Pergamon

Tetrahedron 55 (1999) 12211–12226

TETRAHEDRON

Convenient Synthesis of Propane Aminophosphonic Acids, Aminodiphosphonic Acids and Their Structural Analogues, Mediated by Azetidinium Salts

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Received 21 May 1999; revised 16 July 1999; accepted 5 August 1999

Abstract: The reactions of azetidinium salts with phosphorus nucleophiles $R_2P(O)H$ have been investigated. Treatment of O-benzyl-N,N-diethyl-3-hydroxyazetidinium salt **2** with $R_2P(O)H$ in the presence of sodium hydride gave the corresponding γ-N,N-diethylamino-β-benzyloxypropylphosphonate **6a** or phosphine oxide **6b**. After debenzylation γ-N,N-diethylamino-β-hydroxypropylphosphonate **3a** and phosphine oxide **3b** were obtained. The compound **6a** was converted into its sulfonate ester **8** which underwent elimination to yield **4**. The structure **4** has been employed in Michael addition of $R_2P(O)H$ to form compounds **5** containing two phosphorus centers. Further compounds of type **3** have been transformed into compounds **5** by reaction with $R_2P(O)H$ in the presence of 1.1 equivalents of NaH in boiling toluene. Finally, azetidinium salts **1** have been converted into compounds **5a** by reaction with two equivalents of $R_2P(O)H$ in the presence of 2.1 equivalents of NaH. Molecular mechanics with implementation of the Allinger MM2 force field and semiempirical AM1 and PM3 methods were used to investigate structures **5d** and **5f**.

Keywords: azetidines; molecular modeling; NMR; phosphine oxides; phosphonic acids and derivatives.

INTRODUCTION

Polyfunctional tertiary phosphine derivatives as well as the corresponding phosphine oxides have attracted considerable interest over the last decade for their applications in a number of areas.[1] Recently, a great deal of attention has focused on unsymmetrical phosphorus ligands, particularly those possessing two or more phosphorus centres of different coordination number.[2] An important new trend in the investigation of phosphorus ligands began with the observation[3] that the stereodiscriminating ability of a metal catalyst depends on the additional functionality in the backbone of its chiral ligands. New types of ligand have therefore been designed and synthesized. A particularly great effort has been made to synthesize phosphorus ligands containing hydroxyl[4] or amino[5] groups.

Gaertner[6] and, later, other authors[7] reported that azetidinium salts undergo a ring opening reaction with some nucleophiles. Prior to our studies no attention had been paid to the interaction of azetidinium salts with

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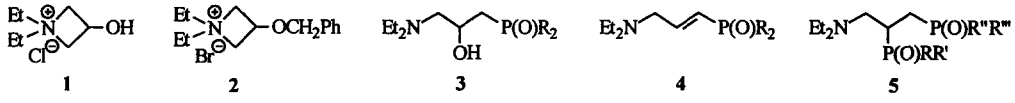
0040-4020/99/$ - see front matter
PII: S0040-4020(99)00698-5

organophosphorus nucleophiles.[8] A communication from this laboratory signalized azetidinium ring opening by phosphorus nucleophiles as a new methodology allowing efficient synthesis of γ-amino-β-hydroxypropylphosphonic acids and their structural analogues.[8]

In this paper, we report the use of the strategy based on ring opening of azetidinium salts **1** and **2** by selected P-nucleophiles. Salts **1** and **2** proved to be an excellent starting materials for the synthesis of compounds **3, 4, 5** - each containing a diethylamino group in the γ-position to the phosphoryl group. To avoid side reactions, protection of the hydroxy group of **1** is essential in reactions leading to compounds **3** and **4**.

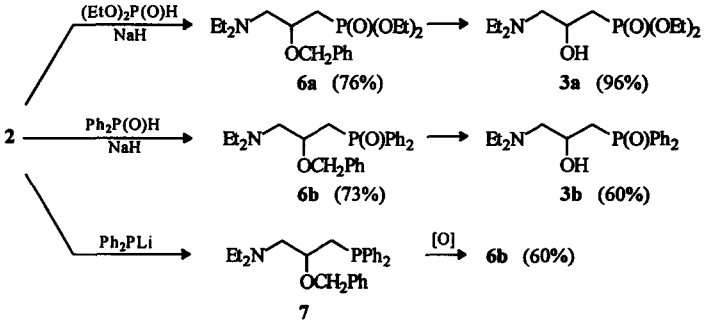


1 **2** **3** **4** **5**

RESULTS AND DISCUSSION

The azetidinium salts **1** are readily available from epichlorohydrin and secondary amines.[9] The modified procedure described in this paper allows efficient synthesis of a series of N,N-dialkylazetidinium salts of type **1**. In this study the N,N-diethyl salt[10] was employed as a model with typical properties but without pronounced steric hindrance at the nitrogen center. Conversion of **1** into the salt **2** was carried out using benzyl bromide. Although the N,N-diethyl azetidinium salt **2** and higher amines show ring-opening behaviour with phosphorus nucleophiles, the N,N-dimethyl salt shows methylating capability.[11]

The reaction of the salt **2** with diethyl phosphite $(EtO)_2P(O)H$ in the presence of a stoichiometric amount of sodium hydride was carried out in dimethoxyethane for 12 hours at room temperature to give the diethyl 2-benzyloxy-3-N,N-diethylaminopropylphosphonate **6a** in 76% yield.

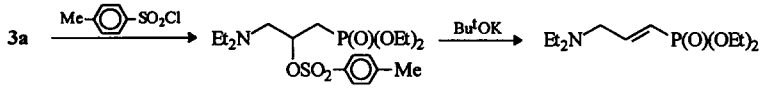


The corresponding reaction with diphenylphosphine oxide $Ph_2P(O)H$ performed in dimethylformamide gave (2-benzyloxy-3-N,N-diethylaminopropyl)diphenylphosphine oxide **6b** in 73% yield. The analogous reaction with lithium diphenylphosphide Ph_2PLi conducted at -40°C in THF gave the compound **7**.

Due to the high susceptibility of phosphine **7**[12] to oxidation we gave up attempts to isolate it. Oxidation *in situ* by tert-butylhydrogen peroxide gave phosphine oxide **6b**. This compound was identical with those prepared by the reaction of diphenylphosphine oxide with the salt **2**.

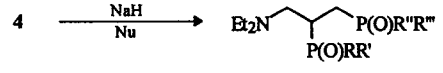
Conventional catalytic deprotection of the benzyl ether **6a** allows recovery of the hydroxyl group affording compound **3a**. Analogous reaction of compound **6b** is unreliable. Therefore in this case we deprotected by reaction with thiophenol in the presence of trifluoroborane etherate.

The 3-amino-2-hydroxypropylphosphonic ester **3a** was converted into the tosylate **8**, which readily underwent elimination with potassium *tert*-butoxide in *tert*-butanol solution to give the vinylphosphonate **4**, which according to NMR spectroscopy has *trans* geometry.



8 (73%) **4** (83%)

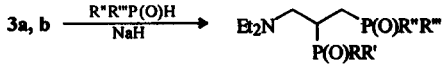
α,β-Unsaturated compound **4** represents a class of compounds which may serve as intermediates in the synthesis of polyfunctional phosphonic acids via Michael addition with a variety of nucleophilic reagents. Here, we report the use of **4** in the synthesis of compounds **5** containing a phosphonic or phosphine oxide function in the β-position.



a: Nu=$(EtO)_2P(O)H$ **5a:** (R = R'= R"= R'''=OEt) (95%)
b: Nu=$Ph_2P(O)H$ **5b:** (R = R'=Ph, R"= R'''=OEt) (91%)

The Michael addition of diethyl phosphite and diphenylphosphine oxide to **4** proceeded in the presence of sodium hydride in over 90% yield.

Compounds containing two phosphorus ligands in the α and β positions can be prepared in a more convenient way: refluxing 2-hydroxypropylphosphonate **3a** or 2-hydroxypropyl phosphine oxide **3b** in toluene with dialkyl phosphite, diphenyl phosphine oxide or *tert*-butylphenylphosphine oxide in the presence of sodium hydride (1.1 molar amount). The expected bis-phosphonate **5a**, bis-phosphine oxide **5b** or hybrid structures **5c,d,e,f** were obtained in good yield (84-88%). In this procedure we avoided the need to prepare α,β-unsaturated compounds of type **4**.

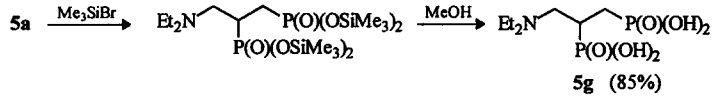


5a: (R = R'= R"= R'''=OEt) (90%) **5d:** (R =Bu^t, R'=Ph, R"= R'''=OEt) (84%)
5b: (R = R'= R"= R'''=Ph) (89%) **5e:** (R = R'=OEt, R"= R'''=Ph) (84%)
5c: (R =R'=Ph, R"= R'''=OEt) (85%) **5f:** (R =Bu^t, R'= R"= R'''=Ph) (88%)

Interaction between β-hydroxy compounds **3** and phosphorus nucleophiles $R_2P(O)H$ in the presence of over one mole equivalent of NaH led to complex equilibria. We assume that α,β-unsaturated compounds **4** are formed initially by elimination of NaO^-; then **4** react with $R_2P\text{-}O^-$ to produce thermodynamically stable compounds **5** in 75-90% yield.

This observation allowed us to work out an even more convenient procedure leading to compounds **5** (R=R'=R"=R'"). When azetidinium salt **1** was allowed to react with three equivalents of $R_2P(O)H$ in the presence of three equivalents of NaH, compounds **5** were formed. A limitation of this procedure is that it can provide only compounds **5** with two identical phosphorus ligands (R=R'=R"=R'"). It is most likely that this reaction involves three steps: a) nucleophilic opening of azetidinium salt **1** leading to the structure **3**, b) an elimination step leading to the α,β-unsaturated structure **4**, c) Michael addition providing the final compound **5**.

Esters of phosphonic acids can be readily transformed into free acids by classic procedures based on transsilylation e.g.



5g (85%)

The successful synthesis of structures **3**, **4** and **5** described in this paper is the first step in a wider study being carried out in our laboratories: the synthesis of P(III) analogues and enantiomeric structures with C and P chiral centers.

Molecular Modelling

In this work molecular mechanics[13] (with implementation of Allinger's MM2 force field) and semi-empirical AM1[14] and PM3[15] methods were used to investigate structures of **5d** and **5f**. Due to the lack of asymmetric induction in the nucleophilic addition of racemic phosphite to propene substrate **4** and formation of the new chiral center on the carbon backbone, we assumed the presence of a mixture of (R_PR), (R_PS), (S_PR) and (S_PS) diastereomers. The geometry of each diastereomer was optimized with respect to all structural parameters (bond lengths, valence and torsional angles). The heat of formation and values of P-C-C-P torsional angles are presented in Table 1. The optimized geometries are shown in Chart 1.

From our data established for **5d** it is apparent that there is no thermodynamic preferences to formation of any particular diastereomer. The heats of formation in vacuum are comparable and are found to be close to 963 kJ/mol. The diastereomers with transoidal conformation around the carbon-carbon bond show slightly smaller energy, however in case of the R_PS diastereomer the comparable energy was also found for the conformer with P-C-C-P torsional angle equal to 56°. The barrier of rotation around C-C bond for P-C-C-P unit is high hence the spontaneous change of conformation can be rather impossible.

Table 1. Geometry of P-C-C-P unit and heat of formation for **5d** and **5f** diastereoisomers. The data are established in vaccum by means of PM3 method.

Compound	Configuration of Chiral Centers	Geometry of -P-C-C-P unit [°]	Heat of Formation [kJ/mol]
5d	P_RC_R	156.95	972.13
	P_SC_R	160.40	967.86
	P_RC_S	123.42	990.89
	P_SC_S	119.41	982.52
5f	P_RC_R	147.40	163.49
	P_SC_R	139.85	156.38
	P_RC_S	132.57	185.68
	P_SC_S	153.49	143.40

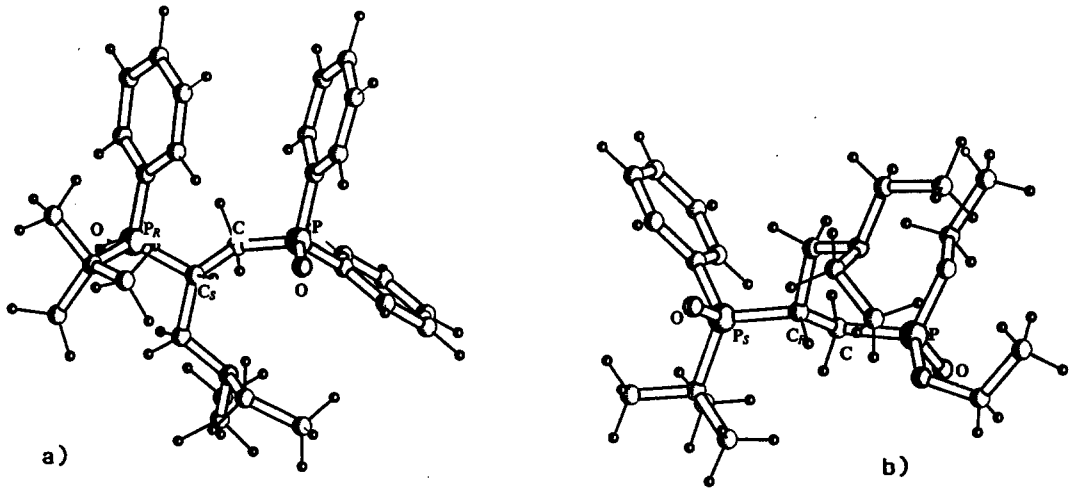


Chart 1

The calculated heat of formation for compound **5f** is *ca* six times larger compared to **5d**. It is interesting to note that established values are different for each diastereomer and this distinction is considerable (from -143.40 kJ/mol to 185.68 kJ/mol). The smallest energy we found for compound with R configuration on phosphorus and S configuration on carbon. As seen in Chart 1b for this sample the aromatic rings attached to α and β phosphorus centers are located in a "face to face" orientation. It seems that in the case of sample **5f** the aromatic-aromatic contacts can be responsible for formation of the more thermodynamically stable diastereomer and/or in the preorganization mechanism this interaction controls the direction of nucleophilic attack.

The tendency to formation of conformers with *trans* geometry is apparent from our calculations and we did not find *cis* conformer of **5f** with comparable energy. From the theoretical studies we predict better selection of nucleophilic addition for sample **5f**.

NMR Spectroscopy Studies

Shown in Figure 1 are one-dimensional ^{31}P broad band proton decoupled NMR spectra of (3-N,N-diethylamino-2-*tert*-butylphenylphosphinoylpropyl)diphenylphosphine oxide **5f** (Fig. 1a) and diethyl (3-N,N-diethylamino-2-*tert*-butylphenylphosphinoylpropyl)phosphonate **5d** (Fig. 1b).

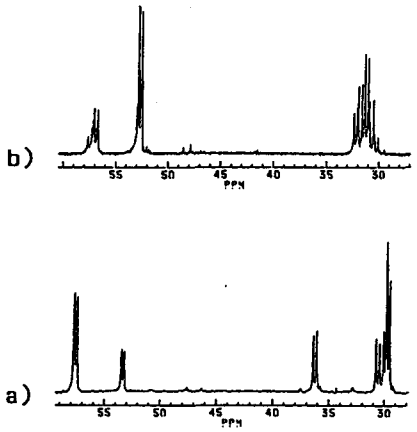


Figure 1

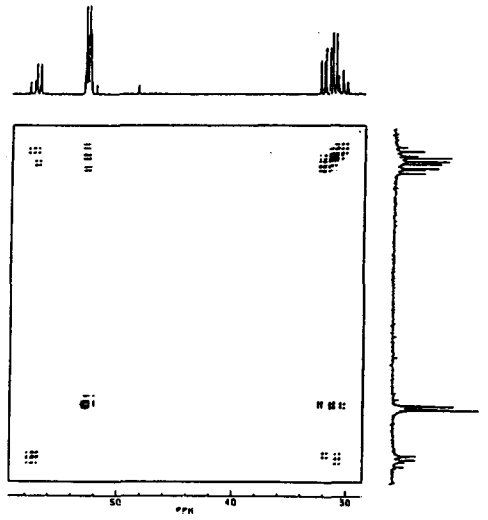


Figure 2

The assignment of the one-dimensional ^{31}P NMR spectra is complicated because of severe overlapping of resonances which correspond to different structures of the obtained products. The ^{31}P chemical shifts were roughly assigned according to NMR data published elsewhere.[16] A downfield shift is assumed for ^{31}P resonances for P(alkyl, aryl) residues versus P(alkoxy) residues of compound **5d**. Care has to be taken in assigning compounds with structural resemblance at both phosphorus residues (for example **5f**). It should be stressed that for resonances separated only by $\Delta\delta$=5.6 ppm, the predicted assignment is ambiguous. Hence, in order to verify the hypothesis which assumed the downfield shift for the Bu^{t}PhP(O)- residue (labelled as α) versus the $Ph_2P(O)$- residue (labelled as β), further results were taken from two-dimensional phosphorus-proton correlation. A long range heteronuclear phosphorus-proton Pulse Field Gradient (PFG) Hetero-Multi Bond Coherence (HMBC) experiment showed the cross-peak between downfield phosphorus signals and signals arising from phenyl and *tert*-butyl protons. The analogous correlation was found for ^{31}P resonances at 35.95 ppm, although the cross-peak from the *tert*-butyl proton was downfield *ca* 1.5 ppm compared to other

tert-butyl signals. The residual cross-peaks from coupled adjacent methylene and/or methine protons were found to be non-diagnostic.

It is known that the phosphorus nucleus, just like other 1/2 spin nuclei, obeys a Karplus-like relationship. Therefore problems regarding the geometry of conformers can be discussed in terms of $^{3}J_{P\text{-}P}$ coupling constants.[17] The crucial information was obtained from detailed analysis of a ^{31}P-^{31}P chemical shift correlated spectroscopy (COSY) experiment. The results were obtained employing a variation on the two-pulse Jeeners's sequence with gated decoupling in order to ascertain the coupling network.[18] Spectra monitored without proton decoupling were observed as broad featureless lines due to strong proton-phosphorus couplings and overlapping of ^{31}P resonances.

Figure 2 displays the contour plot of the two dimensional ^{31}P-^{31}P spectrum for sample **5d**.The off-diagonal or cross-peaks appear for pairs of phosphorus atoms, provided they have mutual scalar coupling. The phosphorus-phosphorus scalar connectivity may be readily apparent from COSY contour plot and cross-section spectra. Cross-peak studies revealed the existence of seven products which are characterized by $^{3}J_{P\text{-}P}$ coupling constants in the range 37-52 Hz. The resonances which correspond to P^{α} residues are found as two sets of signals at 52 ppm and 48 ppm, respectively. The resonances of P^{β} give rise to overlapped doublets found at *ca* 27 ppm. It can be concluded from the data that downfield P^{α} resonances (52 ppm) are characterized by larger phosphorus-phosphorus vicinal coupling constants (*ca* 45 Hz) than upfield P^{α} resonances (48 ppm). Hence, it can be deduced that chemical shifts of P^{α} resonances are strongly affected by changes of P-C-C-P torsional angles. For compound **5f**, it was found that the doublet at δ=57.16 ppm is coupled to the doublet at δ=29.38 ppm; the doublet at δ=52.93 ppm is coupled to the doublet at δ=29.63 and finally the doublet at δ=35.95 ppm is correlated to the doublet at δ=30.31 ppm. The appropriate vicinal phosphorus-phosphorus coupling constants are found to be $^{3}J_{P\text{-}P}$=29.6 Hz, $^{3}J_{P\text{-}P}$26.0 Hz and $^{3}J_{P\text{-}P}$=36.9 Hz, respectively.

Table 2. ^{31}P NMR chemical shifts and $^{3}J_{P\text{-}P}$ coupling constants of **5d** and **5f**

Compound	$^{31}P^{\alpha}$ chemical shifts δ (ppm)	$^{31}P^{\beta}$ chemical shifts δ (ppm)	$^{3}J_{P\text{-}P}$ coupl const. (Hz)
5f	57.16	29.38	29.6
	52.93	29.63	26.0
	35.95	30.31	36.9
5d	52.75	25.97	46.6
	52.41	26.00	46.9
	52.28	27.09	43.4
	48.11	25.53	40.3
	48.03	26.50	38.4
	47.98	26.52	38.4
	47.88	27.55	37.1

In conclusion, the ^{31}P-^{31}P chemical shift correlated spectroscopy was found to be a valuable method in investigation of the coupling network for diastereomeric, bidendate phosphine oxides. This technique allowed the assignment of ^{31}P resonances to the carbon-phosphorus skeleton in a simple, rapid experiment. From the analysis of the phosphorus-phosphorus vicinal coupling constants it has been established that the *trans* conformers are formed for both compounds, however the gauche conformation cannot be excluded. It can be assumed from NMR data that, of the two factors which may be responsible for the trajectory of the nucleophilic attack of P^{III} moieties on the carbon-carbon double bond - namely the steric demands of bulky groups attached to P^{β} phosphorus atom or restricted rotation of P^{β} residues around the C-P bond - the former seems to have greater influence. From molecular modeling we conclude the aromatic-aromatic interactions can be important in asymmetric induction during the formation of new chiral center on carbon. These conclusions have important, synthetic meaning for planning further asymmetric synthesis of bidendate phosphorus ligands.

EXPERIMENTAL

All air and moisture - sensitive reactions were carried out under an atmosphere of argon. Melting points are uncorrected.

All reactions were monitored by ^{31}P NMR spectroscopy or by thin layer chromatography (TLC) using Merck Kieselgel 60 (F_{254}) analytical plates. Spots were detected under UV light or visualized with iodide vapours.

Column chromatography was performed using Merck silica gel 60 (230-400 mesh). Solvents were dried by conventional methods before use. All organic extracts were dried over anhydrous magnesium sulfate and concentrated under reduced pressure. IR spectra were recorded using ATI Mattson Infinity FTIR.

NMR Measurements. Bruker AC-200 and MSL 300 spectrometers operating at 200.13 and 300.13 MHz for ^{1}H, 50.288 and 75.47 MHz for ^{13}C, 80.96 and 121.49 MHz for ^{31}P were used for the NMR spectra. Chemical shifts are reported in ppm (δ) using TMS as internal, H_3PO_4 as external, standard. Coupling constants are given in Hz.

In the 1D NMR spectra the digital resolution was 0.5 Hz per point or better.

In the 2D ^{31}P-^{31}P chemical shift correlated spectra the digital resolution was 7.0 Hz per point. The performed pulse sequence was the modification the basic sequence π/2-τ-π/2-Acquire with broadband proton decoupling during the data acquisition. The ^{31}P-^{1}H 2D chemical shift correlated spectrum was obtained emploing the PFG HMBC pulse sequence in order to ascertain the long range phosphorus-proton connectivities. The digital resolution in the F2 dimension was 5.88 Hz per point and 2.93 Hz per point in the F1 dimension. In the 2D experiments 16 or 32 scans were sufficient to obtain necessary signal-to-noise ratio.

Molecular Modeling. MM+, PM3 and AM1 calculations were carried out using HyperChem™ 5.0 software with IBM Pentium II/333 MHz personal computer. The calculation limit of the energy gradient during the geometry optimization was chosen as 0.08-0.21 kJ mol^{-1} $Å^{-1}$.

N,N-Dialkyl-3-hydroxyazetidinium chlorides 1 and analogues **1a - 1c** were prepared according to the method described in the literature:[9] Equimolar amounts of secondary amine and epichlorohydrin were dissolved in methanol (1 l per 1 mol of starting materials). After the exothermic reaction had finished, the mixture was refluxed for 12 h. The solvent and volatile starting materials were evaporated under reduced pressure. The residue was purified by the crystallization from methanol. The azetidinium chlorides **1 - 1c** were obtained in 90-94% yield as white solids.

1: m.p. 147-150°C; lit.[9b]: m.p. 145-155°. NMR δ_H (300.13 MHz, CD_3OD): 1.32 (t, 6H, $^3J_{H-H}$ = 7.2, N-$CH_2\underline{C}H_3$), 3.50 and 3.62 (each 2xq, 2H, $^3J_{H-H}$ = 7.2, N-$C\underline{H}_2CH_3$), 4.17-4.23 (m, 2H, >$C\underline{H}_2$), 4.55-4.59 (m, 2H, >$C\underline{H}_2$), 4.61-4.92 (m, 1H, >$C\underline{H}$OH). δ_C (75.47 MHz, CD_3OD): 10.78, 11.11, 58.72 and 60.45 ($\underline{C}H_2$ azet.ring), 61.73 ($\underline{C}H_2$-N), 73.20 [>CH(OH)].

N-Pyrrolidino-3-hydroxyazetidinium chloride **1a**: m.p. 134-137°C. IR (nujol) ν_{max} (cm^{-1}): 3388 m b (OH), 3249 m b, 2956 s, 2854 m, 1640 w, 1462 m, 1397 m, 1157 w, 1107 w. δ_H (300.13 MHz, CD_3OD): 2.16-2.21 (m, 4H, N-CH_2-$C\underline{H}_2$), 3.67-3.82 (2xm, 4H, N-$C\underline{H}_2$, 4.30-4.36 (m, 2H, >$C\underline{H}_2$), 4.65-4.72 (m, 2H, N-$C\underline{H}_2$-), 4.89-4.99 (m, 1H, >$C\underline{H}$(OH). δ_C (75.47 MHz, CD_3OD): 24.35, 24.53, 61.82 ($\underline{C}H_2$-N), 67.16 and 68.56 ($\underline{C}H_2$ azet.ring), 74.31 [$\underline{C}$H(OH)]. Anal.calcd for $C_7H_{14}ClNO$: C, 51.4; H, 8.6; Cl, 21.7; N, 8.6. Found: C, 51.3; H, 9.0; Cl, 21.6; N, 8.6%.

N-Pyrimidino-3-hydroxyazetidinium chloride **1b**: m.p. 148-151°C. lit.[9b] m.p. 147-148.5°C. δ_H (300.13 MHz, CD_3OD): 1.60-1.68 (m, 2H) and 1.81-1.91 (m, 4H, N-$CH_2C\underline{H}_2$), 3.50 and 3.60 (each t, J = 5.7, 2H, N-$C\underline{H}_2$), 4.16-4.22 and 4.57-4.63 each m, 2H, >$C\underline{H}_2$ azet.ring), 4.84-4.94 [m, 1H, $C\underline{H}$(OH)]. δ_C (75.47 MHz, CD_3OD): 24.06, 24.45, 23.77, 61.92 ($\underline{C}H_2$-N), 65.07 and 66.63 ($\underline{C}H_2$ azet.ring), 74.13 [>CH(OH)].

N-Morpholino-3-hydroxyazetidinium chloride **1c**: m.p. 116-117°C. lit[9c] m.p. 75-80°C. IR (KBr) ν_{max} (cm^{-1}): 3452 s b (OH), 3267 s b , 2972 w, 2870 w, 1637 w, 1466 m, 1441 m, 1317 m, 1159 s, 1117 s, 1057 w, 968 m, 912 m. δ_H (300.13 MHz, CD_3OD): 2.78-2.88 (m, 4H), 3.00-3.30 (m, 8H), 4.22-4.28 [m, 1H, $C\underline{H}$(OH)]. δ_C (75.47 MHz, CD_3OD): 46.34, 50.51, 50.89, 52.81, 54.05, 61.50, 63.09, 63.81, 64.31 and 65.94 ($\underline{C}H_2$ azet.ring), 73.66 [>$\underline{C}$H(OH)]. Anal.calcd. for $C_7H_{14}ClNO_2$: C, 46.8; H, 7.9; Cl, 19.7; N, 7.8. Found: 46.4; H, 8.2; Cl, 19.7; N, 7.8.

The synthesis of N,N-dialkylamino-3-benzyloxyazetidinium bromide 2

General procedure

To a solution of N,N-dialkyl-3-hydroxyazetidinium chloride **1** (50 mmol) in DMSO (25 cm^3) were added (in one portion) benzyl bromide (60 mmol) and freshly pulverized KOH (60 mmol). The resulting mixture was stirred for 12 h at room temperature. Then calcium hydride (2 g) was added; the suspension was stirred for 2 h at 60°C and allowed to reach room temperature. A precipitate of inorganic salts was filtered off, and the solvent and an excess of benzyl bromide were evaporated in high vacuo (0.05-0.01 mmHg). The crude salts were used for the subsequent reactions.

The reaction of N,N-diethyl-3-benzyloxyazetidinium bromide 2 with sodium dialkyl phosphites

General procedure: 3-Benzyloxyazetidinium bromide **2** (prepared from 3-hydroxyazetidinium chloride **1** (60 mmol) was suspended in DME (50 ml). To a suspension were added dialkyl phosphite (72 mmol) and sodium hydride (72 mmol) and the mixture was stirred at room temperature for 12 h. Then the reaction was quenched with water (100 ml) and the reaction product was extracted with ethyl acetate (3 x 50 ml). After drying and evaporation of solvent, the residue was purified by column chromatography ($CHCl_3$/MeOH 10:1). According to this procedure the following phosphonates **6** were prepared as colorless oils:

6a: (R=OEt): R_f 0.27; Yield: 76%; IR (film) ν_{max} (cm^{-1}): 1194s (P=O), 1053s (P-O-C_2H_5). NMR data were given in the preliminary paper.[8]

Diethyl γ-N-pyrrolidino-β-benzyloxypropyl phosphonate **6a$_1$**: R_f 0.25; Yield: 72%. IR (film) ν_{max} (cm^{-1}): 1240 s (P=O), 1051s and 1023 s (P-OC_2H_5). NMR: δ_P (80.96 MHz, $CDCl_3$): 29.00.

δ_H (300.13 MHz, $CDCl_3$): 1.16-1.25 (m, 6H, P.$OCH_2C\underline{H}_3$), 1.63-1.70 (m, 4H, N-CH_2-$C\underline{H}_2$), 1.94-2.07 and 2.13-2.26 (2 x m, 2H, $C\underline{H}_2$-P), 2.49-2.51 (m, 4H, N-$C\underline{H}_2CH_2$), 2.61-2.64 [m, 2H, N-$C\underline{H}_2C$(OBn)], 3.87-3.94 [m, 1H, $C\underline{H}$(OBn)], 3.96-4.05 (m, 4H, P-O-$C\underline{H}_2CH_3$), 4.58 (AB, J_{AB} 12.0, 2H, $C\underline{H}_2$Ph), 7.18-7.33 (m, 5H, aromatic). δ_C (75.47 MHz, $CDCl_3$): 16.98, 17.01, 17.06, 17.09 ($\underline{C}H_2CH_2$-N), 24.32 ($\underline{C}H_3CH_2O$-P), 30.75 (d, J 139.4, $\underline{C}H_2$P), 55.44 (-$CH_2\underline{C}H_2$-N), 60.71, 60.85 [$\underline{C}$H(OBn)], 61.96, 62.04, 62.16, 62.24 ($CH_3\underline{C}H_2O$-P), 72.47 ($\underline{C}H_2$Ph), 74.61, 74.65 (>N-CH_2-), 128.15, 128.55, 128.89, 139.23. Anal.calcd. for $C_{18}H_{30}O_4N_2P$: C, 58.5; H, 8.2; N, 7.6; P, 8.4. Found: C, 58.7; H, 8.4; N, 7.6; P, 8.2%.

Diethyl γ-N-pyrimidino-β-benzyloxypropyl phosphonate **6a$_2$**: R_f 0.3; Yield: 84%. IR (nujol) ν_{max} (cm^{-1}): 1223 s (P=O), 1028 s (P-OC_2H_5). NMR: δ_P (80.96 MHz, $CDCl_3$): 28.91.

δ_H (300.13 MHz, $CDCl_3$): 1.24-1.37 (m, 6H, $C\underline{H}_3CH_2O$-P), 1.38-1.48 [m, 2H, N-$(CH_2)_2C\underline{H}_2$], 1.51-1.58 (m, 4H, N-CH_2-$C\underline{H}_2$-), 1.97-2.10 and 2.19-2.30 (2 x m, 2H, $C\underline{H}_2$-P), 2.32-2.52 (m, 4H, N-$C\underline{H}_2$-CH_2-), 2.54-2.60 [m, 2H, N-$C\underline{H}_2$CH(OBn)], 3.94-3.99 [m, 1H, $C\underline{H}$(OBn)], 4.01-4.17 (m, 4H, P-O-$C\underline{H}_2CH_3$), 4.63 and 4.68 (AB, J_{AB} 11.4, 2H, $C\underline{H}_2$Ph), 7.23-7.39 (m, 5H, aromatic).

δ_C (75.47 MHz, $CDCl_3$): 16.22, 16.31 ($\underline{C}H_3CH_2$-OP), 24.03, 25.77 (N-$CH_2\underline{C}H_2\underline{C}H_2$-), 29.96 (d, J 139.9, $\underline{C}H_2$-P), 55.12 [N-$\underline{C}H_2$-(CH_2)], 61.18, 61.26, 61.40, 61.49 (P-$O\underline{C}H_2CH_3$), 62.96, 63.11 [$\underline{C}$H(OBn)], 71.74 ($\underline{C}H_2$Ph), 72.40 [>N-$\underline{C}H_2$CH(OBn)], 127.40, 127.84, 127.88, 138.33 (aromatic). Anal.calcd. for $C_{19}H_{32}O_4NP$: C, 61.8; H, 8.7; N, 3.8; P, 8.4. Found: C, 62.0; H, 8.8; N, 3.8; P, 8.6%.

Diethyl 2-benzyloxy-3-N-morpholinopropyl phosphonate **6a$_3$**: R_f 0.27. Yield: 76%. IR (film) ν_{max} (cm^{-1}): 1223 s (P=O), 1028 s (P-OC_2H_5). NMR: δ_P (80.96 MHz, $CDCl_3$): 28.40.

δ_H (300.13 MHz, $CDCl_3$): 1.18-1.30 (m, 6H, $POCH_2C\underline{H}_3$), 1.94-2.06 and 2.08-2.37 (2 x m, 2H, $C\underline{H}_2$-P), 2.42-2.56 [m, 6H, $C\underline{H}_2$-N$(C\underline{H}_2)_2$], 3.54-3.68 [m, 4H, O$(C\underline{H}_2)_2$], 3.86-3.96 [m, 1H, $C\underline{H}$(OBn)], 3.97-4.08 (m, 4H, $CH_3C\underline{H}_2O$-P), 4.58 (s, 2H, CH_2Ph), 7.17-7.36 (m, 5H, aromatic).

δ_C (75.47 MHz, $CDCl_3$): 16.84, 16.92 ($\underline{C}H_3CH_2OP$), 29.36, 30.14, 31.21, 31.86 ($\underline{C}H_2$-P and N-$CH_2\underline{C}H_2$), 36.93, 54.75 (N-$\underline{C}H_2$-CH_2-), 61.85, 61.93, 62.03, 62.11 (P-O-$\underline{C}H_2CH_3$), 62.95, 63.08 [$\underline{C}$H(OBn)], 67.25, 67.45, 72.25, 72.86 [>N-$\underline{C}H_2$CH(OBn)], 128.11, 128.39, 128.77, 138.70 (aromatic). Anal. calcd. for $C_{18}H_{30}O_5NP$: C, 58.2; H, 8.1; N, 3.8; P, 8.3. Found: C, 58.4; H, 8.3; N, 3.8; P, 8.5%.

Reaction of N,N-diethyl-3-benzyloxyazetidinium bromide 2 with sodium salt of diphenyl phosphine oxide. (2-Benzyloxy-3-N,N-diethylaminopropyl)diphenylphosphine oxide 6b.

In the same way, as described above, using DMF as the solvent (2-benzyloxy-3-N,N-diethylaminopropyl)diphenylphosphine oxide **6b** was obtained as pale yellow oil. R_f 0.25. Yield 73%. IR (film) ν_{max} (cm^{-1}): 1440 m (P-Ph), 1236 s (P=O). NMR: δ_P (80.96 MHz, $CDCl_3$): 32.80. δ_H (300.13 MHz, $CDCl_3$): 0.95 (t, J 7.1, 6H, $C\underline{H}_3CH_2N$), 2.41-2.64 [m, 8H, $(CH_3C\underline{H}_2)_2$-N-$C\underline{H}_2$, $C\underline{H}_2P$], 4.01-4.09 [m, 1H, $C\underline{H}$(OBn)], 4.35 and 4.53 (AB, J_{AB} 11.1, 2H, CH_2Ph), 6.92-7.25 (m, 5H, aromatic). δ_C (75.47 MHz, $CDCl_3$): 12.45, 36.03 (d, J 71.7, $\underline{C}H_2$-P), 48.08, 60.81, 60.95, 64.35, 71.75, 72.40, 127.40, 127.84, 127.88, 129.23, 129.39, 131.37, 131.49, 132,48, 138.33. Anal. calcd. for $C_{28}H_{32}O_2NP$: C, 75.5; H, 7.2; N, 3.1; P, 7.00. Found: C, 75.7; H, 7.3; N, 3.1; P, 7.1%.

Reaction of N,N-diethyl-3-hydroxyazetidinium chloride 1 with excess of diethyl phosphite or diphenyl phosphine oxide. Tetraethyl (3-N,N-diethylamino-1,2-propylene)bis-phosphonate 5a and diphenyl (3-N,N-diethylamino-2-diphenylphosphinoylpropyl)phosphine oxide 5b.

General procedure

To a suspension of N,N-diethyl-3-hydroxyazetidinium chloride (30 mmol) in dry toluene (50 ml) were added diethyl phosphite (or diphenyl phosphine oxide) (90 mmol) and sodium hydride (90 mmol). The reaction mixture was stirred and refluxed for 10 h. Then the mixture was poured into water (100 ml), the layers were separated and the water layer was extracted with ethyl acetate (3 x 50 ml). The combined organic extracts were dried and evaporated under reduced pressure. The residue was purified by column chromatography (eluent: $CHCl_3/CH_3OH$, 20:1) to give a pale yellow oil.

5a (R=R'=R"=R'"=OEt); R_f 0.35; Yield: 90%. IR (film) ν_{max} (cm^{-1}): 1223 s (P=O), 1034 s (P-OC_2H_5). NMR data were given in the preliminary paper.[8] Anal. calcd. for $C_{15}H_{35}O_6NP_2$: C, 46.5; H, 9.1; N, 3.6; P, 16.0. Found: C, 46.7; H, 9.0; N, 3.6; P, 16.2%.

5b (R=R'=R"=R'"=Ph); R_f 0.42; Yield: 74%. IR (KBr) ν_{max} (cm^{-1}): 1437 m (P-Ph), 1182 s (P=O). NMR: δ_P (121.49 MHz, $CDCl_3$): 29.05, 30.57, 34.80, 36.32 ($J_{P\text{-}P}$ 36.62). δ_H (300.13 MHz, $CDCl_3$): 0.59 (t, J 7.1, 6H, $C\underline{H}_3CH_2$-N), 2.19-2.30 (m, 4H, J 7.1, $CH_3C\underline{H}_2N$), 2.52-2.59 (m, 2H, $C\underline{H}_2$-P), 2.73-2.80 (m, 2H, N-$C\underline{H}_2$), 3.30-3.67 (m, 1H, $C\underline{H}$-P), 7.26-7.87 (2 x m, 10H, aromatic). δ_C (75.47 MHz, $CDCl_3$): 10.82 ($\underline{C}H_3CH_2$-N), 27.50 (d, J 69.6, $\underline{C}H_2$-P), 31.60 and 31.65 (2 x d, J 69.5, $\underline{C}$H-P), 46.08 ($CH_3\underline{C}H_2N$), 53.78 (N-$\underline{C}H_2$), 128.73-135.28 (m, aromatic). Anal. calcd. for $C_{31}H_{35}O_2NP_2$: C, 72.2; H, 6.8; N, 2.7; P, 12.0. Found: C, 72.4; H, 6.6; N, 2.7; P, 12.2%.

Reaction of diethyl 3-N,N-diethylamino-2-hydroxypropylphosphonate 3a with sodium salts of secondary phosphine oxides. Diethyl (3-N,N-diethylamino-2-diphenylphosphinoyl propyl)phosphonate 5c and diethyl (2-tert-butylphenylphosphinoyl-3-N,N-diethylaminopropyl) phosphonate 5d.

Starting from **3a** (11.3 mmol), diphenyl- (or tert-butylphenyl-)phosphine oxide (12.4 mmol) and sodium hydride (12.4 mmol) and following the procedure described above for the synthesis of **5a** and **5b**, the following compounds were obtained:

5c (R=R'=Ph, R''=R'''=OEt): Yield: 82.5%: IR (film) ν_{max} (cm^{-1}): 1439 s (P-Ph), 1236 s and 1186 s (P=O), 1053 s, 1030 s (P-OC_2H_5). R_f 0.3 ($CHCl_3$/MeOH, 25:1). NMR: δ_P (121.49 MHz, $CDCl_3$): 31.23, 31.34, 31.63, 31.75 [-P(O)$(OEt)_2$] and 35.15, 35.32, 35.44, 35.73 [-P(O)Ph_2]. δ_H (300.13 MHz, $CDCl_3$): 0.76 (t, J 7.1, 6H, $C\underline{H}_3CH_2N$), 1.19 and 1.30 (2 x t, J 7.1, 2 x 3H, $C\underline{H}_3CH_2O$-P), 1.93-2.08 [m, 2H, CH_2P(O)], 2.34-2.45 (m, 4H, $CH_3C\underline{H}_2N$), 2.73-2.87 (m, 2H, N-$C\underline{H}_2$), 3.05-3.11 (m, 1H, C<u>H</u>-P), 3.80-3.93 (m, 2H, $CH_3C\underline{H}_2O$-P), 4.04 (q, J 7.1, 2H, $CH_3C\underline{H}_2$-O-P), 7.30-7.97 (2 x m, 10H, aromatic). δ_C (75.47 MHz, $CDCl_3$): 11.22 (N-$CH_2\underline{C}H_3$), 16.83, 16.93, 17.02, 23.56 (d, J 140.61, <u>C</u>H_2-P), 32.46 (d, J 71.61, <u>C</u>H-P), 46.30, 53.67, 62.03, 62.11, 62.12, 62.21, 62.29, 128.63-132.08 (aromatic). Anal. calcd. for $C_{28}H_{35}O_4NP_2$: C, 61.2; H, 7.8; N, 3.1; P, 13.7. Found: C, 61.4; H, 7.7; N, 3.1; P, 14.0%.

5d (R=Bu^t, R'=Ph, R''=R'''=OEt): Yield: 84%; R_f 0.3 ($CHCl_3$/MeOH, 30:1). IR (film) ν_{max} (cm^{-1}): 1440 m (P-Ph), 1168 s, 1105 s (P=O). NMR: δ_P (121.49 MHz, $CDCl_3$): 29.49-32.42 [m, P(O)$(OEt)_2$], 52.30-52.84 [m, P(O)Bu^tPh], 56.58-57.69 [m, P(O)Bu^tPh]. ^1H NMR spectrum was observed as broad featureless lines. The details concerning ^{31}P NMR spectroscopy of **5d** and **5f** are given in the NMR Spectroscopy section. Anal. calcd. for $C_{21}H_{39}O_4NP_2$: C, 58.5; H, 9.1; N, 3.3; P, 14.4. Found: C, 58.4; H, 9.0; N, 3.3; P, 14.8%.

Reaction of (3-N,N-diethylamino-2-hydroxypropyl)diphenyl phosphine oxide 3b with sodium diethyl phosphite and sodium salts of secondary phosphine oxides. Diphenyl (3-N,N-diethylamino-2-diethoxyphosphonylpropyl) phosphine oxide 5e, (3-N,N-diethylamino-2-diphenylphosphinoylpropyl) diphenyl phosphine oxide 5b and diphenyl 3-N,N-diethylamino-2-*tert*-butylphenyl-phosphinoylpropyl)diphenyl-phosphine oxide 5f.

In the same way as described above, starting from **3b** and sodium diethyl phosphite, sodium salts of diphenyl phosphine oxide and tert-butylphenylphosphine oxide, correspondingly, the **5e**, **5b**, **5f** compounds were obtained:

5e (R=R'=OEt, R''=R'''=Ph). Yield: 84%, R_f 0.35 ($CHCl_3$/MeOH, 20:1). IR ($CHCl_3$) ν_{max} (cm^{-1}): 1439 m (P-Ph), 1236 s, 1190 s (P=O), 1030 (P-OC_2H_5). NMR: δ_P (121.49 MHz, $CDCl_3$): 30.71 and 31.03 [$(P(O)Et)_2$], 32.34 and 32.66 (-P(O)Ph_2), J_{P-P} 39.2 Hz. δ_H (300.13 MHz, $CDCl_3$): 0.88 (t, J 7.1, 6H, $C\underline{H}_3CH_2O$-P), 2.01-2.57 [m, 7H, C<u>H</u>-P, $C\underline{H}_2$-N($C\underline{H}_2CH_3)_2$], 2.59-2.83 (m, 2H, $C\underline{H}_2$P), 3.94-4.12 [m, 4H, P-(O)-$C\underline{H}_2CH_3$], 7.28-7.86 (2 x m, 10H, aromatic). δ_C (75.47 MHz, $CDCl_3$): 11.54, 16.89, 16.95, 17.03, 27.81 (d, J 69.14, <u>C</u>H_2-P), 30.60

(d, J 138.55, CH-P), 46.87, 53.93, 61.96, 62.03, 62.61, 62.68, 129.06-135.74 (aromatic). Anal. calcd. for $C_{28}H_{35}O_4NP_2$: C, 61.2; H, 7.8; N, 3.1; P, 13.7. Found: C, 61.4; H, 7.7; N, 3.1; P, 14.0.

5b (R=R'=R"=R'"=Ph): Yield: 89%. Spectral properties are given above.

5f (R=Bu^t, R'=R"=R'"=Ph). Yield: 88%; R_f 0.4 ($CHCl_3$/MeOH, 20:1). IR (KBr) ν_{max} (cm^{-1}): 1437 m (P-PH), 1182 s, 1163 s (P=O). NMR: δ_P (121.49 MHz, $CDCl_3$): 28.79-30.41 [m, $P(O)Ph_2$], 35.24-36.55 [dd, $P(O)Ph_2$], 52.80-53.04 [2 x d, $P(O)Bu^tPh$], 56.98-57.21 [d, $P(O)Bu^tPh$]. δ_H (300.13 MHz, $CDCl_3$): 0.54-0.99 (2 x t, J 6.4, 6H, CH_3CH_2-N), 1.07-1.25 [m, 9H, $(CH_3)_3C$-P], 2.10-2.23 (m, 2H, CH_2-P), 2.33-2.55 (m, 4H, CH_3CH_2-N), 2.71-2.79 (m, 2H, >N-CH_2-), 3.22-3.41 (m, 1H, CH-P), 7.10-7.86 (4 x m, 15H, aromatic). δ_C (75.47 MHz, $CDCl_3$): 10.07-10.71 (m), 24.92-35.06 (m), 45.45-46.02 (m), 53.64-54.87 (m), 128.26-135.62 (m, aromatic). Anal. calcd. for $C_{25}H_{39}O_2NP_2$: C, 67.1; H, 8.8; N, 3.1; P, 13.8. Found: C, 67.3; H, 8.6; N, 3.1; P, 14.0%.

Debenzylation of diethyl (2-benzyloxy-3-N,N-diethylaminopropyl)phosphonate 6a and diphenyl (2-benzyloxy-3-N,N-diethylaminopropyl)phosphine oxide 6b. Diethyl (3-N,N-diethylaminohydroxy-propyl)phosphonate 3a and (3-N,N-diethylamino-2-hydroxypropyl)diphenylphosphine oxide 3b.

General procedure of catalytic deprotection

To a solution of benzyl ether **6a** or **6b** (10 mmol) in methanol (50 ml) the palladium catalyst (Pd/C, 10%, 200 mg) was added and the suspension stirred under hydrogen atmosphere at room temperature for 24 hr. The catalyst was filtered off and the solvent evaporated under reduced pressure. The residue after the column chromatography ($CHCl_3$/MeOH, 5:1) gave **3a** or **3b** a pale yellow oil.

3a (R=OEt); Yield 96%, R_f 0.2. lit.[20b] b.p. 116°C/0.3 mmHg. NMR data were given in preliminary paper.[8] IR (film) ν_{max} (cm^{-1}): 3383 m (OH), 1222 m, 1165 m (P=O), 1034 s (P-OC_2H_5).

3b (R=Ph); Yield: 90%; R_f 0.17, [(CH_2Cl_2/MeOH, 3:1]. IR (film) ν_{max} (cm^{-1}): 3367 s (OH), 1437 m (P-Ph), 1180 s (P=O). NMR: δ_P (121.49 MHz, $CDCl_3$): 32.77. δ_H (300.13 MHz, $CDCl_3$): 0.94 (t, J 7.1, 6H, CH_3CH_2-N), 2.41-2.66 [m, 8H, CH_2-P, CH_2-N($CH2CH_3$)$_2$], 4.02-4.09 [m, 1H, CH(OH)], 7.42-7.80 (2 x m, aromatic). δ_C (75.47 MHz, $CDCl_3$): 12.45 (CH_3CH_2N), 36.02 (d, J 71.72, CH_2P), 48.08 (CH_3CH_2-N), 60.81, 60.95 [CH(OH)], 64.35 (>N-CH_2), 129.23, 129.39, 131.37, 131.49, 132.48 (aromatic). Anal. calcd. for $C_{19}H_{26}O_2NP$: C, 68.9; H, 7.9; N, 4.2; P, 9.4. Found: C, 68.7; H, 7.9; N, 4.2; P, 9.0%.

Alternatively, **6b** was deprotected to **3b** following the procedure described in the literature.[19] Yield of **3b**: 60%; spectral properties as given above.

Synthesis of diphenyl (2-benzyloxy-3-N,N-diethylaminopropyl) phosphine 7 and its conversion into (2-benzyloxy-3-N,N-diethylaminopropyl)diphenylphosphine oxide 6b.

Butyllithium (13.5 ml - 21.6 mmol of a 1.6 M solution in hexane) was added dropwise from a syringe to a stirred solution of diphenylphosphine oxide (3.2 ml - 18.1 mmol) in DME (120 ml) under argon at -78°C. The resulting red solution was stirred at -78°C for 30 min. Then the solution was added dropwise from a syringe to

a stirred suspension of **2a** (prepared from **1a**, 3.00 g - 18.1 mmol) in DME (50 ml) at -40°C. The reaction mixture was stirred at this temperature for 1 h and at room temperature for 12 h. The reaction mixture was examined by ^{31}P NMR spectroscopy. As the main product diphenyl (2-benzyloxy-N,N-diethyl-aminopropyl) phosphine **7** was observed, δ_P (80.96 MHz) -21.10 ppm. The crude reaction product was submitted to the oxidation.

To a stirred suspension from the previous experiment a saturated aqueous solution of NH_4Cl (18 ml) was added, followed by tert-butyl hydroperoxide (2.3 ml of a 80% solution in di-tert-butyl peroxide) at -10°C. The resulting mixture was stirred at room temperature for 3 h. The excess of tert-butyl hydroperoxide was destroyed by an aqueous solution of Na_2SO_3. The organic solvent was evaporated under reduced pressure. Water (100 ml) and ethylene chloride (100 ml) were added to the residue. The aqueous layer was extracted with $(CH_2Cl)_2$ (3 x 50 ml). The combined organic extracts were dried and concentrated under reduced pressure. The crude phosphinoxide **6b** was chromatographed (eluent: $(CH_2Cl)_2$/MeOH, 3:1) to give **3b** as a pale yellow oil. R_f 0.42; Yield: 4.61 g (60%). Spectroscopic data were in accord with those given in the other experiment.

Diethyl (3-N,N-diethylamino-2-tosyloxypropyl)phosphonate 8

To a solution of **3a** (10.00 g - 37.6 mmol) in anhydrous pyridine (50 ml) tosyl chloride (8.60 g - 45.1 mmol) was added portionwise at 0°C. The mixture was allowed to stand at this temperature for 12 h; then it was poured into hydrochloric acid containing ice. The reaction product was extracted with chloroform (3 x 100 ml), dried and concentrated under reduced pressure. The crude product was purified by column chromatography ($CHCl_3$/MeOH, 20:1) to give a white solid. R_f 0.45. Yield: 11.5 g - 73%.

Synthesis of diethyl (3-N,N-diethylaminopropenyl-1,2)phosphonate 4.

The product of the previous reaction (4.00 g - 95 mmol) was added in one portion to a solution of Bu^tOK [prepared from Bu^tOH and metallic potassium (0.5 g - 0.013 g - atom)] in *tert*-butanol (50 ml) and the mixture was stirred at room temperature for 12 h.

The resulting solution was poured into water containing ice (100 ml) and **7** was extracted with chloroform (3 x 100 ml). The extract was dried, concentrated under reduced pressure and the residue was chromatographed ($CHCl_3$/MeOH, 30:1), R_f 0.65 to give 1.95 g (83%) of **4** as colorless oil. NMR: δ_P (80.96 MHz, $CDCl_3$): 17.85 (lit[20d]: 17 ppm). ^1H and ^{13}C NMR data were given in the preliminary paper.[8]

3-N,N-diethylaminopropan-diyl-1,2-bis-phosphonate 5g

To a solution of **5a** (3.00 g - 7.74 mmol) in dichloromethane (50 ml) trimethylbromosilane (5.928 g - 38.72 mmol) was added in one portion at room temperature. The reaction mixture was stirred at room temperature for 12 h. Then the solvent was evaporated under reduced pressure and anhydrous methanol (20 ml) was added to the residue. The solution was stirred at room temperature for 1 h. The solvent and volatile products were evaporated in vacuo and another portion of methanol (50 ml) was added. The bis-phosphonate **5g** precipitated

as white crystals (1.8 g - 84.5%). M.p. 230-236°C. IR (KBr) ν_{max} (cm^{-1}): 1009 s, 993 vs, 976 vs, 959 s, 918 s. NMR: δ_P (81.015 MHz, D_2O): 21.51, 22.24, 24.89, 25.64 (J_{P-P} 60.56). δ_H (200.13 MHz, D_2O): 1.13 (t, J 7.3, 6H, $C\underline{H}_3CH_2N$), 1.51-1.69 (m, 1H, $C\underline{H}$-P), 1.72-2.33 (m, 2H, $C\underline{H}_2$-P), 3.02-3.24 [m, 6H, $C\underline{H}_2$-$N(C\underline{H}_2CH_3)_2$]. δ_C (50.32 MHz, D_2O): 10.78, 11.02 ($\underline{C}H_3CH_2N$), 29.03 (d, J 122.1, $\underline{C}H_2$-P), 29.13 (d, J 122.2, CH_2-P), 31.62 (d, J 118.2, $\underline{C}$H-P), 49.99, 50.28, 50.52, 50.70, 51.14, 51.54, 56.52. Anal. calcd. for $C_7H_{19}O_6NP_2$: C, 30.6; H, 7.0; N, 5.1; P, 22.5. Found: C, 30.7; H, 7.0; N, 5.1; P, 23.1%.

The Michael addition of diethyl phosphite (and diphenylphosphine oxide) to vinylphosphonate 4

General procedure. To a solution of vinylphosphonate **4** (50 mmol) and diethyl phosphite (diphenylphosphine oxide) (51 mmol) in toluene (50 ml) was added sodium hydride (51 mmol). After the evolution of hydrogen has ceased, the resulting mixture was stirred at 60°C for 3 h. The reaction products were isolated and purified as described in other experiments. According to this procedure bis-phosphonate **5a** (95%) and hybrid structure **5b** (91%) were obtained. The spectral properties of **5a** and **5b** as given above.

ACKNOWLEDGEMENT

The work has been supported by the Polish State Committee for Scientific Research Nr 3TO9A 038 09.

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