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Synthesis of multifunctionalized phosphonic acid esters *via* opening of oxiranes and azetidinium salts with phosphoryl-substituted carbanions

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Ring-opening of *N*,*N*-diethyl-3-benzyloxyazetidinium salt **1b** and *N*,*N*-dibenzyl-2,3-epoxypropylamine **6** by phosphoryl-substituted carbanions generated from phosphonates **2a**–**e** furnishes the multifunctional phosphonates **3a**–**e** and **7a**, **7b**, **7e** bearing the same carbon skeleton. The reaction of the heterocyclic electrophiles **1b** and **6** with the P-allyl anion generated from **2f** demonstrates the strong dependence of the α/γ-regioselectivity on the reaction conditions. Depending on the character of the electrophile and/or the reaction medium the regioselective synthesis of both α- and γ-regioisomers is realized.

Introduction

Oxirane ring-opening with various nucleophiles is well recognized as a useful starting point for the synthesis of multifunctionalized organic compounds.[1] Azetidines are not as highly strained systems as their three-membered analogues—aziridines. However, a considerable part of their chemistry involves ring-opening reactions,[2] which renders them useful synthetic intermediates in some transformations. It was demonstrated[3] that the presence of positive charge on the nitrogen atom of this heterocyclic system supports ring-opening reactions. Therefore, quaternary azetidinium salts and their substituted derivatives react according to this pattern.

In this paper we report the synthesis of 4-(*N*,*N*-dialkylamino)-3-hydroxy- and 4-(*N*,*N*-dialkylamino)-3-benzyloxybutylphosphonates **3** and **7** containing other functionality [*e.g.* –Ph, –CN, –COOEt, –P(O)(OEt)$_2$] and 6-(*N*,*N*-dialkylamino)-4-hydroxy- and 6-(*N*,*N*-dialkylamino)-4-benzyloxyhex-1-enylphosphonates **8** and **9** using the ring-opening reactions of two heterocyclic systems: *N*,*N*-diethyl-3-benzyloxyazetidinium salt **1b** and *N*,*N*-dibenzyl-2,3-epoxypropylamine **6**. The results of these both strategies are complementary.

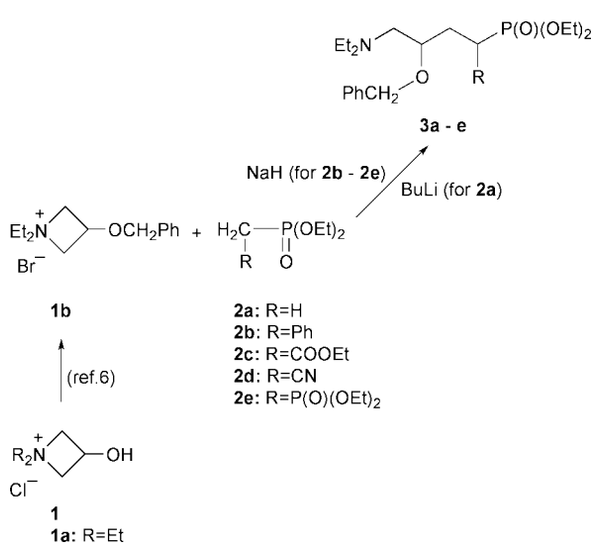
Multifunctionalized phosphonic acids are of importance because of their potential biological activity and utility as versatile intermediate reagents for organic synthesis.[4,5]

Results and discussion

Reactions of heterocyclic systems 1b and 6 with carbanions generated from phosphonates 2a–2e

N,*N*-Dialkyl-3-hydroxyazetidinium chlorides **1**, readily accessible according to Gaertner[6] from 1-chloro-2,3-epoxypropane and dialkylamines were recently applied in this laboratory to the synthesis of (3-dialkylamino-2-hydroxy)propylphosphonic acids and their structural analogues.[7,8] The reaction involved the ring-opening reaction of salts **1** *via* nucleophilic attack of phosphorus nucleophiles on the carbon atom with resultant C–P bond formation. In this work *N*,*N*-diethyl-3-hydroxyazetidinium chloride **1a** was chosen as a model starting heterocyclic reagent. Our experience from the previous studies[8] showed that the hydroxy group of the salt **1a** should be protected in order to avoid secondary reactions of the initially formed products. Therefore, the experiments were carried out using the benzylated salt **1b** as a suitable starting material. The carbanions derived from diethyl methylphosphonate **2a** and its substituted analogues **2b**–**2e** were used as phosphoryl-stabilized nucleophiles. The example of phosphonate **2f**, in which R = –CH=CH$_2$ (*i.e.* allylphosphonate), requires special discussion and will be described in a separate section.

Reaction of **1b** with **2a**–**2e** leads to ring opening of the heterocyclic system and C–C bond formation to give derivatives of phosphonic acids bearing the functional groups at the α-, γ- and δ- positions of the butylphosphonic acid skeleton. The reactions illustrated in Scheme 1 occurred readily in most cases



Scheme 1

in high yields. The carbanions were generated from the corresponding phosphonates by the action of sodium hydride (for phosphonates **2b**–**2e**) or butyllithium (for phosphonates **2a** and **2f**). The representative procedure is a one-pot reaction, which was carried out in the temperature range 25–60 °C (when NaH was used) or −78–25 °C (for BuLi) within 3–10 h. It is noteworthy that when R ≠ H a second stereogenic centre is generated, and therefore, phosphonates **3b**–**3d** were formed as a

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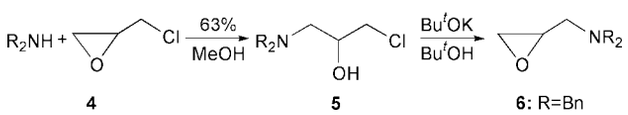
Table 1 Reaction of azetidinium salt **1b** with phosphonates **2**

Starting phosphonate	Base	Solvent(s)	*T*/°C	Reaction time/h	Yield (%)	Diastereomeric ratio of **3**
2a (R = H)	BuLi	DME	−78→20	6	69	—
2b (R = Ph)	NaH	DME–DMSO	60	10	83	12 : 10
2c (R = COOEt)	NaH	DME	60	10	83	15 : 10
2d (R = CN)	NaH	DME	60	10	77	27 : 10
2e [R = P(O)(OEt)$_2$]	NaH	Toluene	60→110	25	11	—

mixture of diastereomers as shown by the presence of two chemical shifts in their ^{31}P NMR spectra. The two diastereomers were usually formed in unequal amounts (Table 1). Unfortunately, we were not able to separate the diastereomers by column chromatography. However, the phosphonate **3b** (R = Ph) was separated by gas chromatography into its diastereomers. Phosphonate **3e** [R = P(O)(OEt)$_2$] shows two ^{31}P NMR signals because of the diastereotopy of the phosphorus atom. The results of the reactions described in Scheme 1 are collected in Table 1.

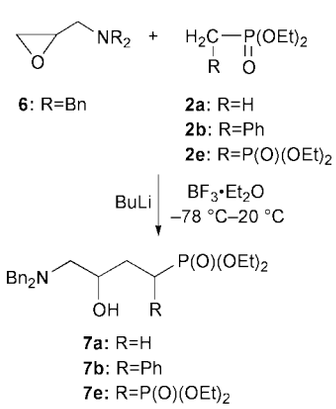
The described procedure requires protection of the OH group in the 3-hydroxyazetidinium salt **1a**. The alternative procedure, avoiding this inconvenience, appears to be the ring-opening reaction of corresponding epoxides with the above-mentioned phosphorus nucleophiles.

A convenient starting material would be the aminomethyl epoxides **6**, which are readily available from 1-chloro-2,3-epoxypropane **4**. As the model epoxide we have chosen *N*,*N*-dibenzyl-2,3-epoxypropylamine **6** (R = Bn), prepared by the sequence of the reactions shown in Scheme 2. The amino



Scheme 2

alcohol **5** (R = Bn), in contrast to the analogous compounds, in which R_2N– = Me_2N–, Et_2N–, morpholino-, piperidino-, does not undergo the cyclization to the corresponding *N*,*N*-dibenzyl-3-hydroxyazetidinium chloride under the conditions described by Gaertner.[6] However, the amino alcohol **5** (R = Bn) can be readily transformed into the amino epoxide **6** (R = Bn) by the conventional procedure.[9] The use of epoxide **6** (R = Bn) in the reaction with carbanions derived from phosphonates **2** allowed us to obtain phosphonates **7**, which possess the same basic structure as the phosphonates **3**, but bear a free hydroxy group. Epoxide **6** (R = Bn) was regioselectively attacked by the nucleophiles at the less hindered site (Scheme 3).

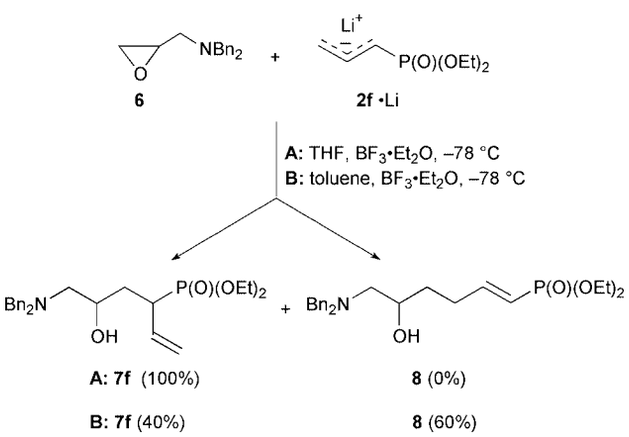


Scheme 3

N,*N*-Dibenzyl-2,3-epoxypropylamine **6** was reacted with the lithio carbanions generated from **2** in the presence of BF_3·Et_2O, as reported for the syntheses α-, β- and γ-hydroxyalkyl-phosphonates.[10–12] This approach to the synthesis of functionalized phosphonates of type **3** using **6** (R = Bn) as the starting material proved to be a complementary method to that using azetidinium salts as electrophiles. The reaction of phosphoryl-substituted carbanions **2** with epoxide **6** (R = Bn) has the following advantages: it proceeds under relatively mild conditions (at −78 to 20 °C) and avoids the steps of protection and deprotection of the hydroxy group.

Reactions of heterocyclic compounds 1b and 6 with the phosphoryl-stabilized allylic system

The allylphosphonate **2f** (R = –CH=CH$_2$) may react with electrophiles at α- or γ-position of the carbon chain leading to **7f** (α-attack) or **8** (γ-attack) (Scheme 4). The reaction of electro-



Scheme 4

philes with allylic anions, stabilized by a phosphoryl group, is a well-studied area of organophosphorus chemistry.[12–24] The sense of α-/γ-selectivity has been found to be highly dependent on a number of factors, particularly, the structure of the electrophile and the nature of the reaction medium. The regioselective reactions of allylic anions with electrophiles provide access to a variety of useful synthetic intermediates.[15,21,22] Investigations have been concentrated on such electrophiles as alkyl[13] and silyl halides,[14,15] carbonyl compounds,[13–19] enones[20,21] and heteroatom electrophiles.[22] Relatively less interest has been devoted to the reaction of epoxides.[23,24] Azetidinium salts, to our knowledge, have not been investigated, not counting the preliminary studies in our laboratory.[7]

The reaction of *N*,*N*-dibenzylamino-2,3-epoxypropylamine **6** with lithiated allylphosphonate **2f** was carried out at −78 °C in THF or toluene in the presence of BF_3·Et_2O, as described above in the reactions of phosphonates **2a**,**b**,**e**. The chemoselectivity of the reaction depended strongly on the solvent (Scheme 4). When the reaction was performed in THF (Scheme 4, pathway A) the only product was the 4-(*N*,*N*-dibenzylamino)-3-hydroxy-1-vinylbutylphosphonate **7f** (δ_P: 29.4, 30.0, mixture of diastereoisomers in the ratio 12 : 10), the result of the exclusive α-attack of the nucleophile. When toluene was used as the reaction medium, a drastic shift to γ-attack by the anion generated from **2f** was observed, giving predominantly the product of γ-attack (60%), the phosphonate **8** (δ_P: +18.5 ppm)

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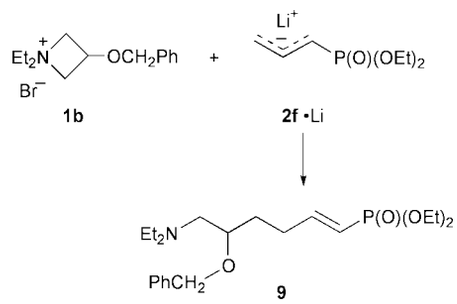
(Scheme 4, pathway B). In either solvent the monosubstituted epoxide **6** was regioselectively attacked by the nucleophile at the less hindered site. The *E*-configuration of the vinyl double bond in phosphonate **8** was established from its ^{1}H NMR spectral data. A similar shift of the regioselectivity induced by a change of solvent was observed by Ergüden and Schaumann[24] for the reaction of lithiated diphenylallylphosphine oxide with a variety of functionalized epoxides. The phosphonate **9** of similar structure to **8** was obtained in the reaction of *N*,*N*-diethyl-3-benzyloxyazetidinium bromide **1b** with diethyl lithioallylphosphonate, generated from the allylphosphonate **2f** and BuLi at −78 °C during 10 h in mixture of DME–DMF



Scheme 5

(1 : 1, v/v). 6-(*N*,*N*-Diethylamino)-5-benzyloxyhex-1-enylphosphonate **9** was the only reaction product. The crude reaction mixture and the product purified by column chromatography showed the same picture: one signal in the ^{31}P NMR at +21.5 ppm. This chemical shift, characteristic of vinyl phosphonates, has been ascribed to the phosphonate **9**, which had to be formed as the result of 100% γ-attack of the allyl anion generated from **2f** on the electrophile—azetidinium salt **1b**.

One can speculate that the observed difference in α-/γ-regioselectivity has been produced by the difference in the solvation effect of the lithium cation in apolar (toluene) and polar (THF) solvents. However, the result of the reaction of azetidinium salt **1b** with phosphoryl allyl anion, carried out in a polar solvent mixture (DME–DMF) indicates that the course of the reaction depends on a variety of factors that influence the α-/γ-regioselectivity of the reactions.

Conclusions

This paper describes two complementary methods giving easy access to multifunctionalized phosphonates using as starting materials simple, readily available heterocyclic systems: azetidinium salts and aminomethyl epoxides. The ring-opening reaction of electrophiles **1b** and **6** (R = Bn) by the P-allyl anion generated from **2f** proved to be strongly dependent on the reaction conditions. The α- and γ-regioisomers are accessible by selection of the appropriate electrophile and reaction medium. Further studies using optically active heterocyclic systems as starting materials are in progress.

Experimental

All air- and moisture-sensitive reactions were carried out under an atmosphere of argon. All solvents were purified by standard procedures and freshly distilled prior to use. All reactions were monitored by ^{31}P NMR spectroscopy and/or by thin layer chromatography (TLC) using Merck Kieselgel 60 (F_{254}) analytical plates. Spots were detected under UV light or visualized with iodine vapour. Column chromatography was performed using Merck silica gel 60 (230–400 mesh). All organic extracts were dried over anhydrous magnesium sulfate and concentrated under reduced pressure. IR spectra were recorded using an ATI Mattson Infinity FTIR instrument. Bruker AC-200 and MSL 300 spectrometers, operating at 200.13 and 300.13 MHz for ^{1}H, 50.288 and 75.17 MHz for ^{13}C and 80.96 and 121.49 MHz for ^{31}P, were used for recording NMR spectra. Chemical shifts are reported in ppm (δ) using TMS as internal and H_3PO_4 as external standard. Coupling constants are given in Hz.

Reaction of *N*,*N*-diethyl-3-benzyloxyazetidinium bromide 1b with phosphonate 2 in the presence of sodium hydride. General procedure

To a suspension of azetidinium bromide **1b**[8] (60 mmol) in a solvent (100 cm^3) were added successively the corresponding phosphonate **2b**–**2e** (72 mmol) and sodium hydride (72 mmol). The reaction mixture was stirred at room temperature until the hydrogen evolution had ceased. Then it was stirred at 60 °C for 10 h. The reaction was quenched by pouring the mixture into water (150 cm^3). The reaction product was extracted with chloroform (3 × 100 cm^3), dried, evaporated and purified by column chromatography (eluent: $CHCl_3$–MeOH). According to this procedure the following functionalized phosphonates were prepared.

Diethyl 4-(*N*,*N*-diethylamino)-3-benzyloxy-1-phenylbutylphosphonate 3b. (Reaction solvent: DME–DMSO, 1 : 1.) Pale yellow oil (yield: 83%); R_f 0.4 ($CHCl_3$–MeOH, 20 : 1); ν_{max} (neat)/cm^{-1}: 3428 (br), 2971, 2931, 2870, 1661, 1454, 1383, 1110 (P=O), 1060, 1028, 963, 738, 699, 562; MS (FAB): 397.5 (M^+ + 1); δ_P (121.5 MHz, $CDCl_3$): 28.75, 29.26 (12 : 10); δ_H (300 MHz, $CDCl_3$): 0.84–1.38 (2 × m, 12H, C*H*$_3$CH$_2$N, C*H*$_3$CH$_2$O), 2.35–2.67 [m, 9H, (CH$_3$C*H*$_2$)$_2$NC*H*$_2$, C*H*$_2$C*H*Ph], 3.37–3.64 (m, 4H, CH$_3$C*H*$_2$O), 3.72–4.07 [2 × m, 1H, C*H*(OBn)], 4.60–4.70 (m, 2H, C*H*$_2$Ph), 7.20–7.34 (m, 10H, aromatic); δ_C (75.5 MHz, $CDCl_3$): 12.47, 12.72 (*C*H$_3$CH$_2$N), 16.86, 16.94, 17.04, 17.12 (*C*H$_3$CH$_2$O), 34.52 (*C*H$_2$CHPh), 41.54 [d, $^1J_{C-P}$ 138.1, *C*H(Ph)P], 41.71 [d, $^1J_{C-P}$ 119.5, *C*H(Ph)P(O)], 48.63, 48.68 (CH$_3$*C*H$_2$N), 55.30, 55.41, 57.47, 58.16, 58.26 (>N*C*H$_2$), 62.35–63.18 (2 × m, CH$_3$*C*H$_2$O), 71.95–72.66 (m, 6 lines, *C*H$_2$-Ph), 75.53 [d, *J* 15.5, *C*H(OBn)], 76.30 [d, *J* 13.2, *C*H(OBn)], 127.68, 128.05, 128.13, 128.25, 128.38, 128.90, 128.97, 129.46 (aromatic), 130.04 (d, *J* 6.6, Ph, C-*ipso*), 130.29 (d, *J* 6.4, Ph, C-*ipso*).

Single diastereoisomer: δ_P (121.5 MHz, $CDCl_3$): 29.56; δ_H (300 MHz, $CDCl_3$): 0.99 (t, *J* 7.1, 6H, C*H*$_3$CH$_2$N), 1.21 (t, *J* 7.0, 6H, C*H*$_3$CH$_2$O), 2.42–2.58 [m, 9H, (CH$_3$C*H*$_2$)$_2$NC*H*$_2$, C*H*$_2$C*H*(Ph)], 3.47–3.65 (m, 4H, CH$_3$C*H*$_2$O), 3.83–4.02 [2 × m, 1H, C*H*(OBn)], 4.65 and 4.74 (AB, J_{AB} 12.0, 2H, C*H*$_2$Ph), 7.22–7.45 (m, 10H, aromatic); δ_C (50.3 MHz, $CDCl_3$): 10.14, 10.88 (*C*H$_3$CH$_2$N), 14.68, 15.77 (*C*H$_3$CH$_2$O), 33.04 (*C*H$_2$CHPh), 40.33 [d, J_{C-P} 137.1, *C*H(Ph)P], 47.35, 47.08 (CH$_3$*C*H$_2$N), 53.85, 56.52 (>N*C*H$_2$), 61.50, 61.64, 62.34, 62.49 (CH$_3$*C*H$_2$O), 71.12, 71.42 (*C*H$_2$Ph), 74.82 [d, *J* 14.2, *C*H(OBn)], 126.48, 126.86, 127.08, 127.38, 127.83, 128.08, 128.47 (aromatic), 128.89 (d, *J* 6.7, Ph, C-*ipso*).

Diethyl 4-(*N*,*N*-diethylamino)-3-benzyloxy-1-ethoxycarbonylbutylphosphonate 3c. (Reaction solvent: DME.) Pale yellow oil (yield: 83%); R_f 0.31 ($CHCl_3$–MeOH, 30 : 1); NMR spectra were given in the preliminary paper.[7]

Diethyl 4-(*N*,*N*-diethylamino)-3-benzyloxy-1-cyanobutylphosphonate 3d. (Reaction solvent: DME.) Pale yellow oil (yield: 77%); R_f 0.31 ($CHCl_3$–MeOH, 30 : 1); ν_{max} (neat)/cm^{-1}: 3400 (br), 2980, 1661, 1455, 1229 (P=O), 1075, 1048, 947, 795, 749, 701, 570. MS (FAB): 397.5 (M^+ + 1), 369.5 (M − HCN); δ_P (121 MHz, $CDCl_3$): 19.14, 19.50 (27 : 10); δ_H (300 MHz, $CDCl_3$): 0.99–1.09 (m, 6H, C*H*$_3$CH$_2$N), 1.36–1.42 (m, 6H, C*H*$_3$CH$_2$O), 1.82–2.38 [2 × m, 2H, C*H*$_2$CH(CN)], 2.41–2.74 [3 × m, 6H, (CH$_3$C*H*$_2$)$_2$NC*H*$_2$], 3.27–3.60 [2 × m, 1H, C*H*(CN)], 3.70–3.78 [m, 1H, C*H*(OBn)], 4.16–4.33 (m, 4H, CH$_3$C*H*$_2$O), 4.52–4.87 (m, 2H, C*H*$_2$Ph), 7.28–7.42 (m, 5H,

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aromatic); δ_C (75.5 MHz, $CDCl_3$): 12.56, 12.73 (CH_3CH_2N), 16.93, 17.06 (CH_3CH_2O), 27.02 [d, $^1J_{C-P}$ 143.13, *C*(CN)P], 27.40 [d, $^1J_{C-P}$ 145.24, *C*(CN)P], 32.06, 32.40 [$CH_2CH(CN)$], 48.50, 48.70 (CH_3CH_2N), 57.70, 58.13 [$NCH_2CH(OBn)$], 64.34, 64.64 (CH_3CH_2O), 72.47, 72.78, 73.31, 75.50 (CH_2Ph), 116.90, 117.01 (*C*N), 128.50–138.97 (5 lines, aromatic).

Tetraethyl 4-(*N*,*N*-diethylamino)-3-benzyloxybutan-1-ylidene-bis(phosphonate) 3e. The reaction was carried out according to the above procedure in toluene at 60 °C (20 h) and under reflux (5 h). Pale yellow oil (yield: 11%); MS (CI): 508.5 ($M^+ + 1$). $C_{28}H_{43}NO_7P_2$ requires M 507.5. δ_P (81 MHz, $CDCl_3$): 24.75, 24.95; δ_H (200 MHz, $CDCl_3$): 0.99 (t, *J* 7.1, 6H, CH_3CH_2N), 1.20–1.41 (m, 12H, CH_3CH_2O), 1.92–2.73 [2 × m, 8H, CH_3CH_2N, $>NCH_2CH(OBn)CH_2$], 2.82 [dddd, *J* 3.7, 8.7, 24.3, 1H, C*H*P(O)], 3.83–3.95 [m, 1H, C*H*(OBn)], 4.51 and 4.75 (AB, J_{AB} 11.4, 2H, CH_2Ph), 7.21–7.35 (m, 5H, aromatic); δ_C (50 MHz, $CDCl_3$): 11.72 (CH_3CH_2N), 16.28 (CH_3CH_2O), 29.87 [CH(OBn)CH_2CHP], 32.54 {t, J_{C-P} 132.0, *C*H[P(O)$(OC_2H_5)_2$]$_2$}, 47.54 (CH_3CH_2N), 57.71 [$>NCH_2CH(OBn)$], 62.10–62.48 (m, OCH_2CH_3), 71.63 (CH_2Ph), 75.40–75.55 [m, *C*H(OBn)], 127.28, 127.59, 128.15, 138.55 (aromatic).

Reaction of *N*,*N*-diethyl-3-benzyloxyazetidinium bromide 1b with diethyl methylphosphonate 2a and diethyl allylphosphonate 2f in the presence of butyllithium. General procedure

To a stirred suspension of *N*,*N*-diethyl-3-benzyloxyazetidinium bromide **1b** prepared from **1a** (60 mmol) and phosphonate **2a** or **2f** (72 mmol) in a solvent (200 cm^3) was added portionwise (from a syringe) a solution of *n*-BuLi (72 mmol) in hexane (1.6 M) at −78 °C. The reaction mixture was stirred at −78 °C for 10 h, then was allowed to warm to room temperature. A saturated aqueous solution of NH_4Cl (150 cm^3) was added to a stirred mixture. The reaction product was extracted with $CHCl_3$ (3 × 50 cm^3), dried, evaporated and purified by column chromatography. According to this procedure the following functionalized phosphonates were prepared.

Diethyl 4-(*N*,*N*-diethylamino)-3-benzyloxybutylphosphonate 3a. (Reaction solvent: DME.) Pale yellow oil (yield: 69%); R_f 0.35 ($CHCl_3$–MeOH, 30 : 1); ^{31}P, ^1H and ^{13}C NMR spectra were described in the preliminary paper.[7]

Diethyl (*E*)-6-(*N*,*N*-diethylamino)-5-benzyloxyhex-1-enylphosphonate 9. (Reaction solvent DME–DMF, 1 : 1.) Pale yellow oil (yield: 67%); R_f 0.35 ($CHCl_3$–MeOH, 20 : 1); ν_{max} (neat)/cm^{-1}: 3404 (br), 2960, 1653, 1455, 1228 (P=O), 1075, 1048, 948, 795, 749, 701, 570; MS (FAB): 398.5 ($M^+ + 1$); δ_P (81 MHz, $CDCl_3$): 21.25; δ_H (300 MHz, $CDCl_3$): 1.025 (t, *J* 7.1, 6H, CH_3CH_2N), 1.29 and 1.30 (each t, *J* 7.1, 6H, CH_3CH_2O), 1.81–1.85 (m, 4H, CH_3CH_2N), 2.47–2.66 (m, 6H $>NCH_2CH_2$-CH_2CH=), 3.85–3.98 [m, C*H*(OBn)], 3.99–4.14 (m, 4H, CH_3CH_2O), 4.56 and 4.66 (AB, J_{AB} 11.49, 2H, CH_2Ph), 6.78 (ddt, degenerated to dq, *J* 6.9, 23.7, 1H, =C*H*P), 7.23–7.34 (m, 6H, C*H*=CHP and aromatic); δ_C (75.5 MHz, $CDCl_3$): 12.41 (CH_3CH_2N), 15.28, 15.54 (CH_3CH_2O), 31.92, 32.07 (CH_2-CH=CH), 48.20 (CH_3CH_2N), 58.04 ($>NCH_2$), 61.79, 61.86, 61.92 (CH_3CH_2O), 72.72 (CH_2Ph), 128.02 (d, J_{C-P} 178.5, =*C*HP), 127.70, 128.13, 128.57, 139.62 (aromatic), 144.53 (d, $^3J_{C-P}$ 11.1, *C*H=CHP).

N,*N*-Dibenzyl-3-chloro-2-hydroxypropylamine 5

Dibenzylamine (15.00 g, 0.076 mol) and 1-chloro-2,3-epoxypropane **4** (7.00 g, 0.76 mol) were dissolved in methanol (100 cm^3) and stirred at room temperature for 24 h. The reaction mixture was concentrated under vacuum and the residue was purified by column chromatography to give **5** as a pale yellow oil (yield: 15.00 g, 68%); R_f 0.6 ($CHCl_3$–hexane, 5 : 1) Found: C, 70.06; H, 6.87; N, 4.83; Cl, 12.68%; M^+, 289.8. $C_{17}H_{20}NOCl$ requires: C, 70.46; H, 6.96; N, 4.83; Cl, 12.23%; M, 289.8; δ_H (300 MHz, $CDCl_3$): 2.28–2.46 (m, 2H, $>NCH_2$), 2.91 (s, 1H, OH), 3.06–3.26 (m, 2H, CH_2Cl), 3.20 and 3.46 (AB, J_{AB} 13.47, CH_2Ph), 3.60–3.72 [m, 1H, C*H*(OH)], 7.03–7.19 (m, 10H, aromatic); δ_C (75.5 MHz, $CDCl_3$): 48.65 (CH_2Cl), 57.70 ($>NCH_2$), 59.64 (CH_2Ph), 69.10 [*C*H(OH)], 128.22, 128.75, 129.24, 129.39, 130.00, 139.67 (aromatic).

N,*N*-Dibenzyl-2,3-epoxypropylamine 6

To a solution of *N*,*N*-dibenzyl-3-chloro-2-hydroxypropylamine **5** (14.00 g, 0.048 mol) in *tert*-butyl alcohol (60 cm^3) was added potassium hydroxide (3.00 g, 0.054 mol) dissolved in a minimal volume of water. The reaction mixture was stirred at room temperature for 24 h. Then the precipitate of KCl was filtered off, the filtrate evaporated and purified by column chromatography. The epoxide **6** was obtained as a pale yellow oil (10.00 g, 83%). R_f 0.38 (MeCOOEt–hexane, 1 : 10). Found: C, 80.94; H, 7.65; N, 5.48%. $C_{17}H_{19}NO$ (253.23) requires: C, 80.60; H, 7.56; N, 5.53%. MS (FAB): 254.2 ($M^+ + 1$); δ_H (300 MHz, $CDCl_3$): 1.97–2.01 (m, 1H), 2.16–2.26 (m, 2H), 2.54–2.62 (m, 1H), 2.77–2.85 [(m, 1H, C*H*(ring)], 3.42 and 3.71 (AB, J_{AB} 13.7, 4H, CH_2Ph), 7.06–7.37 (m, 10H, aromatic); δ_C ($CDCl_3$, 75.5 MHz): 44.94 [OCH_2(ring)], 51.43 (*C*HO), 56.66 ($>NCH_2$), 59.77 (CH_2Ph), 127.97, 128.27, 128.75, 129.25, 129.84, 140.52 (aromatic).

Reaction of the lithiated phosphonates 2 with *N*,*N*-dibenzyl-2,3-epoxypropylamine 6. General procedure

To a stirred solution of phosphonate **2** (30 mmol) in a solvent (50 cm^3) was added portionwise (from a syringe) butyllithium (32 mmol) in hexane (1.6 M) at −78 °C. After the mixture had been stirred for 30 min, it was transferred by stainless steel needle to a stirred solution of epoxide **6** (30 mmol) in a solvent (50 cm^3) at −78 °C. The reaction mixture was stirred for an additional 15 min, then $BF_3{\cdot}Et_2O$ (33 mmol) was introduced by syringe at a temperature of below −78 °C. The stirring was continued for 10 h at the same temperature. The reaction was quenched with saturated aq. NH_4Cl solution (70 cm^3). The temperature was allowed to reach room temperature, and the solvent was evaporated *in vacuo*. The residue was extracted with AcOEt (3 × 50 cm^3), the organic layers were washed with water (2 × 20 cm^3), dried, evaporated and purified by column chromatography. According to this procedure the following phosphonates **7** were prepared.

Diethyl 4-(*N*,*N*-dibenzylamino)-3-hydroxybutylphosphonate 7a. (Reaction solvent: DME.) Pale yellow oil (yield: 63%); R_f 0.60 ($CHCl_3$–MeOH, 20 : 1); ν_{max}(neat)/cm^{-1}: 3378 (OH), 3028, 2982, 2801, 1494, 1453, 1239 (P=O), 1052, 1027, 747, 699; MS (FAB): 406.2 ($M^+ + 1$); δ_P (127.5 MHz, $CDCl_3$): 32.93; δ_H (300 MHz, $CDCl_3$): 1.29 (t, *J* 7.0, 6H, CH_3CH_2O), 1.35–2.16 [m, 4H, $CH_2CH_2P(O)$], 2.44 (d, *J* 6.6, 2H, $>NCH_2$), 3.41 and 3.81 (AB, J_{AB} 13.4, 4H, NCH_2Ph), 3.66–3.74 [m, 1H, C*H*(OH)], 3.98–4.13 (m, 4H, CH_3CH_2O), 7.22–7.38 (m, 10H, aromatic); δ_C (50.3 MHz, $CDCl_3$): 16.31, 16.42 (CH_3CH_2O), 21.66 (d, $^1J_{C-P}$ 142.3, CH_2P), 27.38 (CH_2), 58.43 (NCH_2Ph), 58.70 ($>NCH_2$), 59.05, 59.53, 61.37, 61.49 (CH_3CH_2O), 66.7, 67.06 [*C*H(OH)], 127.24, 128.38, 128.95 (aromatic), 138.33 (aromatic *ipso*).

Diethyl 4-(*N*,*N*-dibenzylamino)-3-hydroxy-1-phenylbutylphosphonate 7b. (Reaction solvent: DME.) Pale yellow oil (yield: 71%); R_f 0.63 ($CHCl_3$–MeOH, 20 : 1); ν_{max}(neat)/cm^{-1}: 3388 (OH), 3062, 3028, 2982, 2931, 2906, 2800, 1495, 1453, 1369, 1234 (P=O), 1056, 1028, 795, 751, 700. Found: N, 2.70; P, 6.40%; ($M^+ + 1$) 482.6. $C_{28}H_{36}O_4NP$ requires: N, 2.91; P, 6.43%; M, 481.6; δ_P (81 MHz, $CDCl_3$): 30.07, 29.04 (11 : 10); δ_H (200.13 MHz, $CDCl_3$): 1.01–1.33 (2 × m, 6H, CH_3CH_2O), 1.78–2.51 [m, 5H, $>NCH_2CH_2CH$(Ph)], 3.33 and 3.71 (AB, J_{AB} 13.3, 4H, NCH_2Ph), 3.79–3.88 [m, 1H, C*H*(OH)], 3.99–4.07 (m,

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4H, CH_3CH_2O), 7.21–7.29 (m, 15H, aromatic); δ_C (75.5 MHz, $CDCl_3$): 15.84, 15.99, 16.12 (CH_3CH_2O), 34.76 [$CH_2CH(Ph)$], 39.93 [d, J_{C-P} 137.12, $CH(Ph)$], 40.27 [d, J_{C-P} 139.15, $CH(Ph)$], 58.16 and 58.27 (NCH_2Ph), 59.67 ($>NCH_2$), 61.57–62.45 (6 lines, CH_3CH_2O), 63.82 [d, J_{C-P} 15.4, $CH(OH)$], 65.18 [d, J_{C-P} 11.6, $CH(OH)$], 126.92, 128.67, 128.77, 128.91, 129.12, 129.25, 129.42, 129.56, 135.25 (d, J 6.8, Ph, C-*ipso*), 136.26 (d, J 6.8, Ph, C-*ipso*), 138.19 (C-*ipso* $PhCH_2N$).

Tetraethyl 4-(*N*,*N*-dibenzylamino)-3-hydroxybutan-1-ylidenebis(phosphonate) 7e. (Reaction solvent: THF.) Pale yellow oil (yield: 32%); R_f 0.34 ($CHCl_3$–MeOH, 20 : 1). Found: C, 57.44; H, 7.72; N, 2.37; P, 10.57%. $C_{26}H_{41}P_2O_7N$ (541.55) requires: C, 57.67; H, 7.63; N, 2.59; P, 11.44%; MS (FAB): 542.3 ($M^+ + 1$), 512.2 ($M^+ - C_2H_5$); ν_{max}(neat)/cm^{-1}: 3402 (OH), 2983, 2933, 2909, 2800, 1651, 1451, 1495, 1452, 1392, 1242 (P=O), 1165, 1028, 974, 800, 750, 700, 526; δ_P (127.5 MHz, $CDCl_3$): 24.43, 24.71; δ_H (500 MHz, $CDCl_3$): 1.21–1.36 (m, 12H, CH_3CH_2O), 1.71–2.11 (m, 2H, CH_2CHP), 2.40–2.50 (m, 2H, $>NCH_2CH$), 2.61–2.73 [m, 1H, $CHP(O)$], 3.51 and 3.72 (AB, J 13.5, 4H, CH_2Ph), 3.56 (s, 1H, OH), 4.03–4.11 [m, 1H, $CH(OH)$], 4.13–4.18 (m, 8H, CH_3CH_2O), 7.23–7.35 (m, 10H, aromatic); δ_C (125.77 MHz, $CDCl_3$): 16.72, 16.77 (CH_3CH_2O), 31.38 (CH_2CHP), 33.29 (t, J_{C-P} 133.2), 58.94 ($PhCH_2$), 59.87 [$>NCH_2CH(OH)$], 62.85–63.42 (m, CH_3CH_2O), 66.34–66.39 [m, $CH(OH)$].

Reaction of the lithiated allylphosphonate 2f with *N*,*N*-dibenzyl-2,3-epoxypropylamine 6

According to the above general procedure, lithiated diethyl allylphosphonate **2f** was reacted in two different solvents.

(a) Reaction in THF. Diethyl 4-(*N*,*N*-dibenzylamino)-3-hydroxy-1-vinylbutylphosphonate **7f** was obtained as a mixture of two diastereoisomers. Pale yellow oil (yield: 66%); R_f 0.58 ($CHCl_3$–MeOH, 20 : 1). Found: N, 3.25; P, 7.18%. $C_{14}H_{34}NO_4P$ requires: N, 3.26; P, 7.00%; MS FAB 432.4 ($M^+ + 1$); ν_{max}(neat)/cm^{-1}: 3393 (OH), 2982, 2932, 2908, 2801, 1636, 1494, 1452, 1240 (P=O), 1055, 1027, 965, 749, 700, 645; δ_P (121.49 MHz, $CDCl_3$): 30.03, 29.38 (11 : 10); δ_H (300.13 MHz, $CDCl_3$): 1.27, 1.29, 1.30 (3 × t, J 7.1, 7.1, 5.3, 6H, CH_3CH_2O), 1.55–1.98 [m, 2H, $CH_2CH(CH=CH_2)P$], 2.35–2.54 (m, 2H, $>NCH_2$), 2.59–3.00 [m, 1H, $CH(CH=CH_2)P$], 3.23 and 3.97 (AB, J_{AB} 13.4, 4H, NCH_2Ph), 4.03–4.18 (m, 4H, CH_3CH_2O), 5.07–5.26 (m, 2H, $CH=CH_2$), 5.53–5.84 (m, 1H, $H_2C=CHC$), 7.15–7.39 (10H, aromatic); δ_C (50.3 MHz, $CDCl_3$): 15.95, 16.06 (CH_3CH_2OP), 32.98 and 33.26 [2 × d, J 3.4, $CH_2CH(CH=CH_2)$], 38.75 [d, $^1J_{C-P}$ 135.0, $(CH_2=CH)CHP$], 38.79 [d, $^1J_{C-P}$ 135.8, $(CH_2=CH)CHP$], 58.15, 58.29 (NCH_2Ph), 59.60 ($>NCH_2$), 61.05–61.89 (m, CH_3CH_2O), 63.78 [d, J 15.0, $CH(OH)$], 65.29 [d, J 12.4, $CH(OH)$], 118.00 (d, J 13.1, $HC=CH_2$), 119.30 (d, J 13.9, $HC=CH_2$), 126.77, 127.95, 128.57 (aromatic), 132.18 (d, J 9.7, $CH=CH_2$), 133.31 (d, J 10.3, $CH=CH_2$), 138.24 (aromatic *ipso*).

(b) Reaction in toluene. Diethyl (*E*)-6-(*N*,*N*-dibenzylamino)-5-hydroxyhex-1-enylphosphonate **8** (60%) was obtained in a mixture with phosphonate **7f** (40%). δ_P (50.3 MHz, $CDCl_3$): **7f**: 29.01, 28.62 (mixture of diastereoisomers), **8**: 18.47. The ratio of **7f** : **8** was 10 : 15. From this mixture the pure phosphonate **8** was separated by repeated development of the mixture on a preparative chromatographic plate. δ_P (121.49 MHz, $CDCl_3$): 18.47; δ_H (200.13 MHz, $CDCl_3$): 1.25–1.38 (m, 6H, CH_3CH_2O), 1.39–1.49 (m, 2H, $>NCH_2$), 2.18–2.50 [m, 4H, CH_2CH_2-$CH(OH)$], 3.37 and 3.85 (AB, J_{AB} 13.4, 4H, CH_2Ph), 3.44–3.76 [m, $CH(OH)$], 4.03–4.15 (m, 4H, CH_3CH_2O), 5.67 (ddt, J 17.1, 1.6, J_{H-P} 20.9, 1H, $=CHP$), 6.76 (ddt, J 17.1, 6.5, J_{H-P} 22.0, 1H, $CH=CHP$), 7.21–7.44 (m, aromatic); δ_C (50.32 MHz, $CDCl_3$): 16.43, 30.08, 30.53, 32.71, 58.46, 59.49, 61.55, 66.17, 117.07 (d, J_{C-P} 187.0, $=CHP$), 127.38, 128.49, 129.05, 138.38 (aromatic), 153.30 ($CH=CHP$).

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