NMR are in d (ppm) (for ^{31}P , H_3PO_4 was used as a reference at 0 ppm): *(a)* P–N_1–C–H_3 (Hz); *(b)* P–N_2–C–H_3 (Hz); *(c)* DJ $^3J_{P-H}{}^a - {}^3J_{P-H}{}^b$ in Hz; *(d)* Based on H_2 syn to P=O; *(e)* Saturationf the doublet at 2.56 ppm induces an "nOe" effect of 5.1% on H_2 (400 MHz); *(f)* Saturation at 2.92 ppm induces an"nOe" de 5% on the doublet at 2.53 ppm (400 MHz); *(g)* The two doublets at 2.48 and 2.42 ppm can be interchanged; H_1 and H_2 have overlapping shifts, no nOe was done; *(h)* Saturation at 2.84 ppm induces an "nOe" effect of 5.2% at 2.46 ppm.

The change of the P-substituent from ethyl to phenyl to chloro induces an increase in planarity of the nitrogen atoms, which is manifested by an increase of $^3J_{P\text{-}N\text{-}C\text{-}H}$ as well as an upfield shift in ^{31}P NMR in the corresponding phosphonamides. Accordingly, it is not inconceivable that the presence of a strong electron rich group, such as a carbanion α to the phosphorus, would result in a more pyramidal hybridization of the nitrogen atoms, and to orient the *N*-Me groups in such a manner so as to create an enantiofacial bias toward an approaching electrophile.

Hybridization and reactivity of α-phosphoryl carbanions

Treatment of *(R,R)*-ethyl phosphonamide **9** with LDA in THF at -78°C followed by the addition of ethyl iodide gave the α-alkylated phosphonamide **15** in 78% yield and 89:11 diastereomeric ratio as determined by ^{31}P NMR (Scheme 6). The anticipated sense of asymmetric induction was confirmed by X-ray structure analysis.[39] As expected the opposite sense of asymmetric induction was obtained when the *(S,S)*-ethyl phosphonamide reagent was used.[39]

Scheme 6



(R,R)

9

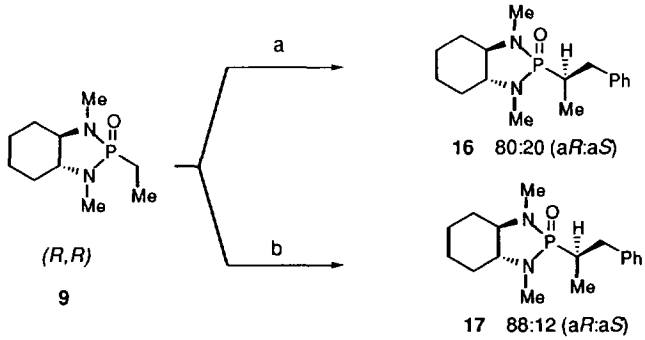
(R,R)

15

In order to rationalize and enhance the levels of diastereoselectivity observed with these chiral systems, we decided to conduct studies with the aim to determine the geometry of the carbanions involved in these bicyclic phosphonamides. Thus, a solution of phosphonamide **9** in $THF_{d\text{-}8}$ was treated with a stoichiometric amount of n-BuLi (10 M in hexanes) at –78°C and the ^1H and ^{13}C NMR spectra were recorded. Although ^1H and ^{13}C NMR spectroscopy has been extensively utilized to study carbanion geometry[40], in our case, the presence of overlapping signals made it difficult to evaluate the hybridization changes in these carbanionic systems with certainty. ^{31}P NMR was more informative with regards to the formation and stability of the α-ethyl carbanion, and it was used to study the effects of concentration and temperature on such carbanions. The formation of the carbanion with n-BuLi in $THF_{d\text{-}8}$ induced a downfield chemical shift ($\Delta\delta=\delta_{anion}-\delta_{neutral}$ = 17.1 ppm), indicative of the polarization of the phosphorus atom through a stabilizing $P^{\delta+}$–$C^{\delta-}$ interaction. While a 0.077 M carbanionic solution showed a single peak at 72.2 ppm (external H_3PO_4 as reference at 0 ppm) which was stable for over 30 min at -78°C, a 0.32 M solution showed the presence of an additional peak at 74.9 ppm. It is possible that such a peak corresponded to the formation of aggregate structures which were not identified further. In the case of the 0.32 M carbanionic solution, ^{31}P NMR spectra were recorded at various temperatures. The dramatic changes in the spectral profile of such an anionic solution obtained from -78°C to 0°C were indicative of a clear and progressive change in the nature of the species present in solution as manifested by the disappearance of the original anionic system with concomitant formation of electronically enriched phosphorus species with signals at 75.6 and 74.9 ppm. Cooling this solution to -78°C resulted in a gradual reappearance of the signal at 72.2 ppm.

In order to evaluate the stability of these carbanions, two solutions (A and B) were prepared from (*R,R*)-ethyl phosphonamide **9** (0.32 M, THF, n-BuLi) at -78°C. The solutions were stirred at -78°C for 15 min., warmed to 0°C and stirred for an additional 10 min. The carbanion present in solution A was quenched with benzyl bromide at 0°C to give the corresponding alkylated phosphonamide **16** in a 80:20 ratio of diastereomers. The carbanion present in solution B was cooled to -78°C then treated with benzyl bromide (at -78°C) to give the same alkylated phosphonamide **17** in 83% yield and 88:12 *de*, (Scheme 7). From these results we concluded that such carbanions were relatively stable towards reasonable variations in temperature, but that the extent of diastereoselectivity depended on the temperature of alkylation.

Scheme 7

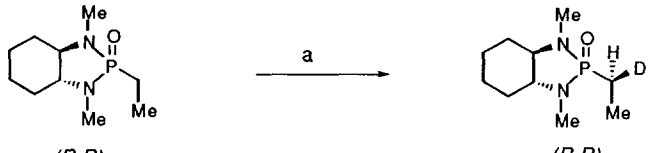


a. i.n-BuLi, -78°C–0°C; ii.BnBr, 85%; 80:20 (a*R*:a*S*)
b. i.n-BuLi, -78°C–0°C to –78°C; ii.BnBr; 85%; 88:12 (a*R*:a*S*)

Hybridization of secondary α-phosphoryl carbanions

Treatment of (*R,R*)-ethyl phosphonamide **9** at -78°C with n-BuLi in THF and quenching of the resulting carbanion with deuteromethanol gave the corresponding α-(*S*)-deutero phosphonamide **18** in near quantitative yield (≥95% deuterium content, MS, ^{1}H and ^{13}C NMR) and an α-(*S*):α-(*R*) ratio of 70:30 (Scheme 8).

Scheme 8



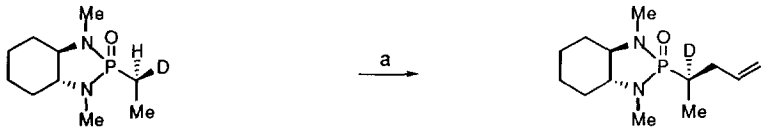
9 **18** 70:30 (a*S*:a*R*)

a. i.n-BuLi, -78°C; ii.CD_3OD (or D_2O), -78°C

The sense and degree of asymmetric induction was ascertained by ^{1}H NMR, J-Resolve technique and nOe studies. Phosphonamide **18** (α-(*S*):α-(*R*): 70:30) was treated with n-BuLi at -78°C in THF, and reacted with allyl bromide to give the corresponding α-allyl phosphonamide **19** in a α-(*R*):α-(*S*): 88:12 ratio (≥92% deuterium content and 83% yield, Scheme 9).

This result was indicative of the clear involvement of a *planar carbanion* in **18** in which the hydrogen atom was preferentially abstracted regardless of its diastereotopic orientation to give a highly deuterium-enriched planar intermediate (Scheme 10). Such an intermediate was then alkylated by the electrophile from the most accessible enantioface (left cleft) to give the α-allyl phosphonamide **19** with a high deuterium content.

Scheme 9

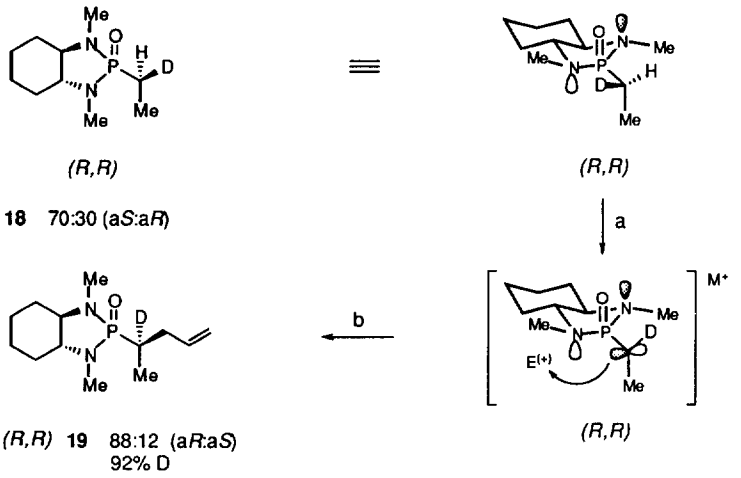


18 70:30 (a*S*:a*R*) **19** 88:12 (a*R*:a*S*) 92% D

a. i.n-BuLi, -78°C, THF; ii.Allyl bromide, 83%

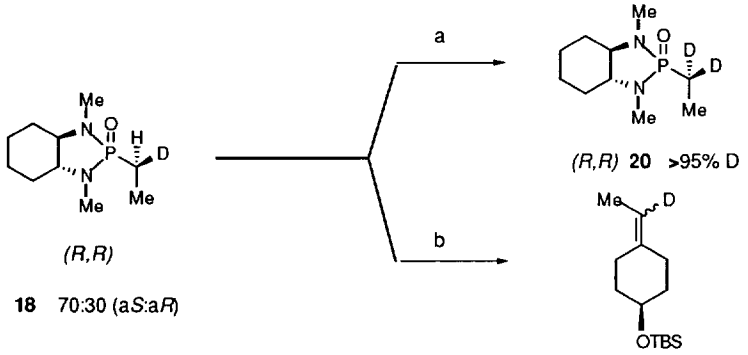
The recorded isotope effect was confirmed by two subsequent experiments: α-deutero phosphonamide **18** [α-(*S*):α-(*R*): 70:30] was treated with n-BuLi at -78°C in THF then: **a)** quenched with excess deuteromethanol to give the corresponding bis-deutero phosphonamide **20** in 98% yield and ≥95% deuterium content (MS, ^{1}H and ^{13}C NMR); and **b)** reacted with 4-tert-butyldimethylsilyloxy cyclohexanone to give after AcOH quench the corresponding deuterated ethylidene 4-tert-butyldimethylsilyloxy cyclohexane **21** in 84% yield and ≥92% deuterium content (Scheme 11). It was not possible to accurately calculate the exact isotope effect due to the presence of diastereomeric mixtures in **18**.

Scheme 10



a. n-BuLi, -78°C, THF; b. Allyl bromide, 83%

Scheme 11

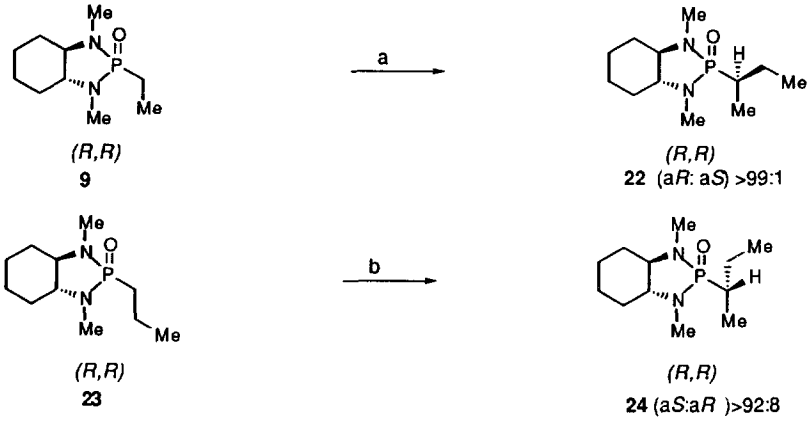


a. i.n-BuLi, -78°C, THF; ii.CD_3OD, 98%
b. i.n-BuLi, -78°C, THF; ii.4-*O*-TBS-cyclohexanone; iii.AcOH, 84%

Hybridization of tertiary α-phosphoryl carbanions

In order to determine the hybridization state in tertiary α-phosphoryl carbanions, we prepared phosphonamides **22** and **24** both derived from (*R,R*)-*N,N'*-dimethyl-1,2-diaminocyclohexane **2**. Thus, ethyl phosphonamide **9** was alkylated with ethyl iodide at -100°C (*vide supra*) to give **24**, in a ratio of (αR: αS)=95:5. This mixture was recrystallized to diastereomeric purity from hexanes (αR: αS = >99:1).

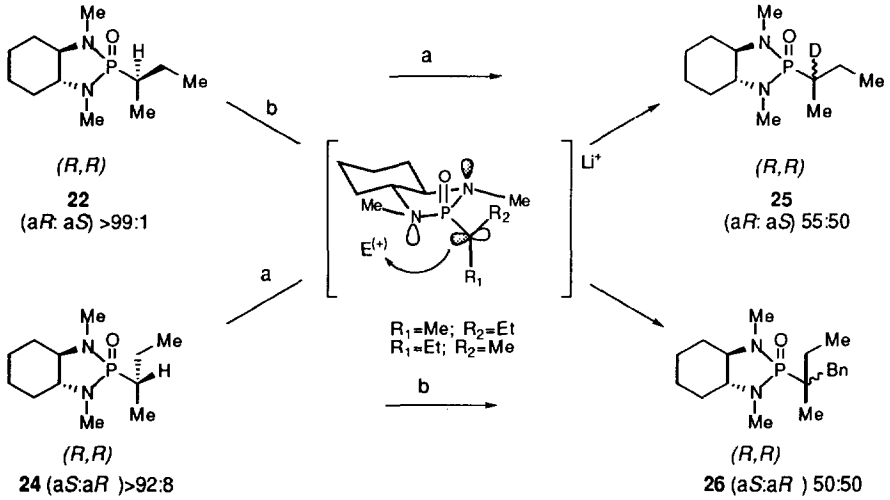
Scheme 12



a. i.n-BuLi, -100°C, THF; ii.Iodoethane, 85%; recrystallization; b. i.n-BuLi, -100°C, THF; ii.Iodomethane

Phosphonamide **24** consisting predominantly of the (αS) diastereomer was prepared from the (*R,R*)-propyl phosphonamide **23** (prepared from **2** and propyl phosphonic dichloride) by alkylation with iodomethane. This reaction proceeded in a ratio of αS: αR = 79:21, which was enriched to a maximum of αS: αR = 92:8 by repeatedly crystallizing out the minor diastereomer from hexanes (Scheme 12). Phosphonamides **22** and **24** were subjected to the same deprotonation/alkylation/deuteration conditions to give, in each case, the deuterated **25** and the alkylated **26** products in an a*S*: a*R* ratio of 50:50 (Scheme 13). These results indicated the intermediacy of a *planar carbanion* due to a low energy barrier of rotation,[14e] since both diastereomers gave the same racemic alkylation/deuteration products.

Scheme 13

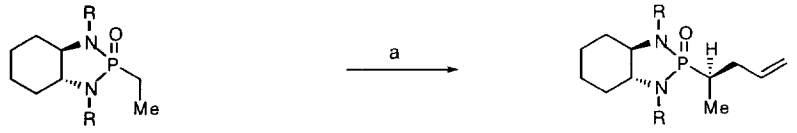


a. i.n-BuLi, -78°C, THF; ii.CD_3OD or D_2O; b. i.n-BuLi, -78°C, THF; ii.BnBr

Alkylation of phosphonamide **9**: *effects of base, temperature, solvent and N,N'-dialkyl groups*

The results of optimization studies for the alkylation of ethyl phosphonamide **9** by examining the effects of various bases, temperatures, solvents and *N,N'*-dialkyl groups, are summarized in Scheme 14 and Table 2. The combination of LDA/THF and −100°C gave the best results in terms of yields of isolated products and diastereomeric ratios.

Scheme 14



(R,R) **9** *(R,R)* **27**

a. Base, solvent, temperature, allyl bromide; See Table 2

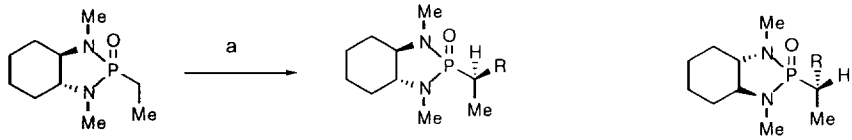
Table 2

Entry	R	Base[a]	Temp.	Solvent	Yield[b]	Ratio (R,S)
a.	Me	n-BuLi	−78°C	THF	82%	89:11
b.	Me	n-BuLi	−78°C	Et_2O	87%	90:10
c.	Me	n-BuLi	−78°C	Toluene	86%	89:11
d.	Me	LDA	−78°C	THF	83%	90:10
e.	Me	LiHMDS	−78°C - 0°C	THF	23%	80:20
f.	Me	NaHMDS	−78°C	THF	–c	–
g.	Me	KHMDS	−78°C	THF	–c	–
h.	Me	n-BuK	−78°C	THF	75%	82:18 (d)
i.	Me	LDA	−100°C	THF	83%	93:7
j.	Et	n-BuLi	−78°C	THF	85%	89:11
k.	Bn	n-BuLi	−78°C	THF	88%	89:11

a. A stoichiometric amount of base was used; b. Yields of isolated purified products; c. No product was isolated; d. Benzyl bromide was used as electrophile.

The above optimized reaction conditions were applied in a systematic manner to generate various α-alkyl α-methyl phosphonamides of type **28** in good yields on 1-5 mmol scales and with excellent de's (Scheme 15, Table 3).

Scheme 15



(R,R) **9** *(R,R)* **28** **29** (from *S,S*-series)

a. LDA, THF, −100°C, RX; see Table 3.

Table 3

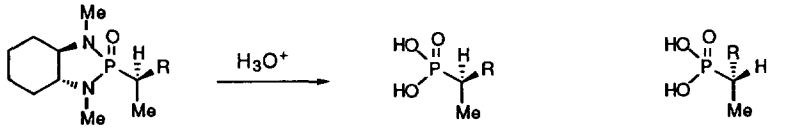
Entry	RX	Temperature	Yield	Ratio (aR, aS)
(*R,R*) series (28)				
a.	CH_3CH_2I	–78°C	78%	89:11
b.	CH_3CH_2I	–100°C	76%	95:5
c.	CH_2=$CHCH_2Br$	–78°C	83%	89:11
d.	CH_2=$CHCH_2Br$	–100°C	83%	94:6
e.	$PhCH_2Br$	–78°C	85%	90:10
f.	$PhCH_2Br$	–100°C	83%	97:3
g.	$TBDPSO(CH_2)_2I$	–100°C	68%	94:6
h.	$TBDPSO(CH_2)_2I$	–100°C	71%	99:1
(*S,S*) series (29)				
i.	CH_3CH_2I	–100°C	78%	5:95
j.	CH_2=$CHCH_2Br$	–100°C	83%	4:96
k.	$PhCH_2Br$	–100°C	84%	4:96

Hydrolysis of α-alkyl phosphonamides: synthesis of α-alkyl α-methyl phosphonic acids

α–Substituted phosphonic acids are an important class of compounds which serve as surrogates for carboxylic acids with numerous applications in medicinal chemistry.[41] For example they are used as mimics of transition states in many enzymatic processes, and in hapten-conjugate antibody chemistry.[42] They also exhibit strong activities as antibiotics[43] and antiviral agents.[44] More recently, α-substituted phosphonic acids, where one enantiomer showed a much higher potency over its antipode, were reported as inhibitors of squalene synthase.[45] Interest in the preparation of these phosphonic acids in an enantioselective fashion has attracted much attention and many methods have been reported to date.[46]

It is well documented that the hydrolysis of an endocyclic P-N bond is much faster than that of an exocyclic P-N bond, particularly in five-membered heterocyclic systems where factors related to ring tension and pseudorotation contribute substantially to the rate of hydrolysis. Quantitative and qualitative studies by Westheimer and Williams[47] on the hydrolysis of monocylic phosphoramides, as well as studies by Mulliez and Wakselman[48] on the acid hydrolysis of alkyl substituted 2,4-dioxo-1,3,2-diazaphospholidines illustrate the lability of the P-N bonds as compared to both P-O and P-C bonds. Treatment of ethyl phosphonamide **9** with 10 equiv. of water in THF for 72 h. did not give any hydrolysis product (^1H and ^{31}P NMR). However, the mono hydrolysis product (one P-N bond) was observed in 1,4-dioxane and in 1 N NaOH. Treatment with 1 N HCl at 25°C for 24 h gave the corresponding phosphonic acid (^1H and ^{31}P NMR). The alkylation products in Table 3 were hydrolyzed to the corresponding phosphonic acids in excellent yields giving enantiomerically pure or enantiomerically enriched α-alkyl phosphonic acids (Scheme 16, Table 4). By analogy to the literature precedents, no racemization was expected to occur during these hydrolyses.[46]

Scheme 16



(R,R) *(R)* *(S)*

28 **30** **31** (from *S,S*-series)

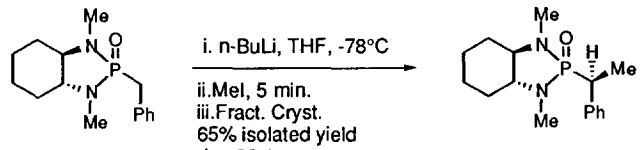
Table 4

Entry	R	Yield	Configuration
***(R,R)* series (30)**			
a.	CH_3CH_2–	90%	*R*
b.	CH_2=$CHCH_2$–	88%	*R*
c.	$PhCH_2$–	86%	*R*
d.	$HO(CH_2)_2$–	94%	*R*
e.	$HO(CH_2)_3$–	92%	*R*
***(S,S)* series (31)**			
f.	CH_3CH_2–	91%	*S*
g.	CH_2=$CHCH_2$–	88%	*S*
h.	$PhCH_2$–	82%	*S*

Asymmetric Synthesis of α-Phenyl Phosphonic Acids

The above described methodology was extended to various alkyl, chloroalkyl, aminoalkyl, and benzyl phosphonamides. Herein, we disclose our results on the alkylation of enantiomerically pure benzyl phosphonamide **32** and the hydrolysis of the resulting compounds to their corresponding phosphonic acids. Phosphonamide **32** was prepared in 80% yield by treatment of *N,N'*-dimethyl-1,2-diaminocyclohexane **6** in benzene with benzyl phosphonic dichloride[49] at 25°C in the presence of triethylamine. A solution of **32** in THF was treated with n-BuLi at –78°C, followed by the addition of a slight excess of MeI to give compound **33** in 95% yield and a diastereomeric ratio of 84:16 (^{1}H and ^{31}P NMR) (Scheme 17). Recrystallization of this material gave a diastereomerically pure compound in 65% yield. The absolute configuration of the newly introduced stereogenic center resulting from the *pro-S* enantioface in the *(R,R)*-series was confirmed by single crystal X-ray analysis (Scheme 17).[50] These results were in accord with previous observations and predictions of an approach of the electrophile from the pro-*S* enantioface (left cleft) in the *(R,R)* series.

Scheme 17



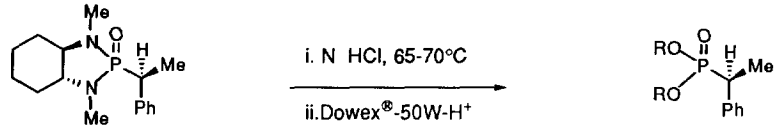
(R,R) *(R,R)*

32 **33**

In order to explore the geometry on the carbanions in these benzylic systems, we have conducted deprotonation/deuteration/alkylation studies in the case of secondary and tertiary α-phenyl phosphonamides of type **32**, in a manner similar to that described above. Our results in this series also show planarity of both secondary and tertiary benzylic α-carbanions.[50] This is in agreement with previously reported results in the case of benzyl phosphorinanes.[4 and 13c,d]

Acid hydrolysis of phosphonamide **33** followed by ion-exchange resin chromatography gave the corresponding phosphonic acid **34** without racemization. Upon treatment with CH_2N_2 the acids gave the corresponding dimethyl phosphonate derivative **35**. The data for **35** were consistent with those reported in the literature[13c,d] (Scheme 18).

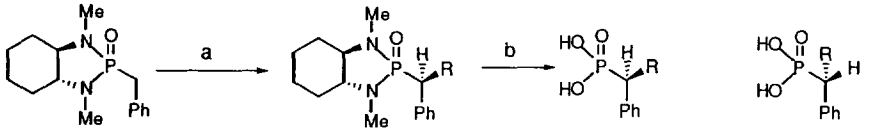
Scheme 18



(R,R) **33**

Alkylations of *(R,R)*-benzyl phosphonamide **32** and its *(S,S)*-antipode using MeI, BnBr and allyl bromide proceeded in good yields and good diastereomeric ratios. Alkylations with EtI and $I(CH_2)_nOTBDPS$, n=1,2; were much slower, which was remedied by using the alkyl triflate counterparts. The yields and selectivities for few representative examples are summarized in Table 5. Unlike the case of ethyl and chloromethyl phosphonamides,[4] lowering the reaction temperature to –100°C and/or using LDA as a base had very little effect on the diastereoselectivities. Using the corresponding *N*-Bn bicyclic phosphonamides did not improve the ratios. From a practical standpoint, it is of interest that the products of type **36** where crystalline and they could be recrystallized to diastereomeric purity. Acid hydrolysis of the diastereomerically pure alkylation products of type **36**, which required moderate heating in this case, gave the corresponding phosphonic acids of type **37** (Scheme 19). The corresponding *(S,S)*-analogs were obtained from the enantiomeric series (**38**).

Scheme 19



(R,R) **32** | *(R,R, aS)* **36** | *(S)* **37** | *(R)* **38** (from *S,S*-series)

a. i.n-BuLi, THF, –78°C, ii.RX; b. H_3O^+

Table 5

	Alkylation			Hydrolysis[b]	
Entry	**R**	**Yield**	**Ratio[a]**	**Yield**	**Config.**
(R,R) series (36)					
a.	$-CH_3$	95%	84:16	96%	**37a** *S*
b.	$-C_3H_5$	91%	89:11	97%	**37b** *S*
c.	$-CH_2Ph$	93%	90:10	92%	**37c** *S*
(S,S) series (38)					
a.	$-CH_3$	95%	15:85	96%	**39a** *R*
b.	$-CH_2Ph$	92%	10:90	90%	**39b** *R*

a. Ratios of crude products before separation were determined by ^1H and ^{31}P NMR. b. The alkylated products were recrystallized to diastereomeric purity prior to hydrolysis.

Conclusion

Enantiomerically pure and topologicaly unique chiral phosphonamides were prepared in high yields from readily available reagents. These phosphonamides were easily deprotonated to yield carbanions which were trapped with a variety of electrophiles (alkyl halides, ketones, imines, α,β-unsaturated carbonyl compounds etc...) in a highly diastereoselective fashion. The resulting alkylated phosphonamides were easily hydrolyzed to the corresponding α'-alkyl α-substituted phosphonic acids with high levels of enantiomeric purity and in good yields. Studies towards understanding the source of enantioselectivity in these systems have led us to conclude that a combination of several factors are important elements that govern the degrees of asymmetric inductions. The planar secondary and tertiary α-carbanions derived from these alkyl phosphonamides are stable up to 0°C, and they can be reacted with electrophiles without significant stereochemical erosion.

EXPERIMENTAL

Melting points were recorded on a Büchi apparatus and are not corrected. IR spectra were recorded on a Perkin Elmer 781 spectrometer. ^{1}NMR spectra were recorded on a Varian VXR-300 in the deuterated solvents mentioned, ^{13}C NMR recorded at 75.43 MHz and ^{31}P NMR at 121.4 MHz using 85% H_3PO_4 in D_2O as an external reference. Mass spectra were recorded on Kratos MS-50 TCTA and HRMS AEI-MS 902 at 70 eV (EI). Elemental analyses were performed by Guelph Laboratories, Ontario, Canada. Optical rotations were measured on a Perkin Elmer model 241 polarimeter. Chromatography was performed on silica gel Kieselgel 60 (E. Merck #9385, 4063 μm). Compounds containing the phosphoryl group were easily detected using a solution of "molybdenum blue".[51] Tetrahydrofuran was distilled under nitrogen over K/benzophenone. Optical rotations were recorded at 25°C.

(*R*, *R*)-1,2-Diaminocyclohexane-*N*,*N*'-diethyl dicarbamate. In a 500 mL three neck round-bottomed flask was added NaOH (36.6 g, 0.93 mol) and water (180 mL). To this solution was added (*R* , *R*)-1,2-diaminocyclohexane[15] **2** (22.8 g, 0.198 mol) and the resulting mixture was stirred vigorously at 0°C for 10 min. A solution of ethyl chloroformate (45.6 g, 0.42 mol) in 180 mL of benzene (toluene can be used equally) was added over a period of 30 min through an addition funnel. The mixture was then stirred vigorously at 25°C for 2 h. The resulting white precipitate was filtered and dried under high vacuum (0.5 mmHg) in the presence of phosphorus pentoxide for 3 h. The solid, thus obtained, was recrystallized from absolute ethanol to give 40.3 g (78%) of the desired dicarbamate, mp. 166.5-168.5°C; $[\alpha]_D$ 45.5° (c 1.0, $CHCl_3$), IR (KBr)ν_{max} 3320, 2950,

1700, 1550 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.00 (m, 2 H, 2 x NHCO), 4.15 (q, 4 H, J=7 Hz, OCH_2), 3.30 (m, 2 H, 2 N-CH), 1.40–2.20 (m, 8 H, 4 x -CH_2, ring), 1.20 (t, 6 H, J=7.0 Hz, 2 x CH_3); ^{13}C ($CDCl_3$) δ 156.94, 154.58, 60.65, 55.22, 32.73, 24.65, 14.45; Anal. calcd. for $C_{12}H_{22}N_2O_4$; C, 55.79; H, 8.59; N, 10.85; found: C, 55.72; H, 8.44; N, 10.80. The (*S,S*)-enantiomer was prepared in the same manner and had an optical rotation of $[\alpha]_D$ -44.3° (c 1.02, $CHCl_3$).

(*R, R*)-*N,N'*-Dimethyl-1,2- diaminocyclohexane (6). To a flame-dried 1 L three neck-round-bottomed flask, equipped with a mechanical stirrer and a reflux condenser connected to a KOH drying tube, was added LAH (11.00 g; 0.29 mol) and 400 mL anhydrous THF. The suspension was cooled to 0°C and solid (*R, R*)-1,2-diaminocyclohexane-*N,N'*-diethyl dicarbamate was added portionwise. The mixture was stirred at RT for 1 h. then refluxed for 14 h. The resulting gray suspension was cooled to 0°C and water (11.0 mL), 15% NaOH (11 mL) and then water (33.0 mL) were sequentially added with *caution*! The mixture was stirred for 1 h. at RT to give a white precipitate which was filtered and rinsed with warm THF (2 x 100 mL). The solvent was evaporated and the residue acidified (10% HCl) (pH ~2) then extracted with dichloromethane (3 x 100 mL). The aqueous layer was treated with NaOH (10%) until basic pH, then extracted with dichloromethane (3 x 200 mL). The organic layer was dried over $MgSO_4$ and evaporated to dryness to give a yellowish residue which solidified to give 5.09 g (92% yield) of the desired diamine; $[\alpha]_D$-144.2° (c 1.15, $CHCl_3$); IR (film)ν_{max} 3300, 2850, 1500, 1440, 1140, 1100, 830 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.35 (s, 6 H, 2 CH_3), 2.06-1.56 (m, 6 H, ring), 1.69 (s, 2 H, 2 x NH), 0.8-1.2 (m, 4 H, ring); ^{13}C NMR ($CDCl_3$) δ 63.01, 33.42, 30.61, 24.84; Anal. calcd. for $C_8H_{18}N_2$; C, 67.55; H, 12.75; N, 19.70; found: C, 67.68; H, 12.62; N, 19.48. The (*S, S*)-enantiomer was prepared in the same manner ; $[\alpha]_D$ +136.4° (c 2.0, $CHCl_3$).

(*R, R*)-*N,N'*-Bis-(trideuteromethyl)-1,2-diaminocyclohexane. This diamine was prepared in the same manner as described above in 81% yield from LAD_4 and (*R, R*)-1,2-diaminocyclohexane-*N,N'*-diethyl dicarbamate; $[\alpha]_D$-139.2° (c 1.02, $CHCl_3$); IR(CCl_4) ν_{max} 3320 (N–H), 2900, 2215, 2190 and 2060 (C–D), 1450, 1245, 1140 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.07 (m, 6 H, ring), 1.74 (m, 2 H, 2 x NH), 0.86-1.3 (m, 4 H, ring); HRMS for $C_8H_{12}D_6N_2$; calcd. 148.1620; found: 148.1618.

(*R, R*)-*N,N'*-Diacetyl-1,2-diaminocyclohexane. To a solution of (*R, R*)-1,2-diaminocyclohexane **2** (2.05 g; 18 mmol) in methanol (20 mL) was added acetic anhydride (3.67 g, 35.9 mmol) over a period of 15 min. at RT. After stirring for 4 h, water (5.0 mL) was added and the resulting mixture was stirred for 12 h. The solvents were evaporated and the residue recrystallized form EtOH:acetone (1:10) to give 2.6 g (73%) of the desired compound; mp. 279°C; $[\alpha]_D$+72.2° (c 1.02, MeOH); IR (film)ν_{max} 3290, 2850, 1640, 1500, 830 cm^{-1}; ^1H NMR (CD_3OD) δ 3.58 (m, 2 H, CHNH), 1.90 (m, 2 H, ring), 1.88 (s, 6 H, N-C(O)CH_3), 1.72 (m, 2 H, ring), 1.29 (m, 2 H, ring); ^{13}C NMR (CD_3OD) δ 173.05, 54.13, 33.15, 25.83, 22.72; MS (CI) e/z 199 (M+1), 167, 139, 123, 109, 97, 81, 69.

(*R, R*)-*N,N'*-Diethyl-1,2-diaminocyclohexane (7). This diamine was prepared in the same manner as described above in 81% yield by reduction of *N,N'*-diacetyl 1,2-diaminocyclohexane with LAH in THF; IR (film)ν_{max} 3300, 2850, 1530, 1460, 830 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.10-0.50 (m, 10 H, ring), 2.60 (q, 4 H, 2 x CH_2), 1.10 (t, 6 H, 2 x CH_3); MS (EI) 170 (M), 97, 91, 81.

(*R,R*)-*N,N'*-Dibenzylidene-1,2-diaminocyclohexane. Benzaldehyde (1.90 g, 17.9 mmol) was added to a solution of (*R, R*)-1,2-diaminocyclohexane **2** (1.04 g, 9.12 mmol) in benzene (20 mL) and the mixture was stirred at room temperature for 45 min. The solvent was evaporated, benzene (10 mL) was added and the water was azeotropically removed. This operation was repeated twice more and the residue was recrystallized from petroleum ether (30-70°) to give 2.01 g (76%) of the desired product; mp. 96-98°C; $[\alpha]_D$ -211.4° (c 1.20, $CHCl_3$); IR(CCl_4)ν_{max}3080, 3060, 3020, 2930, 2850, 1640 (C=N), 1560, 1445, 1375, 1215, 1115, 940 cm^{-1};

^{1}H NMR ($CDCl_3$) δ 8.21 (s, 2 H, 2 x N=CH), 7.58 (m, 4 H, Ar), 7.31 (m, 6 H, Ar), 3.42 (m, 2 H, 2 x CH-N), 1.86 (m, 6H, ring), 1.49 (m, 2 H, ring). ^{13}C NMR ($CDCl_3$) δ 160.86, 136.20, 130.05, 128.21, 127.75, 73.65, 32.81, 24.34. MS(IC) 291 (M+1), 186, 106 104; MS (IE) 290, 187, 144, 130, 117, 104, 91, 80; HRMS for $C_{20}H_{22}N_2$; calcd. 290.1782; found: 290.1785.

(*R, R*)-*N,N'*-Dibenzyl-1,2-diaminocyclohexane (8). To a 50 mL flask, dried under nitrogen, was added *(R,R)-N,N'*-dibenzylidene-1,2-diaminocyclohexane (1.0 g, 3.45 mmol), methanol (20 mL) and the mixture was cooled to 0°C. $NaBH_4$ (300 mg) was added portionwise and the mixture was stirred at 25°C for 4 h. The solvent was evaporated and the residue acidified (10% HCl) then extracted with 3 x 20 mL of CH_2Cl_2. The aqueous phase was treated with NaOH (10%) until pH ~12 and extracted with 3 x 50 mL CH_2Cl_2. The organic layer was dried over $MgSO_4$ and the solvent evaporated to give 723 mg (73%) of the desired diamine as a colorless oil which solidified upon standing; mp. 36-37°C; $[\alpha]_D$ -67.0° (c 1.15, $CHCl_3$). IR (film)ν_{max} 3300 (NH), 3050, 2900, 1600, 1500, 1460 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.32-7.35 (2m, 10 H, ArH), 3.91 (d, 2 H, J=13.1 Hz, C$\underline{H}_2$Ph), 3.67 (d, 2 H, J=13.1 Hz, C$\underline{H}_2$Ph), 2.27 (m, 2 H, ring), 2.18 (m, 2 H, ring), 2.01 (s br., 2 H, 2 x NH), 1.73 (m, 2 H, ring), 1.25 (m, 2 H, ring), 1.15 (m, 2 H, ring); ^{13}C NMR ($CDCl_3$) δ 140.88, 128.18, 127.92, 126.60 (ArH), 60.71 (N–$\underline{C}H_2$Ph), 50.72 (N–CH), 31.38 ($\underline{C}H_2$–CH–N), 24.89 ($\underline{C}H_2$-CH_2-CH–N); MS (CI) 295 (M+1), 293, 188, 107, 91, 79.

Ethyl phosphonic dichloride.[52] To a solution of PCl_3 (25.05 g, 0.182 mol) and ethyl bromide 26.1 mL was added solid $AlCl_3$ (35.9 g) portionwise while keeping the internal temperature between 15°C and 20°C, over a 60 min. period. The resulting solution was dissolved in dichloromethane (150 mL) and cooled to ~–5°C. Water (51 mL) was slowly and *cautiously* added over a 30 min. period. The solid, thus obtained, was filtered and the filtrate evaporated. The residue was distilled (72°C, 16 Torr) to give 18.3 g of the desired ethyl phosphonic dichloride in 50% yield; *d*=1.48 g.mL^{-1}; IR(CCl_4)ν_{max} 2995, 2975, 1460, 1400, 1280, 1250, 1160, 1040, 755 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.60 (dq, 2 H, J=14.9 Hz, J=7.5 Hz, P-C$\underline{H}_2$-), 1.42 (dt, 3 H, J=30.0 Hz, J=7.5 Hz, P-$CH_2C\underline{H}_3$); MS (CI)147 (M), 111 (M–C_2H_5).

(3a*R*, 7a*R*)-2-Ethyl-[3a,4,5,6,7,7a-octahydro-1,3-dimethyl-1,3,2-benzodiazaphosphole]-2-oxide (9).
Method (A): To a solution of *(R,R)-N,N'*-dimethyl-1,2-diaminocyclohexane **6** (5.00 g, 35.1 mmol) in benzene (80 mL) was added triethylamine (9.90 mL, 71 mmol) and the mixture was stirred at 25°C. A solution of ethyl phosphonic dichloride (5.22 g, 53.1 mmol) in benzene (50 mL) was added dropwise over a period of 30 min, and the reaction mixture was vigorously stirred for an additional 90 min at ambient temperature. The resulting precipitate was filtered over a Celite pad and rinsed with ethyl acetate (100 mL). The solvent was evaporated and the residue purified by silica gel choromatography (EtOAc:MeOH 95:5) then distilled at 125°C, 0.5 mmHg using a Kugelröhr to give 5.77 g of the desired ethyl phosphonamide. Recrystallization from hexanes at -12°C afforded 5.7 g of pure product (data following the next paragraph).

Method (B): A solution of *(R,R)-N,N'*-dimethyl-1,2-diaminocyclohexane **6** (3.00 g, 21.1 mmol) and hexamethylphosphorus triamide (HMPT) (3.44 g, 25 mmol) in benzene (20 mL) was heated at 100°C for 16 h. under argon until no more volatile diamine was detected (litmus paper). The solvent was evaporated and the residue distilled (121°C, 0.2 mm.Hg) to give *(3aR,7aR)*-2-dimethylamino-[3a,4,5,6,7,7a-octahydro-1,3-dimethyl-1,3,2-benzodiazaphosphole] **10** in 80% yield; $[\alpha]_D$ -86.8° (c 1.53, $CHCl_3$) [for the (S,S) isomer, $[\alpha]_D$ +84.9° (c 1.05, $CHCl_3$)]; ^{1}H NMR ($CDCl_3$) δ 2.9-2.2 (3 x d and m, 14 H, J=12.3 Hz, J=9.2 Hz, J=7.7 Hz, P-N-$(CH_3)_2$; 2 x P-N-(CH_3), 2 H, 2 x P-N-CH), 2.2-0.98 (mm, 8 H, ring); Anal. calcd. for $C_{10}H_{22}N_3$; (215.27) H, 10.30; N, 19.52; found: H, 10.11; N, 19.32. A solution of the above phospholidine **10** (3.57 g, 16.5 mmol) in benzene (20 mL) was treated with 1.05 mol. equiv. of ethanol and the mixture heated at reflux until complete exlusion of dimethylamine. The mixture was cooled to room temperature, iodoethane (15% mol. equiv.) was

added, and the mixture was heated at reflux for 4 h. The solvent was removed under vacuo and the resulting residue was purified by silica gel choromatography (EtOAc:MeOH 95:5) then distilled at 125°C at 0.5 mmHg using a Kugelröhr to give the desired ethyl phosphonamide **9**; mp. 55-56°C (hexanes); $[\alpha]_D$ -93.5° (c 1.0, $CHCl_3$); IR (CCl_4)ν_{max} 3400, 2900, 2725 et 2685, 1440, 1295, 1245, 1160, 1010 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.70 (ddd, 1 H, J=11.5 Hz, J =9.3 Hz, J=2.7 Hz, NCH, syn to P=O), 2.60 (d, 3 H, N–CH_3, $^3J_{P-H}$=10.0 Hz), 2.56 (d, 3 H, N–CH_3, $^3J_{P-H}$=11.5 Hz), 2.51 (m, 1 H, N-CH, anti to P=O), 2.01-2.05 (m, 2 H, ring), 1.73-1.99 (m, 4 H, CH_2-CH_3; 2 H, ring), 1.22-1.36 (m,3 H, ring), 1.10 (m, 1 H, ring), 1.04 (dt, 3 H, $^2J_{P-H}$=15.5 Hz, $^2J_{H-H}$=9.4 Hz, P-CH_2-CH_3); ^{13}C NMR ($CDCl_3$) δ 64.38 (d, $^2J_{P-C}$=7.0 Hz, N-CH), 64.3 (d, $^2J_{P-C}$=4.1Hz, N-CH), 29.5 (N–CH_3), 28.5 (–CH_2–CH–N), 28.3 (–CH_2–CH–N), 27.9 (N–CH_3), 24.0 (CH_2–CH_2–CH–N), 23.9 (CH_2–CH_2–CH–N), 19.4 (d, $^1J_{P-C}$=114.1 Hz), 6.8 (d, $^2J_{P-C}$=5.8 Hz); ^{31}P NMR ($CDCl_3$) δ +46.7; MS (EI)216 (M), 215 (M–H), 187 (M– C_2H_5), 173, 160, 139, 110; HRMS for $C_{10}H_{21}N_2OP$; calcd. 216.1391; found: 216.1331; Anal. calcd. for $C_{10}H_{21}N_2OP$; C, 55.54; H, 9.79; N, 12.96; found: C, 55.57; H, 9.77; N, 12.81.

(3a*R*, 7a*R*)-2-Ethyl-[3a,4,5,6,7,7a-octahydro-1,3-bis-(trideuteriomethyl)-1,3,2-benzodiazaphosphole]-2-oxide. This compound was prepared according to Method A (above) from *(R,R)-N,N'*-Bis-(trideuteromethyl)-1,2-diaminocyclohexane and ethyl phosphonic dichloride in 88% yield; mp. 55-56°C (hexanes); $[\alpha]_D$ -95.7° (c 1.04, $CHCl_3$); IR(CCl_4)ν_{max} 3400, 2900, 2725 et 2685 2225, 2065, 1445, 1300, 1280, 1260, 1220, 1175, 1145, 1070 cm^{-1}; ^1H NMR($CDCl_3$) δ 2.68 (ddd, 1 H, J=11.3 Hz, J=9.3 Hz, J=2.7 Hz, P-N-C<u>H</u>-CH_2), 2.48 (m, 1 H, P-N-C<u>H</u>-CH_2), 2.0 (m, 2 H, ring), 1.82 (m, 2 H, ring), 1.80 (m, 2 H, P-CH_2-CH_3), 1.28 (m, 3 H, ring), 1.08 (m, 1 H), 1.06 (dt, 3 H, J=18.7 Hz, J=7.7 Hz, P-CH_2-CH_3); ^{13}C NMR ($CDCl_3$) δ 64.48 (d, $^2J_{P-C}$=6.8 Hz, N-CH), 64.26 (d, $^2J_{P-C}$=3.9 Hz, N-CH), 28.53 (d, J=10.2 Hz, –CH_2–CH–N), 28.10 (d, J=7.0 Hz, –CH_2–CH–N), 24.11 (d, J=8.9 Hz, CH_2–CH_2–CH–N), 19.54 (d, $^1J_{P-C}$=113.9 Hz), 7.02 (d, $^2J_{P-C}$=6.1 Hz, P-CH_2-CH_3). , ^{31}P ($CDCl_3$) (85% H_3PO_4 in D_2O) δ +46.63; MS(EI) 222 (M), 193 (M– C_2H_5), 166, 139, 110. Analysis of NMR and MS spectra showed >98% deuterium content.

(3a*S*, 7a*S*)-2-Ethyl-[3a,4,5,6,7,7a-octahydro-1,3-dimethyl-1,3,2-benzodiazaphosphole]-2-oxide. This phosphonamide was prepared according to Method A (yield, 75%); mp. 54-55°C (hexanes), $[\alpha]_D$ +91.6° (c 1.0, $CHCl_3$).

(3a*R*, 7a*R*)-2-[(1*S*)-Deuteroethyl]-[3a,4,5,6,7,7a-octahydro-1,3-dimethyl-1,3,2-benzodiazaphosphole]-2-oxide (18). A 25 mL flask was flame-dried under argon and charged with ethyl phosphonamide **9** (302 mg, 1.39 mmol) and THF (5.0 mL), then cooled to -78°C. n-BuLi (0.615 mL, of a 2.5 M solution in hexanes, 1.53 mmol) was added and the mixture stirred at this temperature for 20 min. CD_3OD (CIL®, 99% D) (0.5 mL) was added and the reaction mixture allowed to warm to 25°C. EtOAc (20 mL) was added followed by water (2 x 3 mL) and brine (2 x 3 ml) then the organic layer was dried over $MgSO_4$ and evaporated. The residue was purified by flash chromatography (AcOEt:MeOH 95:5) to give 293 mg (97%) of a crystalline material; mp. 54°C (hexanes); $[\alpha]_D$ -100.7° (c 3.07, $CHCl_3$); IR(CCl_4)ν_{max} 3400, 2930, 2855, 2800, 2700, 2650, 1445, 1365, 1300, 1250, 1210, 1170, 1115, 1010, 980, 920, 890, 850 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.69 (ddd, 1 H, J=11.4 Hz, J=9.3 Hz, J=2.6 Hz, P-N-C<u>H</u>-CH_2), 2.54 (d, 3 H, J=10.0 Hz, P-N-CH_3), 2.50 (d, 3 H, J=11.7 Hz, P-N-CH_3), 2.50 (m, 1 H, P-N-C<u>H</u>-CH_2), 2.05 (m, 2 H, ring), 1.83 (m, 2 H, ring), 1.75 (m, 1 H, P-C<u>H</u>D-CH_3), 1.40-1.20 (m, 3 H, ring), 1.09 (m, 1 H, ring), 1.08 (dd, 3 H, J=18.8 Hz, J=7.5 Hz, P-CHD-C<u>H</u>$_3$); ^{13}C NMR ($CDCl_3$) δ 64.2 (d, $^2J_{P-C}$=6.8 Hz, N-CH), 64.0 (d, $^2J_{P-C}$=4.1 Hz, N-CH), 29.3 (P-N-<u>C</u>H_3), 28.2 (d, J=9.9 Hz, –CH_2–CH–N), 27.8 (d, J=7.1 Hz, –CH_2–CH–N), 27.7 (s, P-N-<u>C</u>H_3), 23.8 (d, J=8.2 Hz, CH_2–CH_2–CH–N), 18.9 (d, $^1J_{P-C}$=113.8 Hz), 6.5 (t, $^2J_{P-C-D}$=6.2 Hz); ^{31}P NMR ($CDCl_3$) δ +46.7; MS(EI) 217, 187, 174, 162, 145, 139, 131, 110, 83, 78, 70; HRMS for $C_{10}H_2DN_2OP$; calcd. 217.142; found: 217.146. The deuterium content was >95±3% on the basis of ^1H, ^{13}C NMR and HRMS.

(3a*R*, 7a-*R*)-2-Chloro-(3a,4,5,6,7,7a-octa-hydro-1,3-dimethyl-1,3,2–benzodiazaphosphole)-2-oxide (12). This product was prepared by the general method for the preparation of phosphonamides (diamine, phosphorus trichloride/Et_3N-benzene) in 72% yield; mp. 51-52°C; $[\alpha]_D$ -49.2° (c 1.85, $CHCl_3$); IR (CCl_4)ν_{max} 3050, 2900, 2705, 2655, 1740, 1445, 1300, 1250, 1235, 1215, 1180, 1020, 1010 cm^{-1}; ^1H NMR ($CDCl_3$) d 2.84 (m, 1 H, P-N-C<u>H</u>-), 2.48 (m, 1 H, P-N-C<u>H</u>-),2.48 (d, 3 H, J=11.4 Hz, N-CH_3), 2.42 (d, 3 H, J=11.4 Hz, N-CH_3), 2.0 (m, 2 H, ring), 1.86 (m, 2 H, ring), 1.45-1.13 (m, 4 H, ring); ^{31}P NMR (CD_3OD) δ +33.29; HRMS for $C_8H_{16}N_2OPCl$; calcd. 222.068; found: 222.073.

(3a*R*,7a*R*)-2-Phenyl-[3a,4,5,6,7,7a-octahydro-1,3-dimethyl-1,3,2-benzodiazaphosphole]-2–oxide (13). This product was prepared by the general Method A for the preparation of phosphonamides in 95% yield; mp. 144-145°C; $[\alpha]_D$ -33.3° (c 0.9, $CHCl_3$); IR(CCl_4)ν_{max} 3050, 2900, 2705, 2655, 1740, 1445, 1300, 1250, 1235, 1215, 1180, 1020, 1010 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.92 (m, 1 H, P-N-C<u>H</u>-CH_2), 2.61 (m, 1 H, P-N-C<u>H</u>-CH_2), 2.53 (d, 3 H, $^3J_{P-H}$=11.6 Hz, P-N-CH_3), 2.41 (d, 3 H, $^3J_{P-H}$=11.0 Hz, P-N-CH_3), 2.15 (m, 1 H, ring), 2.0 (m, 1 H, ring), 1.77 (m, 2 H, ring), 1.5-1.17 (m, 4 H, ring); ^{31}P NMR (CD_3OD) δ +31.08; HRMS for $C_{14}H_{15}N_2OP$; calcd. 258.092; found: 258.092.

(3a*R*, 7a*R*)-2-(1-Bis-deuteroethyl)-[3a,4,5,6,7,7a-octahydro-1,3-dimethyl-1,3,2-benzodiazaphosphole]-2-oxide (20). A 25 mL flask was flame-dried under argon and charged with monodeuteroethyl phosphonamide **18** (95 mg, 0.43 mmol) and THF (2.0 mL) then cooled to -78°C. n-BuLi (0.240 mL, of a 2.5 M solution in hexanes, 0.47 mmol) was added and the mixture stirred at this temperature for 20 min. CD_3OD (CIL®, 99% D) (0.5 mL) was added and the reaction mixture allowed to warm to 25°C. EtOAc (20 mL) was added followed by water (2 x 3 mL) and brine (2 x 3 ml). The organic layer was dried over $MgSO_4$, evaporated and the residue was purified by chromatography (AcOEt:MeOH 95:5) to give 84 mg (88%) of a crystalline material; mp. 54°C (hexanes); $[\alpha]_D$ -99.7° (c 0.35, $CHCl_3$); IR(CCl_4)ν_{max} 3400, 2930, 2855, 2800, 2700, 2650 1445, 1365, 1300, 1250, 1210, 1170, 1115, 1010, 985, 920, 890 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.63 (ddd, 1 H, J=11.4 Hz, J=9.4 Hz, J=2.7 Hz, P-N-C<u>H</u>-CH_2), 2.52 (d, 3 H, J=10.25 Hz, P-N-CH_3), 2.50 (d, 3 H, J=12.1 Hz, P-N-CH_3), 2.44 (m, 1 H, P-N-C<u>H</u>-CH_2), 1.95 (m, 2 H, ring), 1.77 (m, 2 H, ring), 1.35-1.10 (m, 3 H, ring), 1.02 (m, 1 H, ring), 0.99 (d, 3 H, $^3J_{P-H}$=18.7 Hz, P-CD_2-C<u>H</u>$_3$); ^{13}C NMR($CDCl_3$) δ 64.4 (d, $^2J_{P-C}$=7.1 Hz, N-CH), 64.3 (d, $^2J_{P-C}$=4.1 Hz, N-CH), 29.6 (P-N-<u>C</u>H_3), 28.4 (d, J=10.1 Hz, –<u>C</u>H_2–CH–N), 28.0 (d, J=6.9 Hz, –<u>C</u>H_2–CH–N), 27.99 (s, P-N-<u>C</u>H_3), 24.0 (d, J=8.2 Hz, -<u>C</u>H_2–CH_2–CH–N), 18.93 (d, $^1J_{P-C}$=113.8 Hz), 6.54 (d, $^2J_{P-C}$=6.1 Hz); MS(CI) 219 (M+1), 218 (M), 217, 189, 187, 174, 141, 110; MS(EI) 218 (M), 217 (M-1), 203, 188, 187, 175, 141, 131, 112, 110, 96, 84, 83, 70, 68, 57. The deuterium content was >95±3% on the basis of ^1H, ^{13}C NMR and HRMS.

4-(1-Deuteroethylidene)-1-tert-butyl dimethylsilyloxycyclohexane (21). A 25 mL flask was flame-dried under argon and charged with monodeuteroethyl phosphonamide **18** (104 mg, 0.48 mmol) and THF (2.5 mL) then cooled to -78°C. n-BuLi (0.260 mL, of a 2.5 M solution in hexanes, 0.51 mmol) was added and the mixture stirred at this temperature for 20 min. a solution of 4-*tert*-butyldimethylsilyloxycyclohexanone (99.2 mg, 0.43 mmoles) in THF (2.5 mL) over a 5 min period. The mixture was stirred at –78°C for 1 h. then quenched with acetic acid (0.5 mL) and allowed to warm to 25°C. Stirring was continued for an additional 30 min. then ether (20 mL) was added. The mixture was washed with water (2 x 3 mL) followed by brine (2 x 3 mL). The organic layer was separated and dried over $MgSO_4$ and the solvent evaporated. The residue was purified by chromatography (hexanes:EtOAc 98:2) to give 90 mg (87%) of the desired olefin; IR (CCl_4)ν_{max} 2900, 2210, 1470, 1450, 1250, 1100, 1050, 1000 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.16 (q, 1 H, J=6.6 Hz, C=C<u>H</u>-CH_3, 8%), 3.82 (septet, 1 H, J=3.7 Hz, SiO-C<u>H</u>-(CH_2)2, 100%), 2.45 (m, 1 H, ring), 2.28 (m, 1 H, ring), 1.95 (m, 2 H, ring), 1.73 (m, 2 H, ring), 1.57 (s, 3 H, C=CD-C<u>H</u>$_3$), 1.48 (m, 2 H, ring), 0.90 (s, 9 H, t-Bu), 0.06 (s, 6 H, Si-(CH_3)2); ^{13}C NMR ($CDCl_3$) d 138.4, 115.2 (t, J=23.1 Hz, C=<u>C</u>D-CH_3, this carbon is coupled to the isotope D, which reduces its intensity by 80%), 69.8, 36.5, 35.5, 32.8, 25.7, 24.0, 18.0, 12.5, -4.7; MS(EI) 240 (M-H), 207, 164,

108, 95, 75; HRMS for $C_{14}H_{27}DOSi$; Calcd. 241.3111, found: 241.1920. Deuterium content was evaluated at >92±3% using ^1H; ^{13}C NMR and HRMS. The corresponding non-deuterated olefin was prepared as described above in 84% yield using ethyl phosphonamide **9**. In this case the intensity and integration for the α-silyloxy and the vinylic protons were equal. However, in the case of the monodeuterated olefin the ratios of the corresponding protons are 11.5:1. Furthermore, the vinylic methyl group shows a doublet (δ 1.57, d, J=6.6 Hz) for the non-labeled olefin and a singlet at δ 1.56 ppm for the labeled olefin **21**.

(3a*R*, 7a*R*)-2-[(1*R*)-Methyl-2-phenethyl]-[3a,4,5,6,7,7a-octahydro-1,3-dimethyl-1,3,2-benzodiazaphosphole]-2-oxide (28f). A 25 mL flask was flame-dried under argon and added with iPr_2NH [0.195 mL, 1.40 mmol), THF (5.0 mL) and n-BuLi (0.95 mL of a 1.47 M solution in hexanes) at -20°C. The mixture was warmed to 0°C for 20 min., then cooled to -100°C. A solution of ethyl phosphonamide **9** (200 mg, 0.92 mmol) in THF (2.5 mL) was added and the mixture stirred at this temperature for 30 min. Benzyl bromide (140 μL, 1.15 mmol) was added and the mixture stirred for 15 min. Methanol (0.5 mL) was added at -100°C and the reaction mixture was allowed to warm to 25°C. EtOAc (30 ml) was added and the mixture washed with water (2 x 5 mL) and brine (2 x 5 ml). The organic layer was dried over $MgSO_4$ and the solvent evaporated. The residue was purified by chromatography (AcOEt:MeOH, 97:3) to give 227 mg of the desired product. This material was recrystallized from ether: pet. ether to give a white solid (83%) ; mp. 95-97°C; $[\alpha]_D$ –35.2° (c 1.2, $CHCl_3$); IR (film)ν_{max} 3450, 2900, 1600, 1490, 1450, 1365, 1295, 1240, 1200, 1150, 1110 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.23 (m, 5 H, ArH), 3.46 (m, 1 H, P–C<u>H</u>–CH_3), 2.20-2.75 (m, 4 H, CH_2Ph, 2 x N-CH), 2.65 (d, 3 H, $^3J_{P-H}$=5.2 Hz, N–CH_3), 2.61 (d, 3 H, $^3J_{P-H}$=7.2 Hz, N–CH_3), 2.10-1.00 (m, 8 H, ring), 0.90 (dd, 3 H, P–CH–C<u>H</u>$_3$, J=6.7 Hz, J=3.5 Hz); ^{13}C NMR ($CDCl_3$) δ 139.87 (d, J=18.3 Hz, Ar), 128.85 (Ar), 128.1 (Ar), 125.99 (Ar), 65.02 (d, $^2J_{P-C}$=3.4 Hz), 64.30 (d, $^2J_{P-C}$=5.7 Hz), 36.8, 35.88, 34.4, 31.0, 28.2, 27.9, 24.1, 12.7; ^{31}P NMR ($CDCl_3$) δ +44.09 (major); +43.77 (minor) diastereomeric ratio: (96:4); MS(CI)307 (M+1), 188, 141, 110, 98, 87, 70; HRMS for $C_{17}H_{27}N_2OP$; calcd. 306.186; found: 306.183.

(3a*S*, 7a*S*)-2-[(1*S*)-Methyl 2-phenethyl]-[3a,4,5,6,7,7a-octahydro-1,3-dimethyl-1,3,2-benzodiazaphosphole]-2-oxide (29k). This product was prepared in an identical manner as described above from the *(S,S)*-ethyl phosphonamide (84%); mp. 96-97°C; $[\alpha]_D$ +33.6° (c 1.0, $CHCl_3$); ^{31}P NMR ($CDCl_3$) δ +44.41 (major); +44.08 (minor); diastereomeric ratio = 96:4.

(3a*R*,7a*R*)-2-[(2*R*)-butyl]-[3a,4,5,6,7,7a-octahydro-1,3-dimethyl-1,3,2-benzodiazaphosphole]-2-oxide (28b). This product was prepared in an identical manner as described above from *(R,R)*-ethyl phosphonamide and iodoethane (yield, 76%); mp. 95-96°C; $[\alpha]_D$ -81.5° (c 1.0, $CHCl_3$); IR (film)ν_{max} 3400, 2950, 1440, 1295, 1240, 1210, 1195, 1160 cm^{-1}; ^1H ($CDCl_3$) δ 2.50-2.70 (m, 2 H, 2 x N-CH), 2.60 (d, 3 H, $J_{P-N-CH3}$=9.2 Hz, N-CH_3), 2.52 (d, 3H, $J_{P-N-CH3}$=11.3 Hz, N-CH_3), 1.08-1.41 et 1.77-2.15 (m, 11 H, $C\underline{H}_2$-CH_3, cycle (8 H) et CH-CH_3), 1.04 (dd, 3 H, J=11.3 Hz, P-CH-CH_3), 0.98 (t, 3 H, CH_3–C<u>H</u>$_2$, J=7.3 Hz); ^{13}C NMR ($CDCl_3$) δ 65.00, 64.45, 34.62 (d, J_{P-C}=113 Hz), 30.88, 28.33, 28.19, 27.89, 24.28, 24.1, 23.7, 12.68, 12.43; ^{31}P NMR ($CDCl_3$) δ +45.05 (major); +44.80 (minor); diastereomeric ratio = 94.7:5.3; MS(CI) 245 (M+1), 187; HRMS for $C_{12}H_{25}N_2OP$; calcd. 244.1732; found: 244.1709; Anal. calcd. for $C_{12}H_{25}N_2OP$: C, 58.99; H, 10.31; N, 11.46; found: C, 58.77; H, 9.96; N, 11.46.

(3a*S*, 7a*S*)-2-[(2*S*)-butyl]-[3a,4,5,6,7,7a-octahydro-1,3-dimethyl-1,3,2-benzodiazaphosphole] 2-oxide (29i). This product was prepared in an identical manner as described above from *(S,S)*-ethyl phosphonamide and iodoethane (yield, 78%); mp. 92-95°C; $[\alpha]_D$ +79.2° (c 1.0, $CHCl_3$); ^{31}P NMR ($CDCl_3$) δ +45.12 (major); +44.97 (minor); diastereomeric ratio = 94.7:5.3.

(3a*R*, 7a*R*)-2-[(1*R*)-Methyl-3-butene]-[3a,4,5,6,7,7a-octahydro-1,3-dimethyl-1,3,2-benzodiazaphosphole] -2-oxide (28d). This product was prepared in an identical manner as described above from *(R,R)*-ethyl phosphonamide and allyl bromide (yield, 84%); mp. 88°C; $[\alpha]_D$ -91.5° (c 1.0, $CHCl_3$); IR (film)ν_{max} 3460, 2950, 1600, 1490, 1450, 1360, 1290, 1245, 1150 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.73 (m, 1 H, C<u>H</u>=CH_2), 5.06 (m, 2 H, CH=C<u>H</u>$_2$), 2.80 (m, 2 H, P-CH(Me)-C<u>H</u>$_2$-CH_3), 2.55-2.70 (m, 2 H, 2 x CH-N), 2.61 (d, 3 H, $^3J_{P-H}$=9.2 Hz, N-CH_3), 2.54 (d, 3 H, $^3J_{P-H}$=11.3 Hz, N-CH_3), 1.08-1.33 and 1.75-1.22 (2 x m, 9 H, C<u>H</u>-CH_2-CH=CH_2, 4 x -C<u>H</u>$_2$), 0.99 (dd, 3 H, C<u>H</u>$_3$-CH, J=7.0 Hz, J=3.4 Hz); ^{13}C NMR δ 136.31 (d, J=16.2 Hz, C=C), 116.49, 64.98 (d, $^2J_{P-C}$=3.5 Hz, P–N–CH), 64.25 (d, $^2J_{P-C}$=6.7 Hz, P–N–CH), 35.12, 32.48 (d, J_{P-C}=113.4 Hz), 30.80, 28.40, 28.08, 27.80, 24.09 (d, J=13.6 Hz), 12.84; ^{31}P NMR ($CDCl_3$) δ +44.51 (major); +44.15 (minor); diastereomeric ratio = 96:4; MS (CI) 257 (M+1), 187; MS (EI) 256 (M), 214, 187, 141, 110, 98, 70; HRMS for $C_{13}H_{25}N_2OP$; calcd. 256.1687; found: 256.1688.

(3a*R*, 7a*R*)-2-[(1*R*)-Methyl-1-deutero-3-butene]-[3a,4,5,6,7,7a-octahydro-1,3-dimethyl-1,3,2-benzodiaza phosphole] -2-oxide (19). A solution of *(R,R)*-α-monodeuteroethyl phosphonamide **18**, (119 mg, 0.55 mmol) in THF (2.5 ml) is cooled at -78°C and treated with n-BuLi (265 μL of a 2.3 M, solution in hexane). The reaction mixture was stirred at -78°C for 45 min. and allyl bromide (60 μL) was added. The reaction mixture was stirred at -78°C for 5 min. and methanol (0.5 mL) was added and the mixture allowed to warm to 25°C. EtOAc (10 ml) was added and the mixture was processed as usual. The residue was purified by chormatography (AcOEt:MeOH 97:3) to give 117 mg of the desired product (yield, 83%); mp. 87°C; $[\alpha]_D$ -93.7° (c 1.43, $CHCl_3$); IR(CCl_4)ν_{max} 2950, 1490, 1450, 1365, 1280, 1245, 1150 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.75 (m, 1 H, -CH_2C<u>H</u>=CH_2), 5.07 (m, 2 H, CH_2CH=C<u>H</u>$_2$), 2.70 (m, 1 H, P-N-CH), 2.65 (m, 2 H, P-N-CH et P-CH(Me)-C<u>H</u>a), 2.63 (d, 3 H, J=9.2 Hz, P-N-CH_3), 2.56 (d, 3 H, J=11.3Hz, P-N-CH_3), 2.0 (m, 3 H, cycle et P-CH(Me)-C<u>H</u>$_b$), 1.8 (m, 2 H, cycle), 1.2 (m, 3 H, ring), 0.94 (d, 3 H, ^{3}J=7.0 Hz, P-CH-(CH_3); ^{13}C NMR ($CDCl_3$) d 136.12 (d, J=15.7 Hz, -C<u>H</u>=CH_2), 116.10, 64.80 (d, J=3.6 Hz), 64.0 (d, J=7.0 Hz), 34.83, 32.0 (dt, J=113.3 Hz, P-C<u>D</u>-(Me)-CH_2-) 30.48, 28.21 (d, J=10.0 Hz), 27.87 (d, J=6.3 Hz), 27.53 (d, J=5.2 Hz), 12.55 (d, J=3.1 Hz, P-CD-C<u>H</u>$_3$);^{31}P NMR ($CDCl_3$) δ +44.53 (major); +44.13 (minor); diastereomeric ratio = 88:12, MS (CI) 257 (M), 215, 187, 141, 110, 98, 83, 70; HRMS for $C_{13}H_{24}DN_2OP$; calcd. 257.1722; found: 257.1869.

(3a*S*, 7a*S*)-2-[(1*S*)-Methyl-3-butene]-[3a,4,5,6,7,7a-octahydro-1,3-dimethyl-1,3,2-benzo diazaphosphole]-2-oxide (29j). This product was prepared in an identical manner as described above in the general procedure from *(S,S)*-ethyl phosphonamide and allyl bromide (yield, 83%); mp. 87-89°C; $[\alpha]_D$ +91.0° (c 1.0, $CHCl_3$); ^{31}P NMR ($CDCl_3$) δ +44.65 (major); +44.25 (minor); diastereomeric ratio = 96:4.

1-Iodo-2-*tert*-butyldiphenylsilyloxy ethane. A 100 mL anhydrous flask was charged with 2-chloroethanol (2.5 g, 32.0 mmol), acetone (25 mL), sodium iodide (11.5 g) and the mixture heated at reflux for 36 h. in the dark. The resulting precipitate was filtered off, the solvent was evaporated and the residue distilled. The fraction that distilled at 62°C and 16 mmHg gave 2.86 g of the desired iodo alcohol (53%). This material (2.84 g, 0.016 mol) was dissolved in dichloromethane and treated with imidazole (2.25 g, 0.033 mol), DMAP (275 mg; 10 mol%) and 0.1 mL of DMF. The mixture was stirred at 0°C while tert-butyldiphenylsilyl chloride (5.02 g, 0.018 mol) in dichloromethane was slowly added over a 20 min. period. The mixture was stirred for 1 h. at 25°C, filtered over Celite and rinsed with CH_2Cl_2 (25 mL). Dichloromethane (100 ml) was added and the mixture washed with 1 N HCl (2 x 20 mL); water (2 x 20 mL) and brine (1 x 20 mL). The organic layer was dried over MgSO4 and the solvent evaporated to give 6.28 g (93%) of a viscous oil, which was essentially pure; IR (film)ν_{max} 3040, 2900, 1590, 1470, 1430, 1180, 1110, 1050, 930, 825, 700 cm^{-1}; ^1H NMR (CDCl3) d 7.70 (m, 4 H, ArH), 7.42 (m, 6 H, ArH), 3.88 (t, 2 H, J=6.8 Hz, I-C<u>H</u>$_2$-CH_2-O), 3.24 (t, 2 H, J=6.8 Hz, -CH_2-C<u>H</u>$_2$-O), 1.09 (s, 9 H, t-Bu); ^{13}C NMR δ 135.4, 133.15, 129.7, 129.6, 64.48, 26.66, 19.13, 6.65; MS (EI) 352 (M-*t*-Bu).

(3a*R*, 7a*R*)-2-[(1*R*)-methyl-3-*tert*-butyl diphenylsilyloxypropane]-[3a,4,5,6,7,7a-octa hydro-1,3-dimethyl-1,3,2-benzodiazaphosphole]-2-oxide (28g). This product was prepared in an identical manner as described above in the general procedure from *(R,R)*-ethyl phosphonamide **9** and 1-iodo-2-tert-butyldiphenylsilyloxy ethane; the reaction was complete in 60 min. after the addition of the electrophile (yield, 78%); (oil); $[\alpha]_D$ -32.5° (c 1.03, $CHCl_3$); IR (film) 3450, 2950, 1600, 1470, 1290, 1145 cm^{-1}; ^1H NMR ($CDCl_3$) d 7.65 et 7.42 (2 m, 10 H, ArH) 3.75 (m, 2 H, CH_2OSi-), 2.65 (m, 3 H, 2 x N-C<u>H</u>, P-C<u>H</u>-CH_3) 2.60, (d, 3 H, N-CH_3, $^3J_{P-H}$=9.2 Hz), 2.52 (d, 3 H, N-CH_3, $^3J_{P-H}$=11.3 Hz), 2.25 (m, 2 H, C<u>H</u>$_2$-CH_2-OSi), 1.10-2.10 (m, 8H, 4 x -C<u>H</u>$_2$-, ring), 1.06 et 1.00 (dd, 3 H, P-CH(R)-C<u>H</u>$_3$, J=7.3 Hz, J=5.7 Hz), 1.04 (s, 9 H, t-butyl); ^{13}C NMR δ 135.40, 133.62, 129.46, 127.49, 64.77 (d, $^2J_{P-C}$=3.5 Hz, N-CH), 64.42 (d, $^2J_{P-C}$=6.6 Hz, N-CH), 61.45 (d, J=15.8 Hz, Si–O–CH_2), 33.07, 30.48, 28.80 (d, J_{P-C}=107.6 Hz), 28.40, 28.13, 26.69, 24.26, 19.05, 13.32; ^{31}P NMR ($CDCl_3$) δ +44.72 (major); 44.25 (minor); diastereomeric ratio (94:6); MS (CI) 497 (M-1), 421, 388, 353, 309, 216, 199, 187, 135; HRMS for $C_{28}H_{43}N_2O_2SiP$; calcd. 498.3150; found: 498.2840.

1-Iodo-3-*tert*-butyldiphenylsilyloxy propane. This material was prepared in the same manner as described for 1-iodo-3-*tert*-butyldiphenylsilyloxy ethane in 47% yield for iodination and 94% for the silylation reaction; IR(film) ν_{max} 3040, 2900, 1590, 1470, 1430, 1180, 1110, 1055, 930, 825 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.73 (m, 4 H, ArH), 7.43 (m, 6 H, ArH), 3.77 (t, 2 H, J=5.6 Hz, I-CH_2-), 3.39 (t, 2 H, J=6.8 Hz, -CH_2-CH_2-O), 2.10 (septuplet, 2 H, J=5.8 Hz, -C<u>H</u>$_2$-CH_2-O), 1.11 (s, 9 H, t-Bu); ^{13}C NMR δ 135.41, 133.38, 129.54, 127.55, 63.02, 35.96, 26.70, 19.09, 3.34; MS (EI) 366 (M - t-Bu).

(3a*R*, 7a*R*)-2-[(1*R*)-Methyl 4-*tert*-butyl diphenylsilyloxybutane)-[3a,4,5,6,7,7a-octahydro-1,3-dimethyl-1,3,2-benzodiazaphosphole]-2–oxide (28h). This product was prepared in an identical manner as described above in the general procedure from *(R,R)*-ethyl phosphonamide **9** and 1-iodo-2-tert-butyldiphenylsilyloxy ethane. The reaction was complete in 60 min. after the addition of the electrophile; (yield, 80%); $[\alpha]_D$ -35.5° (c 1.1, $CHCl_3$); IR (film) 3445, 2950, 1600, 1450, 1290, 1250, 1145 cm^{-1};^1H NMR ($CDCl_3$) d 7.65 et 7.43 (2 m, 10 H, ArH), 3.66 (m, 2 H, CH_2OSi-), 2.60 (m, 3 H, 2 x C<u>H</u>-N, CH_3-C<u>H</u>-P), 2.61 (d, 3 H, N-CH_3, $^3J_{P-H}$=9.2 Hz), 2.53 (d, 3 H, N-CH_3, $^3J_{P-H}$ = 11.3 Hz), 2.05–1.08 (4 m, 12 H, 4 x CH_2, cycle, C<u>H</u>$_2$-CH_2-OSi-C<u>H</u>$_2$-CH_2-CH_2-OSi-), 1.06 et 1.00 (dd, 3 H, C<u>H</u>$_3$-CH, J=7.1 Hz, J=4.0 Hz), 1.05 (s, 9 H, t-butyl); ^{13}C NMR δ 135.33, 133.70, 129.36, 127.42, 64.87 (d, J_{P-C}=3.2 Hz, N-CH), 64.36 (d, J_{P-C}=6.3 Hz, N-CH), 63.62, 32.71 (d, J_{P-C}=133.0 Hz, P-C<u>H</u>–CH_3), 30.65, 28.37 (d, J=9.7 Hz), 28.08 (d, J=6.1 Hz), 27.85 (d, J=5.8 Hz), 26.99, 26.66, 24.11, 13.32; ^{31}P NMR ($CDCl_3$) δ +44.81; diastereomeric ratio > 99:1; MS (CI) 513 (M+1), 455, 199, 187, 141, 110, 91; HRMS for $C_{29}H_{45}N_2O_2SiP$; calcd. 512.3313; found: 512.2950.

General procedure for the hydrolysis of α-methyl α-alkyl phosphonamides – (1*R*)-(+)-1-Methyl-2-phenethyl phosphonic acid (30c). Typical procedure: The α-methyl phenethyl phosphonamide (100 mg, 0.327 mmol)) was treated with 1 N HCl (5.0 ml) and the mixture stirred at room temperature for 12 h. The reaction can be monitored by TLC (BuOH, EtOH, NH_4OH, H_2O in a 4:4:4:1 ratio). The solvent was evaporated and the residue taken in 1.0 ml of MeOH:H_2O (1:1) and passed through a Dowex-50W-H^+ column (12 cm by 1 cm) using MeOH:H_2O (4:1) as eluent. The molybdenum blue positive fractions are collected and the solvents evaporated. The residue was dried in the presence of P_2O_5 for 24 h. under high vacuo (yield, 86%); mp. 122-125°C; $[\alpha]_D$ +23.6° (c 2.2, MeOH); IR (film)ν_{max} 3500 (OH), 2970, 2940, 1640, 1490, 1450, 1250, 1210, 1110, 1000, 690 cm^{-1}; ^1H NMR (CD_3OD) δ 7.22 (m, 5 H, ArH), 3.22 (ddd, 1 H, J_{P-H}=13.5 Hz, J=9.4 Hz, J=3.3 Hz, CH_aPh), 2.41 (ddd, 1 H, J_{P-H}=27.1 Hz, J=9.4 Hz, J=6.60 Hz, CH_bPh), 2.00 (ddd, 1 H, J_{P-H}=27.1 Hz, J=9.4 Hz, J=3.3 Hz, C<u>H</u>-CH_3), 1.00 (dd, 3 H, P–CH–C<u>H</u>$_3$, J=18.1 Hz, J=7.1 Hz); ^{13}C (CD_3OD), d 140.98 (d, J=15.6 Hz) 129.98, 129.40, 127.25, 37.38, 34.90 (d, J=138.4 Hz), 12.93; ^{31}P NMR (CD_3OD) δ +33.25; MS (EI) 200 (M), 118, 91, 69; HRMS for $C_9H_{13}O_3P$; calcd. 200.058; found: 200.061.

(1*S*)-(–)-1-Methyl-2-phenethyl phosphonic acid (31h). This acid was prepared according to the general method described above (yield, 82%); mp. 122-124°C; $[\alpha]_D$ -22.8° (c 1.0, MeOH).

(1*R*)-(+)-1-Methyl propyl phosphonic acid (30a). This acid was prepared according to the general method described above (yield, 90%); mp. 54-57°C; $[\alpha]_D$ +6.2° (c 1.0, MeOH); IR (film)ν_{max} 3500, 2970, 2940, 1250, 1210, 1110, 1000 cm^{-1}; ^1H NMR (CD_3OD) d 1.82 (m, 1 H, CH-CH_{2a}-CH_3), 1.62 (m, 1 H, CH-CH_{2b}-CH_3), 1.35 (m, 1 H, P-CH-CH_3), 1.14 (dd, 3 H, CH_3-CH, J=34.4 Hz, J=7.1 Hz), 0.99 (t, 2 H, CH_3-CH_2, J=7.30 Hz); ^{13}C NMR(CD_3OD) δ 34.41 (d, J=138.1 Hz), 24.40, 13.30, 12.45; ^{31}P NMR (CD_3OD) δ +34.53; MS (EI) 123 (M-CH_3), 110, 82; HRMS for $C_4H_{19}O_3P$; calcd. 138.0860; found: 123.0215 (M-CH_3).

(1*S*)-(–)-1-Methyl propyl phosphonic acid (31f). This acid was prepared according to the general method described above (yield, 91%); mp. 54-56°C; $[\alpha]_D$ -6.1° (c 1.0, MeOH).

(1*R*)-(–)-1-Methyl-3-butene phosphonic acid (30b). This acid was prepared according to the general method described above (yield, 88%); $[\alpha]_D$ -1.15° (c 1.75, MeOH); IR (film)ν_{max} 3500, 2960, 2940, 1250, 1210, 1110, 1000 cm^{-1};^1H NMR (CD_3OD) δ 5.82 (m, 1 H, CH=CH_2), 5.00 (m, 2 H, CH_2=CH), 2.56 (m, 1 H, P-CH-CH_3), 2.02 (m, 1 H, CH_{2a}–CH=CH_2), 1.78 (m, 1 H, CH_{2b}–CH=CH_2), 1.12 (dd, 3 H, CH_3-CH, J=18.1 Hz, J=7.0 Hz); ^{13}C NMR (CD_3OD) δ 137.47, 117.02, 35.84, 32.50 (d, J=140,4 Hz), 13.37; ^{31}P NMR (CD_3OD) δ +33.42; MS (EI) 150, 135, 118, 109, 96, 83; HRMS for $C_5H_{11}O_3P$; calcd. 150.0443; found: 150.0970.

(1*S*)-(+)-1-Methyl-3-butene phosphonic acid (31g). This acid was prepared according to the general method described above (yield, 88%), $[\alpha]_D$ +1.43° (c 1.40, MeOH).

(1*R*)-(+)-1-Methyl -3-propanol phosphonic acid (30d). This acid was prepared according to the general method described above (yield, 94%); mp. 35°C; $[\alpha]_D$ +7.0° (c 1.25, MeOH); IR (film)ν_{max} 3500, 2900-2500, 1460, 1385, 1250, 1210, 1110 cm^{-1}; ^1H NMR(CD_3OD) δ 3.65 (m, 2 H, CH_2–OH), 1.98 (m, 2 H, CH_2–CH_2–OH), 1.52 (m, 1 H, P-CH-CH_3), 1.17 (dd, 3 H, CH_3-CH, J=18.2 Hz, J=7.1 Hz); ^{13}C NMR (CD_3OD) δ 60.48 (d, ^3J=13.7 Hz, CH_2-CH_2-OH), 34.24 (d, ^2J=2.8 Hz, P-C-(CH_3)-CH_2-), 29.38 (d, J_{P-C}=104.9 Hz, P–CH), 13.79 (d, ^2J=4.5 Hz, -CH_3); ^{31}P NMR(CD_3OD) δ +34.29; MS (EI) 154, 91, 87; HRMS for $C_4H_{11}O_4P$; calcd. 154.0393; found: 152.0315.

(1*R*)-(+)-1-Methyl-4-butanol phosphonic acid (30e). This acid was prepared according to the general method described above (yield, 92%); $[\alpha]_D$ +23.8° (c 1.1, MeOH); IR (film)ν_{max} 3500 , 2900-2500, 1460, 1385, 1250, 1210, 1110 cm^{-1}; ^1H NMR (CD_3OD) δ 4.20 (m, 2 H, -CH_2-OH), 2.10 1.60 (mm, 5 H, P-CH-CH_3, -CH_2-CH_2-CH_2-OH, -CH_2-CH_2-CH_2-OH), 1.17 (dd, 3 H, CH_3-CH-P, J=18.3 Hz, J=6.9 Hz); ^{13}C NMR (CD_3OD) δ 70.96 (d, ^4J=6.0 Hz, CH_2–CH_2–OH),31.90 (d, ^2J=6.5 Hz, P-C-(CH_3)-CH_2-), 31.35 (d, ^1J=129.0 Hz, P-CH), 27.43 (d, ^3J=5.1 Hz, P-C-(CH_3)-CH_2-), 14.15 (d, ^2J=5.2 Hz, CH_3); ^{31}P NMR (CD_3OD) δ +34.30; MS (EI) 168, 91, 87; HRMS for $C_5H_{13}O_4P$; calcd. 168.0550; found: 168.0512.

(3a*R*, 7a*R*)-2-Propyl-[3a,4,5,6,7,7a-octahydro-1,3-dimethyl-1,3,2-benzodiazaphosphole]-2-oxide (23). This material was prepared in the same manner as described for ethyl phosphonamide **9** using propyl phosphonic dichloride and (*R,R*)-1,2-diaminocyclohexane (Et_3N, benzene) (yield, 78%); mp. 48°C (hexanes); $[\alpha]_D$ -91.25° (c 1.28, $CHCl_3$); IR (film)n_{max} 3450, 2900, 1450, 1310, 1255, 1215, 1170, 1015 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.68 (m, 1 H, N-CH), 2.57 (d, 3 H, N-CH_3, $^3J_{P-H}$=10.1 Hz), 2.54 (d, 3 H, N-CH_3, $^3J_{P-H}$=11.5 Hz), 2.48 (m, 1H, N-CH), 2.0 (m, 2 H, ring), 1.9-1.1(mm, 10 H, cycle et P-CH_2-CH_2-), 0.99 (dt, 3 H, -CH_2-CH_3, J=7.3, J=1.75); ^{31}P NMR ($CDCl_3$) δ +43.71; MS (EI) 230 (M), 187 (M-C_3H_7), 162, 141, 110, 98, 81, 70; HRMS for $C_{11}H_{23}N_2OP$; calcd. 230.154; found: 230.155.

(3a*R*, 7a*R*)-2-[(1*S*)-Methyl propyl]-[3a,4,5,6,7,7a-octahydro-1,3-dimethyl-1,3,2-benzodiazaphosphole]-2-oxide (24). A solution of (*R,R*)-propyl phosphonamide **23** (372 mg, 1.617 mmol) in THF (7.0 mL) was cooled at -100°C and treated with n-BuLi (0.725 mL of a 2.45 M solution in hexane) and stirred for 30 min. Iodomethane (2.5 equiv.) was added and the mixture stirred for an additional 20 min at -100°C. MeOH (0.5 mL) was added and the reaction mixture allowed to warm to 25°C. EtOAc (20 ml) was added and the mixture washed with water (2 x 10 mL) and brine (2 x 10 mL). The organic layer was dried over $MgSO_4$ and the solvent evaporated. The residue was purified by chromatography. (AcOEt:MeOH, 99:1) and the oily product obtained consisted of a mixture of diastereomers (αC_S):(αC_R) = 79:21. The minor diastereomer was crystallized out of the mixture from hexanes, leaving the major component as a (αC_S):(αC_R) 92:8 mixture (yield, 88%); $[\alpha]_D$ -89.9° (c 0.78, $CHCl_3$); IR (film)ν_{max} 3450, 2900, 1450, 1310, 1255, 1215, 1170, 1015 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.62 (m, 2 H, P-N-CH), 2.61 (d, 3 H, J=11.1 Hz, P-N-CH_3), 2.54 (d, 3 H, J=11.5 Hz, P-N-CH_3), 2.00 (m, 2 H, ring), 1.95-1.62 (m, 3 H, $C\underline{H}_2CH_3$), 1.72 (m, 2 H, ring), 1.28 (m, 3 H, ring), 1.21 (dd, 3 H, J=17.5 Hz, J=7.2 Hz, P-CH(Et)-$C\underline{H}_3$) 1.05 (m, 1 H, ring), 0.97 (t, 3 H, J=7.3 Hz, P-CH-($CH_2C\underline{H}_3$)-CH_3; ^{31}P NMR ($CDCl_3$) δ + 45.45 (minor); 45.16 (major); MS (EI) 230 (M), 187 (M– C_3H_7), 162, 141, 110, 98, 81, 70; HRMS for $C_{11}H_{23}N_2OP$; calcd. 230.288; found: 230.155.

(3a*R*, 7a*R*)-2-[1-(*rac*)-Methyl-1-deuteropropyl]-[3a,4,5,6,7,7a-octahydro-1,3-dimethyl-1,3,2-benzodiaza-phosphole]-2-oxide (25). This phosphonamide was prepared according the method described above with the exception of utilizing CD_3OD (or CD_3CO_2D) as electrophile (yield, 95%); IR(CCl_4)ν_{max} 3450 , 2900 (C-H), 1450, 1310, 1255, 1215, 1175, 1015 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.72-2.50 (m, 2 H, 2 x N-CH), [2.61 (d, 3 H, $^3J_{P-H}$=8.75 Hz, N–CH_3), 2.52 (d, 3 H, $^3J_{P-H}$=11.1 Hz, N-CH_3), diastereoisomer A], [2.62 (d, 3 H, $^3J_{P-H}$=8.75 Hz, N–CH_3), 2.52 (d, 3 H, $^3J_{P-H}$=11.0 Hz, N–CH_3), diastereoisomer B] 2.11-1.60 (m, 7 H, $C\underline{H}_2$–CH_3, cycle et C$\underline{H}$-CH_3), 1.28 (m, 3 H, ring), [1.2 (d, 3H, 17.7 Hz, P-CD-(Et)-$C\underline{H}_3$), A, 1.02 (d, 3 H, 17.9 Hz, P-CD-(Et)-$C\underline{H}_3$), B], 1.02 (m, 1 H, ring), [0.99 (t, 3 H, J=6.15 Hz, P-CD (Me)-CH_2-$C\underline{H}_3$ A); 0.965 (t, 3 H,J=6.15 Hz, P-CD (Me)-CH_2-$C\underline{H}_3$); ^{13}C NMR ($CDCl_3$) δ 65.00, 64.45, 34.45 (t, J_{P-C}=113.2 Hz), 30.90, 28.31, 28.18, 27.89, 24.28, 24.11, 23.73 (d), 12.70,12.43. 64.98., 64.35, 34.45 (t, J_{P-C}=113.2 Hz), 30.77, 28.23, 28.15,27.83, 24.22, 23.92, 23.25 (d), 12.99 (d), 12.60, 12.34 (t) (both diastereomers; ^{31}P NMR ($CDCl_3$) δ +45.57; +45.29 (*R*):(*S*) 50:50; HRMS for $C_{12}H_{25}DN_2OP$; calcd. 245.175; found: 245.170.

(3a*R* , 7a*R*)-2-[1-(*rac*)-Methyl-1-methyl-2-phenylpropyl]-[3a,4,5,6,7,7a-octahydro-1,3-dimethyl-1,3,2-benzo-diazaphosphole]-2–oxide (26). A solution of (3aR, 7aR)-2-[(1*S*)-methyl propyl]-[3a,4,5,6,7,7a-octahydro-1,3-dimethyl-1,3,2-benzodiaza-phosphole]-2-oxide (29 mg, 0.118 mmol) in THF (1.0 mL) was cooled to -78°C and treated with n-BuLi (1.05 equiv.). The mixture was stirred at -78°C for 2.5 h. and added with benzyl bromide (1.1 equiv.). The reaction mixture was stirred at -78°C for 5 h., then quenched with methanol (0.5 mL) and allowed to warm to 25°C. EtOAc (20 ml) was added and the mixture washed with water (2 x 10 mL) and brine (2 x 10 mL). The organic layer was dried over $MgSO_4$ and the solvent evaporated. The residue was purified by chromatography (AcOEt:MeOH, 98:2) to give 31 mg of the desired alkylation product as an oil (yield, 78%); IR (film)ν_{max} 3450, 2900, 1600, 1490, 1450, 1365, 1295, 1240, 1200, 1150, 1110 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.32-7.18 (m, 5 H, Ar.), 2.99 (m, 1 H, P-C$\underline{H}$-CH_2), 2.97 (m, 2 H, Ph-$C\underline{H}_2$), 2.79 (m, 1 H, P-N-C$\underline{H}$-CH_2), [2.72 (dd, 3 H, J=8.75 Hz, J=0.6 Hz, P-N-CH_3), 2.65 (dd, 3 H, J=9.0 Hz, J=0.6 Hz, P-N-CH_3), diastereoisomer A), 2.635 (dd, 3 H, J=11.25 Hz, J=0.7 Hz, P-N-CH_3), 2.63 (dd, 3 H, J=11.1 Hz, J=0.7 Hz, P-N-CH_3), diastereoisomer B), 2.05 (m, 2 H, ring), 1.82 (m, 2 H, ring), 1.55 (m, 4 H, cycle, $C\underline{H}_2$-CH_3), 1.3 (m, 3 H, ring), [1.15 (d, 3 H, J = 26.3 Hz, P-CH(Bn)-$C\underline{H}_3$, diastereoisomer A), 1.07 (d, 3 H, J=26.0 Hz, P-CH(Bn)-$C\underline{H}_3$, diastereoisomer B), 1.06 (m, 1 H, ring), [1.08 (t, 3 H, J=9.2 Hz, $C\underline{H}_3$-CH_2), diastereoisomer A, 0.99 (t, 3 H, J=8.5 Hz, $C\underline{H}_3$-CH_2), diastereoisomer B]; ^{31}P NMR ($CDCl_3$) δ +48.62 and 48.53; diastereoselectivity: ~52:48; HRMS for $C_{19}H_{31}N_2OP$; calcd. 334.217; found: 334.213.

(3a*R*,7a*R*)-2-Benzyl-[3a,4,5,6,7,7a-octahydro-1,3-dimethyl-1,3,2-benzodiazaphosphole]-2-oxide (32). A 250 mL round-bottom flask was flame-dried under an Argon atmosphere and charged with *(R,R)-N,N'*-dimethyl 1,2-diaminocyclohexane (5.0 g, 35.15 mmol), anhydrous benzene (80.0 mL), Et_3N (9.90 mL, 71.0 mmol) and the mixture was stirred at room temperature. A solution of benzyl phosphonic dichloride (6.96 g, 35.15 mmol) in anhydrous benzene (50 mL) was added dropwise over a period of 30 min with vigorous stirring. The reaction mixture was stirred at 25°C for an additional 90 min., then filtered over a short pad of Celite followed by rinsing with EtOAc (100 mL). The solvents are evaporated and the residue purified by silica gel chromatography (EtOAc:hexanes, 80:20 to EtOAc:MeOH, 95:5) to give 7.81 g (80% yield); of the desired phosphonamide; mp. 104-105°C (hexanes); $[\alpha]_D$ -109.0° (c 1.29, $CHCl_3$); IR(CCl_4)ν_{max} 3090, 3065, 3040, 2945, 2865, 2820, 2708, 2665, 1550, 1450, 1310, 1260, 1220, 1215, 1015 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.31-7.18 (m, 5 H, Ar), 3.32 (dd, 1 H, $^2J_{P-H}$=19.8 Hz, J_{H-H}=14.5 Hz, P-C<u>H</u>a), 3.06 (dd, 1 H, $^2J_{P-H}$=16.9 Hz, J_{H-H}=14.6 Hz, P-C<u>H</u>b), 2.65 (m, 1 H, N-CH), 2.58 (d, 3 H, $^3J_{P-H}$=10.1 Hz), 2.41 (d, 3 H, $^3J_{P-H}$=11.4 Hz), 2.0-1.73 (m, 5 H, N-CH, 4 H, ring), 1.29-0.89 (m, 4 H, ring); ^{13}C NMR (75.43 MHz, $CDCl_3$) δ 132.8 (d, $^2J_{P-C}$=9.0 Hz, P-CH_2-<u>C</u>), 129.9 (d, J=5.9 Hz, Ar), 127.9, 126.2 (d, J=3.3 Hz, Ar), 64.2 (d, J=4.7 Hz, N-<u>C</u>H), 63.8 (d, J=7.2 Hz, N-<u>C</u>H), 33.3 (d, J_{P-C}=107.2 Hz, P-C), 29.3, 28.3, 28.0, 27.8, 27.7, 24.0; ^{31}P NMR (121.4 MHz, $CDCl_3$) (85% H_3PO_4 in D_2O as a reference) δ +37.74; MS (EI) 278 (M), 187 (M– C_7H_7), 139, 110, 91, 81; Anal. calcd. for $C_{15}H_{23}N_2OP$; C, 64.55; N, 10.04; H, 8.33; found: C, 64.46; N, 10.01; H, 8.37.

(3a*R*,7a*R*)-2-[1-(*S*)-Phenethyl]-[3a,4,5,6,7,7a-octahydro-1,3-dimethyl-1,3,2-benzodiazaphosphole]-2-oxide (33). Typical procedure: A solution of benzyl phosphonamide **31** (323 mg, 1.16 mmol) in anhydrous THF (8.0 mL) cooled to –100°C in a 25 mL flame-dried flask. n-BuLi (0.50 mL, 1.23 mmol of a 2.45 M solution in hexane) was added and the homogenous solution stirred for an additional 20 min., then quenched with MeI (0.21 mL, 3.48 mmol) at –100°C. Stirring was continued for 10 more minutes, the mixture was quenched with water (0.5 mL) and warmed to room temperature. EtOAc (20 mL) was added and the mixture washed with water (2 x 5 mL). The organic layer was separated and dried over $MgSO_4$ and the solvents were evaporated. The residue was purified over a silica gel column (18 cm x 2.5 cm), using (AcOEt:hexanes, 80:20 to AcOEt:MeOH, 95:5) to give the desired compound in 98% yield. The crude material showed a ratio of 84:16 by ^1H and ^{31}P NMR. Recrystallization from hexanes at -12°C, gave a diastereomerically pure material in 65% yield; mp. 124-125°C (hexanes) $[\alpha]_D$ -86.5° (c 0.95, $CHCl_3$); IR(CCl_4)ν_{max} 2950, 2865, 1555, 1450, 1310, 1260, 1220, 1215, 1015 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.28-7.18 (m, 5 H, Ar), 3.29 (dq, 1 H, $^2J_{P-H}$=18.3 Hz, J_{H-H}=7.5 Hz, P-C<u>H</u>), 2.55 (m, 1 H, N-CH), 2.58 (d, 3 H, $^3J_{P-H}$=9.5 Hz, P-N-CH_3), 2.47 (s, 3 H, P-N-CH_3), 1.92-1.60 (m, 5H, N-CH, 4 H ring), 1.63 (dd, 3 H, J=16.4 Hz, J=7.33), 1.27-0.84 (m, 4 H, ring); RMN, ^{13}C (75.43 MHz, $CDCl_3$) d 139.0 (d, P-CH_2-<u>C</u>, $^2J_{P-C}$=6.2 Hz), 128.9 (d, J=5.7 Hz, Ar), 127.8, 126.6 , 65.2 (d, J=3.9 Hz, P-N-<u>C</u>H), 63.0 (d, J=6.9 Hz, P-N-<u>C</u>H), 40.6 (d, J_{P-C}=108.6 Hz, P-C), 31.0, 28.0, 27.9, 27.8, 27.6, 24.0, 16.7 (d, J=4.4 Hz, P-CH-<u>C</u>H_3); ^{31}P NMR (121.4 MHz, $CDCl_3$) (85% H_3PO_4 in D_2O as external reference) δ +40.24 (major), 39.49 (minor) in ratio of 84:16; MS(EI) 292 (M), 187 (M- C_7H_7), 169, 139, 110, 83; HRMS for $C_{16}H_{25}N_2OP$; calcd. 292.1704; found: 292.1682. The absolute configuration of this material was substantiated by X-ray crystallography (see ref 28). Alkylation of the *(S,S)*-benzyl phosphonamide with MeI, proceeded in 97% yield. The product was recrystallized to diastereomeric purity in 63% yield; mp. 124°C (hexanes); $[\alpha]_D$ +87.0° (c 0.75, $CHCl_3$).

(3a*R*,7a*R*)-2-[1-(*S*)-Phenyl-3-butene)-[3a,4,5,6,7,7a-octahydro-1,3-dimethyl-1,3,2-benzodiazaphosphole]-2-oxide (36b). This compound was obtained by the stereoselective alkylation of phosphonamide **31** with allyl bromide. The reaction was complete over a 2 h period to give the desired material in 91% yield; mp. 38°C; $[\alpha]_D$ -33.9° (c 1.0, $CHCl_3$); IR(CCl_4)ν_{max} 2950, 2865, 1555, 1450, 1310, 1260, 1220, 1215, 1015 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.31-7.18 (m, 5 H, Ar), 5.54 (m, 1 H, C<u>H</u>=CH_2), 4.87 (m, 2 H, CH=C<u>H</u>$_2$), 3.28 (ddd, 1 H, $^2J_{P-H}$=18.3 Hz, J=12.3 Hz, J=3.3 Hz, P-C<u>H</u>-), 3.06 (m, 1 H, P-CH-C<u>H</u>a-CH=CH_2), 2.74 (m, 1 H, P-CH-C<u>H</u>b-

$CH=CH_2$), 2.57 (d, 3 H, $^3J_{P-H}$=11.1 Hz, P-N-CH_3), 2.49 (d, 3 H, $^3J_{P-H}$=9.5 Hz, P-N-CH_3), 2.0-0.89 (m, 10 H, ring); ^{13}C NMR (75.43 MHz, $CDCl_3$) δ 136.5, 135.6, 129.7, 127.7, 126.8, 116.4, 65.3, 63.0, 46.9 (d, J_{P-C}=107.1 Hz, P–C), 34.8, 30.9, 27.9, 27.9, 27.8, 24.1, 23.9; ^{31}P NMR (121.4 MHz, $CDCl_3$) (85% H_3PO_4 in D_2O as external reference) δ +38.90 (major), +37.97 (minor) ratio 88:12; MS (EI) 318 (M), 276, 187, 169, 141, 130, 110, 91, 79; HRMS for $C_{18}H_{27}N_2OP$; calcd. 318.1865; found: 318.1853.

(3a*R*,7a*R*)-2-[1-(*S*)-1,2-Diphenylethyl]-[3a,4,5,6,7,7a-octahydro-1,3-dimethyl-1,3,2-benzodiazaphosphole]-2-oxide (36c). This compound was obtained by the stereoselective alkylation of phosphonamide **31** with benzyl bromide. The reaction was complete over a 2 h period to give the desired material in 93% yield; mp. 116-117°C; $[\alpha]_D$+71.2° (c 1.0, $CHCl_3$); IR(CCl_4)ν_{max} 2950, 2865, 1555, 1450, 1310, 1260, 1220, 1215, 1015 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.33-7.02 (m, 10 H, Ar), 3.77 (m, 1 H, P-CH-C<u>H</u>$_a$-Ph), 3.54 (ddd, 1 H, $^2J_{P-H}$=24.1 Hz, J=18.5 Hz, J=2.7 Hz, P-C<u>H</u>-), 3.24 (m, 1 H, P-CH-C<u>H</u>$_b$-Ph), 2.69 (d, 3 H,J=11.0 Hz, N-CH_3), 2.56 (d, 3H, J=9.5 Hz, N-CH_3), 2.05-1.02 (m, 10 H, ring); ^{13}C NMR (75.43 MHz, $CDCl_3$) δ 129.9, 128.6, 127.9, 127.6, 126.7, 125.8, 65.3, 63.2, 49.2 (d, $^1J_{P-C}$=106.2 Hz, P-C), 36.8, 31.0, 28.0, 27.97, 27.9, 27.8, 24.2, 23.9, 21.9; ^{31}P NMR (121.432 MHz, $CDCl_3$) (85% H_3PO_4 in D_2O as external reference) δ +38.75 (major), +38.14 (minor), ratio: 90:10; MS(EI) 368 (M), 187, 110, 83, 70; HRMS for $C_{22}H_{29}N_2OP$; calcd. 368.2017; found: 368.1951. Anal. calcd. for $C_{22}H_{29}N_2OP$; C, 71.69; H, 7.93; N, 7.60; found: C, 71.62; H, 8.38; N, 8.00.

(1*S*)-(–)-Phenethyl phosphonic acid (37a). Typical procedure: 1N Hydrochloric acid (8 mL) was added to a solution of phosphonamide **32** (81 mg, 0.28 mmol) in THF (0.5 mL) and the mixture was heated at 70°C (bath temperature) for 12 h. The reaction mixture was cooled to 25°C and evaporated to dryness. The residue was dissolved in MeOH:H_2O 3:1 (0.5 mL) and passed through a Dowex-50(H^+) column (12 cm x 1 cm) using methanol as eluent. The "molybdenum blue" positive fractions were collected and the solvent evaporated to give 49.5 mg, 96% yield of the desired acid as a solid; mp.117-119°C; $[\alpha]_D$ -3.7° (c 1.2, MeOH), $[\alpha]_{578}$ -3.92°, $[\alpha]_{546}$ -4.95°, $[\alpha]_{436}$ -12.16°, $[\alpha]_{365}$ -28.16°; IR (film)ν_{max} 3500-2500 (OH, CH), 1245, 1140, 1000, 930, 800, 760, 700 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 7.36-7.18 (m, 5 H, Ar), 3.13 (dq, 1 H, $^2J_{P-H}$=22.4 Hz, J=7.4 Hz, P-C<u>H</u>(CH_3)-Ph), 1.55 (dd, 3 H, $^3J_{P-H}$=18.0 Hz, J=8.3 Hz, P-CH(C<u>H</u>$_3$)-Ph); ^{31}P NMR (121.432 MHz, CD_3OD) (85% H_3PO_4 in D_2O as external reference) δ +29.23; MS(EI) 186, 167, 149, 129, 105, 91, 83, 79, 77, 71, 57; HRMS for $C_8H_{11}O_3P$; calcd. 186.0910; found: 186.0441.

(1*R*)-(–)-Phenethyl phosphonic acid (39a). This compound was prepared according the method described above: mp. 115°C; $[\alpha]_D$ 4.8° (c 0.9, MeOH), $[\alpha]_{578}$ 4.8°; $[\alpha]_{546}$ 6.1°; $[\alpha]_{436}$ 15.6°; $[\alpha]_{365}$ 35.9°.

(1*S*)-(–)-1-Phenethyl dimethylphosphonate (35). A solution of (1*S*)-(–)-phenylethyl phosphonic acid (50.0 mg) (0.268) in diethyl ether (5.0 mL) was cooled to 0°C. Freshly prepared diazomethane was slowly added until the yellow color persisted. The mixture was stirred at room temperature for 15 minutes and nitrogen was slowly bubbled through for an additional 15 min. The solvent was evaporated and the residue was purified using a short pad of silica gel to give the desired phosphonate in 97% yield as an oil; $[\alpha]_D$ -4.07° (c 0.925, $CHCl_3$); $[\alpha]_{405}$ -16.8°; $[\alpha]_{365}$ -27.0°; IR (film)ν_{max} 2960, 1500, 1460, 1255, 1190, 1065, 1035, 830 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34-7.24 (m, 5 H, Ar), 3.68 (d, 3 H, CH_3O-P, J=10.6 Hz), 3.52 (d, 3 H, CH_3O-P, J=10.5 Hz), 3.20 (dq, 1 H, P-C<u>H</u>-Ph, J=22.73 Hz, J=7.4 Hz), 157 (dd, 3 H, P-CH-C<u>H</u>$_3$, J=7.4 Hz, J=7.5 Hz); ^{31}P NMR (121.4 MHz, $CDCl_3$) (85% H_3PO_4 in D_2O as external reference) δ +29.78; HRMS for $C_{10}H_{15}O_3P$; calcd. 214.0758; found: 214.0751

(1*R*)-(+)-1-Phenethyl dimethyl phosphonate. This compound was prepared according the method described above: $[\alpha]_D$ +5.17° (c 1.15, $CHCl_3$); $[\alpha]_{405}$ +18.7°; $[\alpha]_{365}$ +30.7°.

(1*S*)-(+)-Phenyl-3-butene phosphonic acid (37b). This compound was prepared in 96% yield according to the typical procedure described above; mp. 100°C; $[\alpha]_D$+23.8° (c 1.02, MeOH); IR (film)ν_{max} 3500-2500, 1600, 1490, 1450, 1150, 1000, 925, 795, 765 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 7.34-7.18 (m, 5 H, Ar), 5.61 (m, 1 H, C<u>H</u>=CH_2), 4.94 (m, 2 H, CH=C<u>H</u>$_2$), 3.04 (ddd, 1 H, P-CH-, $^2J_{P-H}$=21.9 Hz, J=21.9 Hz, J=3.6 Hz), 2.84 (m, 1 H, P-CH-(Ar)-C<u>H</u>$_a$-CH=CH_2), 2.68 (m, 1 H, P-CH-(Ar)-C<u>H</u>$_b$-CH=CH_2); ^{13}C NMR (75.4 MHz, CD_3OD) δ 138.22 (d, J=6.5 Hz), 137.15 (d, J=17.0 Hz), 130.55 (d, J=6.5 Hz), 129.27, 127.79, 116.84, 46.88 (d, J_{P-C}=135.4 Hz), 35.43; ^{31}P NMR (121.4 MHz, CD_3OD) (85% H_3PO_4 in D_2O as external reference) δ +27.5; MS(EI) 212 (M), 197, 171, 130, 117, 107, 91, 79, 71, 65, 57, 51; HRMS for $C_{10}H_{13}O_3P$; calcd. 212.060; found: 212.060.

(1*S*)-(+)-1,2-Diphenylethyl phosphonic acid (37c). This compound was prepared in 92% yield according to the typical procedure described above; mp. 143-145°C; $[\alpha]_D$+103.6° (c 1.15, MeOH); IR (film)ν_{max} 3500-2500 (OH, CH), 1600, 1490, 1450, 1150, 1000, 925, 795, 765, 695 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 7.26-6.96 (m, 10H, Ar), 3.56 (m, 1H), 3.48 (m, 1 H), 3.20 (m, 1 H); ^{13}C NMR (75.4 MHz, CD_3OD) δ 130.73 (d, J=6.6 Hz), 129.83, 129.08 (d, J=3.8 Hz), 127.74, 127.0262.80, 33.76 (d, J=544.6 Hz); ^{31}P NMR (121.432 MHz, CD_3OD) (85% H_3PO_4 in D_2O as external reference) δ +27.45; MS(EI) 262, 180, 165, 152, 130, 105, 91, 77, 65, 51; HRMS for $C_{14}H_{15}O_3P$; calcd. 262.0752; found: 262.0751.

(1*R*)-(−)-1,2-Diphenylethyl phosphonic acid (39b). This compound was prepared according the method described above (yield, 91%); mp. 143°C; $[\alpha]_D$ -106.2° (c 0.78, MeOH).

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REFERENCES

1. For a recent monograph, see Seyden-Penne, J.; *"Chiral Auxiliaries and Ligands in Asymmetric Synthesis"* J. Wiley &Sons, Inc. New York, N.Y., 1995; and references cited therein.
2. *"Catalytic Asymmetric Synthesis"* Ojima, I. Ed., **1993**, VCH, New York, N.Y.; and references therein.
3. a) Posner, G.H. in *"Asymmetric Synthesis"* vol. 2; J.D. Morrison, ed. Academic, New York, N.Y. **1983**; b) Nudelman, *"The Chemistry of Optically Active Sulfur Compounds"*, Gordon and Breach, New York, N.Y., **1984**; c) Solladié, G.; Almario, A. *Tetrahedron Lett.* **1994**, *35*, 1939 and references cited therein.
4. Denmark, S. E.; Reed, R.W.; Chen, C.-T. In *"Advances in Carbanion Chemistry"*; Snieckus, V., ed. JAI Press, Inc. Greenwich, CT; **1995** and references cited therein.
5. Hanessian, S.; Delorme, D.; Beaudoin, S.; Leblanc, Y. *J. Am. Chem. Soc.* **1984**, *106*, 5754.
6. Hanessian, S.; Delorme, D.; Beaudoin, S.; Leblanc, Y. *Chem. Scripta* **1985**, *25*, 5.
7. Hanessian, S; Bennani, Y.L.; Delorme, D. *Tetrahedron Lett.* **1990**, *31*, 6461.
8. Hanessian, S; Bennani, Y.L. *Tetrahedron Lett.* **1990**, *31*, 6465.
9. Hanessian, S; Bennani, Y.L.; Hervé, Y. *Synlett* **1993**, 65.
10. Hanessian, S; Bennani, Y.L.; *Synthesis* **1994**, 1272.
11. Hanessian, S.; Beaudoin, S. *Tetrahedron Lett.* **1992**, *33*, 7655; Hanessian, S.; Beaudoin, S. *Tetrahedron Lett.* **1992**, *33*, 7659.
12. a) Hanessian, S.; Gomtsyan, A.; Payne, A.; Hervé, Y.; Beaudoin, S. *J. Org. Chem.* **1994**, *59*, 2922; b) Hanessian, S.; Gomtsyan, A. *Tetrahedron Lett.* **1994**, 35, 7509.
13. Hanessian, S.; Andreotti, D.; Gomtsyan, A. *J. Am. Chem. Soc.* **1995**, *117*, 10393.
14. a) Hua, D. H.; Chan-Yu-K., R.; McKie, J.A.; Myer, L.; *J. Am Chem. Soc.* **1987**, *109*, 5026; b) Haynes, R.K.; Vonwiller, S.C.; Hambley, T.W. *J. Org. Chem.* **1989**, *54*, 5162; c) Denmark, S.E.; Chen, C.T., *J. Org. Chem.* **1994**, *59*, 2922; d) Denmark, S.E.; Dorow, R.L.; *J. Org. Chem.* **1990**, *55*, 5926 e) Cramer, C.J., Denmark. S.E.; Niller, P.C.; Dorow, R.L.; Swiss, K.A.; Wilson, S.R. *J. Am. Chem. Soc.* **1994**, *116*, 2437 and references cited therein. f) Blazis, V. J.; Koeller, K.J.; Kevin, J.; Spilling, C.D. *Tetrahedron: Asymmetry* **1994**, *5*, 499 and references cited therein.; g) Denmark, S.E.; Chen, C.T., *J. Am. Chem. Soc.* **1995**, *117*, 11879; h) Krantz, M.; Denmark, S.E.; *J. Org. Chem.* **1995**, *60*, 5867; i) Devitt, P.G., Kee, T.P. *Tetrahedron* **1995**, *51*, 10987.
15. Glasbøl, F.; Steenbøl, P.; Sondergaard, G.; Sørensen, S. B. *Acta Chem. Scand.* **1980**, *26*, 3605.

16. Onuma, K.; Ito, T.; Nakamura, A. *Bull. Chem . Soc. Japan* **1980**, *53*, 2012.
17. Hanessian, S.; Meffre, P.; Girard, M.; Beaudoin, S., Sancéau, J.-Y.; Bennani, Y.L. *J. Org. Chem.* **1993**, *58*, 1991.
18. Burgada, R. *Bull. Soc. Chim. Fr.* **1972**, 4161.
19. Blazis, V. J.; Koeller, K.J.; Spilling, C.D. *J. Org. Chem.* **1995**, *60*, 931.
20. PCMODEL®-MM2 from "Serena Software".
21. Albrand, J.P.; Gogne, A.; Gagnaire, D.; Robert, J.B. *Tetrahedron* **1972**, *28*, 819.
22. a) Setzer, A.; Black, B. G.; Hovanes, B. A. *J. Org. Chem.* **1989**, *54*, 1709; b) Devilliers, J.; Cornu, M.; Roussel, J.; Navech, J. *Org. Mag. Res.* **1974**, *6*, 205; c) Devilliers, J.; Cornu, M.; Navech, J. *Org. Mag. Res.* **1974**, *6*, 210.
23. a) Kraemer, R.; Navech, J. *Bull. Soc. Chim. Fr.* **1971**, 3580; b) Revel, M.; Navech, J. *Bull. Soc. Chim. Fr.* **1973**, 1195.
24. Pitzer, K.S.; Donath, W.E. *J. Am. Chem. Soc.* **1959**, *81* , 3213.
25. Altona, A.; Buys, H.R.; Havinga, E. *Rec. Trav. Chim. Pays-Bas* **1966**, *85*, 973.
26. a) Altona, A.; Giese, H.J.; Romers, C. *Tetrahedron* **1968**, *24*, 13; b) Buys, H.R.; Altona, A.; Havinga E. *Rec. Trav. Chim. Pays-Bas* **1966**, *85*, 998.
27. Allinger, N.L.; Hirsh, J. A.; Miller, M.A.; Tyminsky, I.J.; Van-Catledge, F.A. *J. Amer. Chem. Soc.* **1968**, *90*, 1199.
28. a) Bélanger-Gariépy, F.; Bennani, Y.L.; Hanessian, S. Brisse, F. *Acta Cryst.* **1989**, *C45*, 289; b) Bennani, Y.L; Bélanger-Gariépy, F.; Hanessian, S. *Acta Cryst.* **1990**, *C46*, 653; c) Bennani, Y.L.; Hanessian, S. *Acta Cryst.* **1991**, *C47*, 1230; d) Bélanger-Gariépy, F.; Bennani, Y.L; Beaudoin, S.; Hanessian, S. *Acta Cryst.* **1992**, *C48*, 1533-1535; e)See references 5-13 and citations therein.
29. a) Wenkert, E.; Roychandhuri, D. *J. Am. Chem. Soc.* **1956**, *78*, 6417; b) Bohlmann, F. *Ber.* **1958**, *91*, 2157. c) Wiewiorowski, M.; Edwards, O. E.; Bratek-Wiewiorowska, M.D. *Can. J. Chem.* **1967**, *45*, 1447.
30. a) Kraemer, R.; Navech, J. *Bull. Soc. Chim. Fr.* **1971**, 3580; b) Cooper, D.B.; Hall, C.R.; Harrisson, J. M.; Inch, T.D. *J. Chem. Soc. Perkin Trans. I*, **1977**, 1969; c) Hall, C.R.; Inch, T.D.; Williams, N.E. *J. Chem. Soc. Perkin Trans. I*, **1982**, 639; d) Cooper, D.B.; Harrisson, J. M.; Inch, T.D. *Tetrahedron Lett.* **1974**, 2697;
31. a) Koizumi, T.; Yanada, R.; Tagaki, H.; Hirai, H.Yoshii, E. *Tetrahedron Lett.* **1981**, 477; c) Hall, L.D.; Malcom, R.B. *Can. J. Chem.* **1972**, *50*, 2092; c) Setzer, W.N.; Black, B.G.; Hovanes, B.A. *J. Org. Chem.* **1989**, *54* , 1709; d) Bentrude, W.G.; Hargis, J.H. *J. Chem. Soc. Chem.Comm.* **1969**, 1113; e) Evelyn, L.; Hall, L.D.; Steiner, P.R.; Stokes, D.H. *Org. Mag. Resonance* **1973**, *5*, 141.
32. Hanessian, S.; Bennani, Y. L.; Leblanc, Y. *Heterocycles* **1993**, *35*, 1411; see also Bousquet, A.; Navech, J.; *C. R. Acad. Sc.* Paris, 246, serie C, **1971.**
33. Derome, A.E.; "*Modern NMR Techniques for Chemistry Research*", Pergamon Press, 1987, New York, N.Y.
34. Bentrude, W.G.; Setzer, N.W. in *"Stereospecificity in 31P-Element Couplings: Proton-Phosphorus Couplings"*; Chap. 11, *"Phosphorus-31 NMR Spectroscopy in Stereochemical Analysis"*, VCH, **1987**, New York, N.Y.; Gorenstein, D.G. in *"Phosphorus-31 NMR, Principles and Applications"* Academic, New York, N.Y. **1984.**
35. Mathis, F. *Phosphorus and Sulfur* **1976**, *1*, 109.
36. a) Cambridge Data Base; b) See references 5-13, 28 and 39.
37. Cowley, A.H.; Pinnell, R.P. *J. Am. Chem. Soc.* **1965**, *87*, 4454.
38. Huchins, R.O.; Maryanoff, B.E.; Albrand, J.P.; Cogne, A.; Gagnaire, D.; Robert, J.B. *J. Am. Chem. Soc.* **1972**, *94*, 9151.
39. Belanger-Gariépy, F.; Delorme, D.; Hanessian, S, S. Brisse, F. *Acta Cryst.* **1986**,*C45*, 856.
40. a) Bottin-Strzalko, T.; Seyden-Penne, J.; Pouet, M.-J.; Simmonin, M.-P. *J. Org. Chem.* **1978**, *43*, 4346; b) Bottin-Strzalko, T.; Seyden-Penne, J.; Pouet, M.-J.; Simmonin, M.-P. *J. Chem. Soc. Perkin Trans I.* **1985**, 1801; c) Bottin-Strzalko, T.; Corset, J.; Froment, F.; Pouet, M.-J.; Seyden-Penne, J.; Simmonin, M.-P. *J. Org. Chem.* **1980**, *45*, 1270; d) Seyden-Penne, J. *Bull. Soc. Chim. Fr.* **1988**, 238; e) Denmark, S. E.; Dorow, R.L. *J. Am. Chem. Soc.* **1990**, *112*, 864; f) Denmark, S.E., Cramer, C.J. *J. Org. Chem.* **1990**, *55*, 1806.
41. Hilderbrand, R. L. in *"The Role of Phosphonates in Living Systems"*, CRC Press: Boca Raton, Fl **1983.**
42. a) Giannousis, P. P.; Bartlett, P. A. *J. Med. Chem.* **1987**, *30*, 1603; b) Kupczyk-Subotkowska, L; Mastalertz, P. *Int. J. Peptide Protein Res.* **1983**, *21*, 485; c) Allen, M. C.; Fuhrer, W.; Tuck, B.; Wade, R.; Wood, J. M. *J. Med. Chem.* **1989**, *32*, 1652. For applications in catalytic antibodies, see Lerner, R.A.; Benkovic, S.J.; Schultz, P.G. *Science* **1991**, *252*, 659.
43. a) Hassall, C. H., in "*Antibiotics*"; F. E. Hahn ed., Springer-Verlag, Berlin, **1983**,

Vol. VI, 1-11; b) Atherton, F. R., Hassall, C. H., Lambert, R. W. *J. Med. Chem.* **1986**, *29*, 29; c) Moroni, M. *Europ. Urol.* **1987**, *13* suppl. 1, 1014.
44. a) McKenna, C. E.; Khawli, L. A.; Bapat, A.; Harutinian, V.; Cheng, Y.-C. *Biochemical Pharmacol.* **1987**, *36*, 3103. b) Camp, N. P.; Hawkins, P. C. D.; Hitchcock, P. B.; Gani, D. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 1047.
45. Magnin, D.R.; Biller, S.A.; Beyer, B.D.; Chen, Y.; Dickson Jr., J.K.; DiMarco, J.D.; Fryszman, O.M., Gougoutas, J.Z.; Lawrence, R.M.; Logan, J.V.H.; Sulsky, R.; Taylor, S.C. Fourth International Symposium on Carbanion Chemistry, Aug. 12-16, **1995**, Fort Collins, Colorado USA.
46. a) Dhawan, B.; Redmore, D. *Phosphorus and Sulfur*; **1987**, *32*, 119 and references cited therein. b) Jacquier, R.; Ouazzani, F.; Roumestant, M-L.; Viallefont, P. *Phosphorus & Sulfur* **1988**, *36*, 73. c) Sawamura, M.; Ito, Y.; Hayashi, T. *Tetrahedron Lett.* **1989**, *17*, 2247; d) Sting, M.; Steglich, W.; *Synthesis*, **1990**, 132; e) Yokomatsu, T.; Shibuya, S. *Tetrahedron: Asymmetry* **1992**, *2*, 377. f) Laschat, S.; Kunz, H. *Synthesis*, **1992**, 90. g) Gajda, T. *Tetrahedron: Asymmetry* **1994**, *5*, 1965. h) Yager, K. M.; Taylor, C. M., Smith III, A. B. *J. Am. Chem. Soc.* **1994**, *116*, 9377. J) Denmark, S. E.; Chen, C-T. *J. Org. Chem.* **1994**, *59*, 2922 and references cited therein; h) Sasai, H.; Arai, S.; Tahara, Y.; Shibasaki, M. *J. Org. Chem.* **1995**, *60*, 6656.
47. a) Westheimer, F.H. *Acc. Chem. Res.* **1968**, *1*, 70; b) Gorenstein, D.G. *Chem Rev.* **1987**, *87*, 1047; c) Trippett, S. *Phosphorus and Sulfur* **1976**, *1*, 89.
48. Mulliez, M. Wakselman, M. *Phosphorus and Sulfur* **1980**, *8*, 27; 37; and 41.
49. Bhongle, N. N.; Notter, R. H.; Turcotte, J. G. *Synth. Comm.* **1987**, *17*, 1071.
50. Bennani, Y.L.; *Ph.D.* Thesis, Université de Montréal, (1991).
51. Maille, R.J.; Fischesser, G.J.; Anderson, M.M. *J. Chromatography* **1977**, *132*, 366.
52. Kinnear, A. M.; Perren, E. A. *J. Chem. Soc. 1952*, 3437.

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