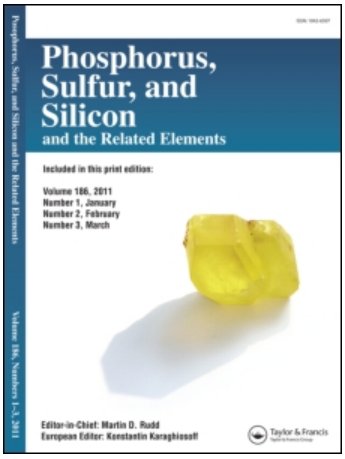

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Towards Convenient Precursors for α -Phosphonylated Aziridinium Ions

Dorota G. Piotrowska[a]; Andrzej E. Wróblewski[a]
[a] Bioorganic Chemistry Laboratory, Faculty of Pharmacy, Medical University of Łódź, Łódź, Poland

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Towards Convenient Precursors for α-Phosphonylated Aziridinium Ions

Dorota G. Piotrowska and Andrzej E. Wróblewski
Bioorganic Chemistry Laboratory, Faculty of Pharmacy, Medical University of Łódź, Łódź, Poland

*Mixtures of the respective 2-(*N,N-*dibenzylamino)-1-chloro- and 1-(*N,N-*dibenzylamino)-2-chlorophosphonates were obtained after mesylation of dimethyl (1*R*,2*S*)-2-(*N,N-*dibenzylamino)-1-hydroxy-3-methylbutylphosphonate and diethyl (1*R*,2*S*)-2-(*N,N-*dibenzylamino)-1-hydroxy-3-phenylpropylphosphonate with mesyl chloride in the presence of tetraethylammonium chloride. These mixtures are considered as useful precursors to α-phosphonylated aziridinium ions.*

Keywords 2-Amino-1-hydroxyphosphonates; aziridinium ions; 1-chlorophosphonates; 2-chlorophosphonates; regioselectivity

INTRODUCTION

Synthetic organic chemistry involving aziridinium ions has remained an active field of research for decades.[1] Recently, we have demonstrated that the transformation of the readily available dimethyl (1*R**,2*S**)-2-(*N*,*N*-dibenzylamino)-1-hydroxy-2-phenylethylphosphonate[2] (1*R**,2*S**)-**1** into 2-substituted dimethyl (1*S**,2*R**)-1-(*N*,*N*-dibenzylamino)-2-phenylethylphosphonates (1*S**, 2*R**)-**3** could be accomplished in good yields and also occurred via aziridinium ion **2** (Scheme 1).[3] It would be interesting to investigate the scope of this reaction. In this article, we report on the synthesis of 1-*O*-mesylates of the 2-(*N*,*N*-dibenzylamino)-1-hydroxyethylphosphonates **4** (R = H, *i*-Pr, Bn) and on their reaction with tetraethylammonium

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Dedicated to Professor Marian Mikołajczyk from the CBMiM PAN in Łódź, Poland, on the occasion of his 70th birthday.
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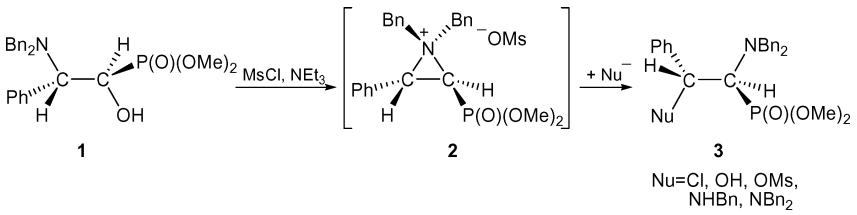
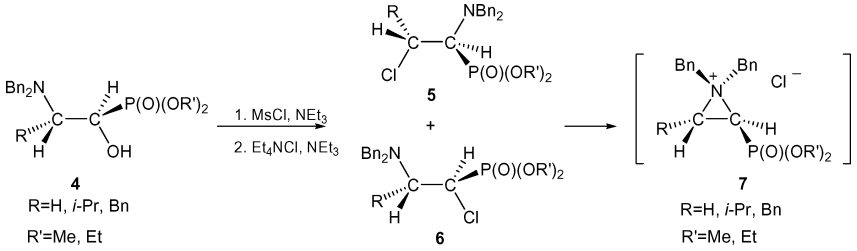
Address correspondence to Dorota G. Piotrowska, Bioorganic Chemistry Laboratory, Faculty of Pharmacy, Medical University of Łódź, Muszyńskiego 1, 90-151 Łódź, Poland. E-mail: dorota@ich.pharm.am.lodz.pl



SCHEME 1

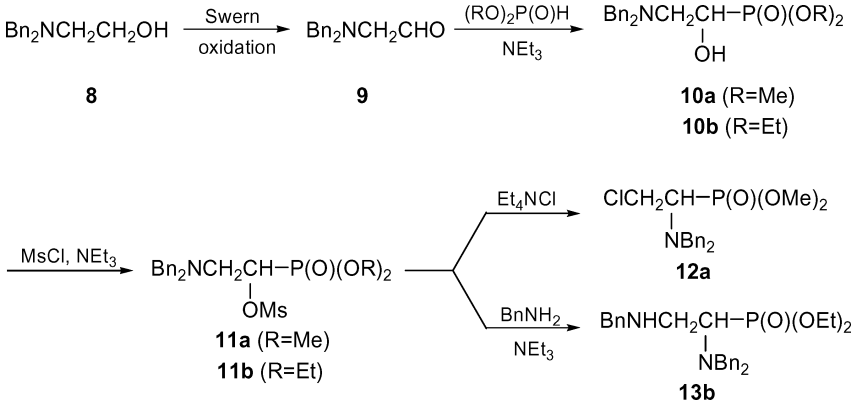
chloride in order to prepare the corresponding β-chloroamines **5** and/or **6** as a convenient reservoir[1p] of α-phosphonylated aziridinium ions **7** (Scheme 2).



SCHEME 2

RESULTS AND DISCUSSION

Standard benzylation of 2-aminoethanol gave *N,N*-dibenzylaminoethanol **8**[4] in 79% yield after chromatographic purification (Scheme 3). This compound was subjected to Swern oxidation to

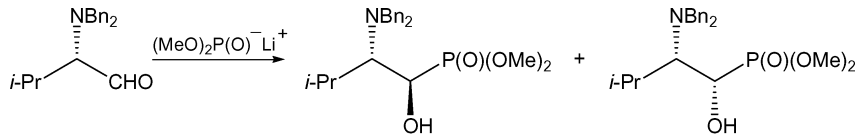


SCHEME 3

provide *N*,*N*-dibenzylaminoacetaldehyde **9**,[5] which was immediately reacted with dimethyl or diethyl phosphites in the presence of catalytic amounts of triethylamine to afford racemic dimethyl or diethyl 2-(*N*,*N*-dibenzylamino)-1-hydroxyethylphosphonates **10a** or **10b** in 79% and 74% yield, respectively. When phosphonate **10a** was treated with mesyl chloride at 0°C, the 1-*O*-mesylate **11a** was formed quantitatively. Inspection of the ^{1}H and ^{31}P NMR spectra of the crude **11a** proved that it was pure enough to be used in the next step. Addition of tetraethylammonium chloride to the dichloromethane solution of crude **11a** triggered transformation of the 1-*O*-mesylate **11a** into dimethyl 1-(*N*,*N*-dibenzylamino)-2-chloroethylphosphonate **12a**. Monitoring of this reaction by ^{31}P NMR spectroscopy showed a new signal at 26.5 ppm formed at the expense of the resonance at 20.2 ppm, which completely disappeared after 10 days at room temperature. The crude 2-chlorophosphonate **12a** was slightly (less than 10%) contaminated by an unidentified impurity (δ^{31}P = 22.3 ppm). After chromatographic purification, phosphonate **12a** was separated in 22% yield.

When the 1-*O*-mesylate **11a** was treated with benzylamine at 60°C for 7 h, significant demethylation of the phosphonate residue occurred, as indicated by the appearance of ^{31}P NMR signals at 19.8 and 18.7 ppm in the spectrum of the crude product. However, the presence of the ^{31}P NMR resonance at 30.0 ppm, showing the formation of the desired dimethyl 1-(*N*,*N*-dibenzylamino)-2-(*N*-benzylamino)ethylphosphonate, encouraged us to prepare *O*,*O*-diethyl ester **10b**. Indeed, when 1-*O*-mesylate **11b** was reacted with benzylamine at 70–75°C for 20 h, diethyl 1-(*N*,*N*-dibenzylamino)-2-(*N*-benzylamino)ethylphosphonate **13b** (δ^{31}P = 27.1 ppm) was produced together with several impurities, but the formation of dealkylation products was not observed. Chromatographic purification allowed us to obtain **13b** in 30% yield.

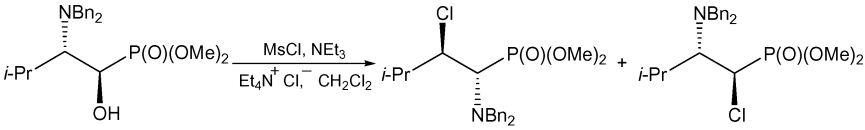
Phosphonylation of *N*,*N*-dibenzyl-L-valinal **14**[6] with lithium *O*,*O*-dimethyl phosphonate at –70°C proceeded in a highly stereoselective manner to produce almost exclusively dimethyl (1*R*,2*S*)-2-(*N*,*N*-dibenzylamino)-1-hydroxy-3-methylbutylphosphonate (1*R*,2*S*)-**15a** (δ^{31}P = 26.9 ppm) (Scheme 4). Another signal at 26.4 ppm in the ^{31}P NMR spectrum of the crude product (ca. 2%) could be assigned to (1*S*,2*S*)-**15b**, but due to the low amount, this compound was not separated and characterized. The absolute configuration at C1 of the major diastereoisomer was deduced from the known stereochemical outcome of the nucleophilic additions to 2-(*N*,*N*-dibenzylamino)aldehydes.[7] It was further supported by our studies on phosphonylation of *N*,*N*-dibenzyl-L-phenylglycinal.[3]



14 (1*R*,2*S*)-**15a** (98%) (1*S*,2*S*)-**15b** (2%)

SCHEME 4

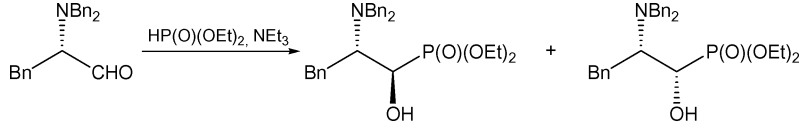
Treatment of phosphonate (1*R*,2*S*)-**15a** with mesyl chloride in the presence of triethylamine and tetraethylammonium chloride at room temperature for 24 h led to the formation of (1*S*,2*R*)-1-(*N*,*N*-dibenzylamino)-2-chloro-3-methylbutylphosphonate (1*S*,2*R*)-**16** and (1*S*,2*S*)-2-(*N*,*N*-dibenzylamino)-1-chloro-3-methylbutylphosphonate (1*S*,2*S*)-**17** in a 90:10 ratio (Scheme 5), which did not change when the reaction time was extended. Unfortunately, this mixture could not be separated, giving fractions enriched in (1*S*,2*S*)-**17**, at best, up to 20%.



(1*R*,2*S*)-**15a** (1*S*,2*R*)-**16** (90%) (1*S*,2*S*)-**17** (10%)

SCHEME 5

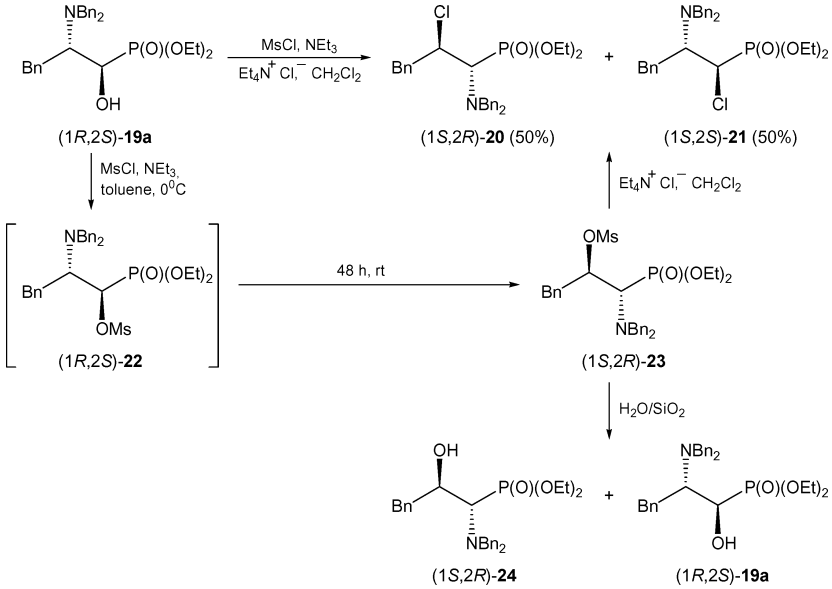
Triethylamine-catalyzed phosphonylation of *N*,*N*-dibenzyl-L-phenylalaninal **18**[7] with diethyl phosphite (Scheme 6) gave a 83:17 mixture of the known[8] diethyl (1*R*,2*S*)- and (1*S*,2*S*)-2-(*N*,*N*-dibenzylamino)-1-hydroxy-3-phenylpropylphosphonates (1*R*,2*S*)-**19a** (δ^{31}P = 25.1 ppm) and (1*S*,2*S*)-**19b** (δ^{31}P = 24.5 ppm). Diastereoselectivity of the triethylamine-catalyzed addition is slightly higher than that observed earlier for the phosphonylation of **18** with *tert*-butyldimethylsilyl diethyl phosphite (74:26).[8] The major phosphonate (1*R*,2*S*)-**19a** was isolated by silica gel chromatography and finally purified by crystallization.



18 (1*R*,2*S*)-**19a** (83%) (1*S*,2*S*)-**19b** (17%)

SCHEME 6

When (1*R*,2*S*)-**19a** was treated with mesyl chloride followed by tetraethylammonium chloride as described for (1*R*,2*S*)-**15a**, a 50:50 equilibrium mixture of diethyl (1*S*,2*R*)-1-(*N*,*N*-dibenzylamino)-2-chloro-3-phenylpropylphosphonate (1*S*,2*R*)-**20** and diethyl (1*S*,2*S*)-2-(*N*,*N*-dibenzylamino)-1-chloro-3-phenylpropylphosphonate (1*S*,2*S*)-**21** was obtained (Scheme 7). Unfortunately, all attempts to separate the regioisomeric phosphonates (1*S*,2*R*)-**20** and (1*S*,2*S*)-**21** on a silica gel column failed despite trying several solvent mixtures as eluents.



SCHEME 7

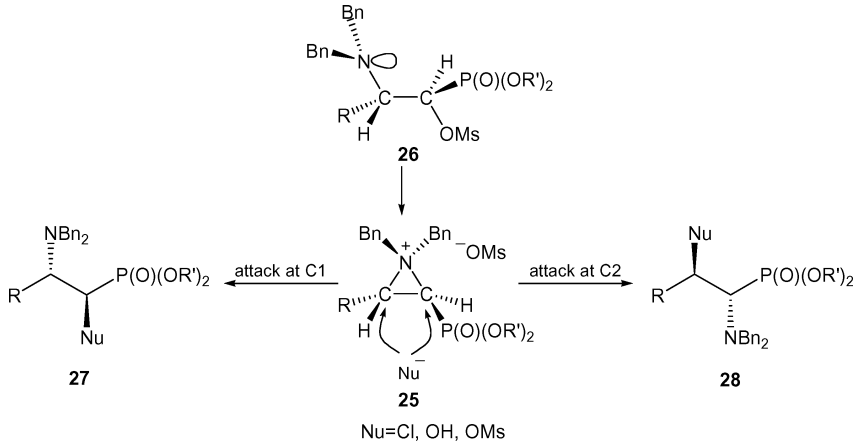
Alternatively, phosphonates (1*S*,2*R*)-**20** and (1*S*,2*S*)-**21** were formed (also in a 50:50 ratio) from diethyl (1*S*,2*R*)-1-(*N*,*N*-dibenzylamino)-2-mesyloxy-3-phenylpropylphosphonate (1*S*,2*R*)-**23** after treatment with tetraethylammonium chloride (Scheme 7). We found that a chloroform solution containing ca. 95% of the 2-mesyloxyphosphonate (1*S*,2*R*)-**23** ($\delta^{31}P = 23.5$ ppm) was obtained when phosphonate (1*R*,2*S*)-**19a** was subjected to mesylation with mesyl chloride in toluene at 0°C, ammonium salts were quickly washed out with cold water, and the resulting mixture was left at room temperature for 48 h. Undoubtedly, the 1-mesyloxyphosphonate (1*R*,2*S*)-**22** was produced first, and it was later transformed into the 2-mesyloxyphosphonate (1*S*,2*R*)-**23** in a similar manner as described earlier.[3] However, after chromatographic purification of a 50:50 mixture of

chlorophosphonates (1*S*,2*R*)-**20** and (1*S*,2*S*)-**21** prepared from (1*S*,2*R*)-**23**, it appeared that they were contaminated with two other phosphonates, namely the starting 1-hydroxyphosphonate (1*R*,2*S*)-**19a** (δ^{31}P = 25.1 ppm) (ca. 2%) and the 2-hydroxyphosphonate (1*S*,2*R*)-**24** (δ^{31}P = 29.7 ppm) (ca. 5%). Moisture present in tetraethylammonium chloride is probably the most likely cause of their formation. To prove the structure of (1*S*,2*R*)-**24**, we returned to our previous observation of the functional group transposition.[3] Based on this experience, the crude 2-mesyloxyphosphonate (1*S*,2*R*)-**23** was left on silica gel for 48 h. Indeed, the 2-hydroxyphosphonate (1*S*,2*R*)-**24** was the major product of the reaction mixture, which in addition contained the 1-hydroxyphosphonate (1*R*,2*S*)-**19a**, minute quantities of both chlorophosphonates (1*S*,2*R*)-**20** and (1*S*,2*S*)-**21**, and traces of an unidentified phosphonate (δ^{31}P = 28.4 ppm). After careful examination of the ^{1}H and ^{31}P NMR spectra of the crude (1*S*,2*R*)-**23**, it became apparent that chlorophosphonates (1*S*,2*R*)-**20** and (1*S*,2*S*)-**21** were formed even during mesylation with mesyl chloride in toluene at 0°C.

In structural studies of all new compounds, comparisons of several ^{1}H and ^{13}C NMR spectroscopic features were employed. Transformations of 2-(*N*,*N*-dibenzylamino)phosphonates into 1-(*N*,*N*-dibenzylamino)phosphonates resulted in significant upfield shifts of *H*CP and *C*P, because the nitrogen atom is less electronegative than the oxygen atom (OH, OMs) attached to C1 in the starting materials. Thus, *H*CP in 1-(*N*,*N*-dibenzylamino)phosphonates **12a**, **13b**, (1*S*,2*R*)-**16**, (1*S*,2*R*)-**20**, (1*S*,2*R*)-**23**, and (1*S*,2*R*)-**24** resonated at 3.12–3.42 ppm, while the signals of the same proton in 2-(*N*,*N*-dibenzylamino)phosphonates **10a**, **10b**, (1*R*,2*S*)-**15a**, and (1*R*,2*S*)-**19a** appeared between 3.98–4.32 ppm. Other NMR parameters of 1-(*N*,*N*-dibenzylamino)phosphonates and the starting materials useful in structural assignments include the *C*P ^{13}C NMR shifts (55–61 ppm vs. 64–66 ppm) and one-bond CP coupling constants (131–147 Hz vs. 154–167 Hz). The presence of three-bond Ph*C*H$_2$NC*P* coupling constants (1.5–4.8 Hz) also supported the formation of 1-(*N*,*N*-dibenzylamino)phosphonates. For the identification of 1-chlorophosphonates (1*S*,2*S*)-**17** and (1*S*,2*S*)-**21**, *C*P ^{13}C NMR shifts were extremely diagnostic, since they appeared at around 51 ppm,[9,10] far upfield compared to those of the respective 1-hydroxyphosphonates (1*R*,2*S*)-**15a** and (1*R*,2*S*)-**19a** (around 66 ppm).

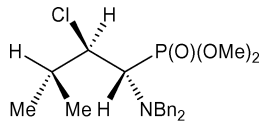
Configurational assignments in 1-chlorophosphonates (1*S*,2*S*)-**17** and (1*S*,2*S*)-**21**, 2-chlorophosphonates (1*S*,2*R*)-**16** and (1*S*,2*R*)-**20**, as well as in phosphonates (1*S*,2*R*)-**23** and (1*S*,2*R*)-**24** are based on the stereochemistry of their formation via intermediate aziridinium ions **25** (Scheme 8). The ring closure in 1-mesyloxyphosphonates (1*R*,2*S*)-**26**

takes place with inversion of configuration at C1 and leads to the ions **25**. The nucleophiles (Cl^-, water, MsO^-) can attack C1 to give 2-(*N*,*N*-dibenzylamino)phosphonates **27** [in this article: (1*S*,2*S*)-**17**, (1*S*,2*S*)-**21**, and (1*R*,2*S*)-**19a**] or C2 to afford 1-(*N*,*N*-dibenzylamino)phosphonates **28**, exemplified here by (1*S*,2*R*)-**16**, (1*S*,2*R*)-**20**, (1*S*,2*R*)-**23**, and (1*S*,2*R*)-**24**. These openings also occur with the inversion of configuration.[1]



SCHEME 8

Additional support for these conclusions comes from the conformational analysis of (1*S*,2*R*)-**16**. This acyclic phosphonate exists in a preferred conformation shown in Scheme 9, in which *H*C1 and *H*C2 are antiperiplanar ($^3J_{H1H2}$ = 9.9 Hz and $^3J_{PH2}$ = 8.1 Hz),[11,12] *H*C2 and *H*C3 are gauche oriented ($^3J_{H2H3}$ = 2.7 Hz),[11] and *H*C3 and the phosphorus atom are situated in plane ($^4J_{PH3}$ = 1.5 Hz, W-coupling).[13] Although in this conformer, $^3J_{PC}$ would be expected to exceed 10 Hz to conform with the antiperiplanar arrangement of *CCCP* atoms,[14] the lower value of the observed coupling (7.5 Hz) probably arises from the influence of two electron-withdrawing substituents present along the coupling pathway.[15]



(1*S*,2*R*)-**16**

SCHEME 9

CONCLUSIONS

Treatment of 2-(*N*,*N*-dibenzylamino)-1-hydroxyphosphonates **4** (R = *i*-Pr, Bn) with mesyl chloride followed by tetraethylammonium chloride led to the formation of mixtures of 1-(*N*,*N*-dibenzylamino)-2-chloro- and 2-(*N*,*N*-dibenzylamino)-1-chlorophosphonates **5** and **6**, while from 2-(*N*,*N*-dibenzylamino)-1-hydroxyethylphosphonate **4** (R = H), 1-(*N*,*N*-dibenzylamino)-2-chloroethylphosphonate **5** (R = H) was produced (Scheme 2). Both carbon sites in the intermediate aziridinium ions **7** (R = *i*-Pr, Bn) are attacked by chloride. Alternatively, in the aziridinium ion **7** (R = H), less hindered C2 is preferrebly attacked. Despite the lack of regioselectivity mixtures of 1-(*N*,*N*-dibenzylamino)-2-chloro- and 2-(*N*,*N*-dibenzylamino)-1-chlorophosphonates, **5** and **6** (R = *i*-Pr, Bn) will be converted to the same aziridinium ions before reacting with stronger nucleophiles. Thus, the immediate precursors to several aziridinium phosphonates became easily available.

EXPERIMENTAL

^{1}H NMR spectra were recorded with a Varian Mercury-300 spectrometer; chemical shifts δ in ppm are given with respect to TMS; coupling constants J are given in Hz. ^{13}C and ^{31}P NMR spectra were recorded with a Varian Mercury-300 instrument at 75.5 and 121.5 MHz, respectively. IR spectral data were measured with an Infinity MI-60 FT-IR spectrophotometer. Melting points were determined on a Boetius apparatus and are uncorrected. Elemental analyses were performed by the Microanalytical Laboratory of this faculty with a Perkin Elmer PE 2400 CHNS analyzer. Polarimetric measurements were conducted with a Perkin Elmer 241 MC apparatus. The following absorbents were used: for column chromatography—Merck silica gel 60 (70−230 mesh); for analytical TLC—Merck TLC plastic sheets silica gel 60 F_{254}.

N,N-Dibenzylaminoethanol 8

To a solution of 2-aminoethanol (6.11 g, 100 mmol) in acetonitrile (100 mL) containing potassium carbonate (27.7 g, 200 mmol) and tetrabutylammonium iodide (3.7 g, 10 mmol), benzyl bromide (23.8 mL, 200 mmol) was added dropwise at room temperature, and the suspension was stirred for 20 h. After the addition of chloroform (15 mL), the solid was filtered off and washed with chloroform (2 × 10 mL). All volatiles were carefully evaporated, and the crude product (19.2 g) was subjected to chromatography on a silica gel column with ethyl acetate:hexanes (4:1, v/v) to give *N*,*N*-dibenzylaminoethanol **8** (26.26 g,

79%) as a colorless oil. ^{1}H NMR ($CDCl_3$): $\delta = 7.36$–7.20 (m, 10H), 3.63 (s, 4H, $PhCH_2N$), 3.58 (t, $J = 5.4$ Hz, 2H, H_2C1), 2.66 (t, $J = 5.4$ Hz, 2H, H_2C2), 2.60 (br s, 1H, HO).

N,N-Dibenzylaminoacetaldehyde 9

To a solution of oxalyl chloride (0.497 mL, 5.82 mmol) in dichloromethane (15 mL) cooled to –70°C, a solution of dimethyl sulfoxide (0.895 mL, 12.6 mmol) in dichloromethane (10 mL) was added dropwise. After stirring for 15 min at this temperature, *N,N*-dibenzylaminoethanol **8** (1.20 g, 4.85 mmol) dissolved in dichloromethane (15 mL) was slowly transferred via cannula to the Swern reagent, and the reaction mixture was stirred for another 30 min. Then triethylamine (2.03 mL, 14.5 mmol) was added dropwise, and the mixture was stirred at –70°C for 1.5 h. After the addition of saturated sodium bicarbonate (17 mL), the solution was allowed to warm up to room temperature. The phases were separated, and the aqueous layer was extracted with dichloromethane (20 mL). The combined organic extracts were washed with brine (10 mL) and dried over $MgSO_4$. All volatiles were evaporated at room temperature to afford the crude *N,N*-dibenzylaminoacetaldehyde **9** (1.16 g, 100%) as a colorless oil, which was immediately used in the next step. ^{1}H NMR ($CDCl_3$) $\delta = 9.53$ (t, $J = 2.0$ Hz, 1H, CHO), 7.40–7.23 (m, 10H), 3.70 (s, 4H, $PhCH_2N$), 3.19 (d, $J = 2.0$ Hz, 2H, H_2CCHO).

Dimethyl 2-(*N,N*-Dibenzylamino)-1-hydroxyethylphosphonate 10a

To a solution of the crude aldehyde **9** prepared as described above (4.85 mmol) and dimethyl phosphite (0.445 mL, 4.85 mmol) in dichloromethane (2 mL), triethylamine (0.068 mL, 0.049 mmol) was added. The reaction mixture was stirred at room temperature for 8 h, diluted with dichloromethane (10 mL), and washed with water (10 mL). The aqueous phase was extracted with dichloromethane (2 × 10 mL). The organic phases were collected, washed with water (2 × 15 mL), and dried over $MgSO_4$. All volatiles were removed in vacuo, and the crude phosphonate was chromatographed on a silica gel column with chloroform:methanol (100:1, v/v) to give phosphonate **10a** (1.393 g, 79%) as a colorless oil. IR (film) $\nu =$ 3306, 3028, 2954, 1495, 1453, 1237, 1033 cm^{-1}. ^{1}H NMR ($CDCl_3$) $\delta = 7.37$–7.18 (m, 10H), 3.98 (ddd, $^3J_{H2aH1} = 10.8$ Hz, $^3J_{PH1} = 5.7$ Hz, $^3J_{H2bH1} = 3.6$ Hz, 1H, *H*CP), 3.83 (d, $J = 13.5$ Hz, 2H, Ph*H*CHN), 3.72 (d, $J = 10.2$ Hz, 3H, CH_3OPOCH_3),

3.67 (d, $J = 10.2$ Hz, 3H, CH_3OPOCH_3), 3.51 (d, $J = 13.5$ Hz, 2H, PhHCHN), 2.95 (ddAB, $J_{AB} = 13.2$ Hz, $^3J_{H2aH1} = 10.8$ Hz, $^3J_{PH} = 10.2$ Hz, 1H, H_aCHCP), 2.84 (ddAB, $J_{AB} = 13.2$ Hz, $^3J_{H2bH1} = 3.6$ Hz, $^3J_{PH} = 2.4$ Hz, 1H, HCH_bCP). ^{13}C NMR ($CDCl_3$): $\delta = 137.9$ (brs), 129.2, 128.6, 127.6, 63.8 (d, $^1J_{PC} = 167.5$ Hz, C1), 58.3 (CH$_2$Ph), 53.8 (d, $J = 3.5$ Hz, C2), 53.7 (d, $J = 6.6$ Hz, CH$_3$OPOCH$_3$), 53.2 (d, $J = 6.6$ Hz, CH$_3$OPOCH$_3$). ^{31}P NMR ($CDCl_3$): $\delta = 26.2$. Anal. Calcd for $C_{18}H_{24}NO_4P$: C, 61.88; H, 6.92; N, 4.01. Found: C, 61.70; H, 7.14; N, 4.06%.

Diethyl 2-(*N,N*-Dibenzylamino)-1-hydroxyethylphosphonate 10b

As described above, the crude product obtained from aldehyde **9** (14.0 mmol) and diethyl phosphite (1.79 mL, 14.0 mmol) in the presence of triethylamine (0.15 mL, 1.4 mmol) was purified on a silica gel column with chloroform:methanol (50:1, v/v). The appropriate fractions were collected to afford phosphonate **10b** (3.95 g, 74%) as a colorless oil. IR (film) $\nu = 3307$, 2982, 2928, 1602, 1495, 1453, 1231, 1052, 1027, 968 cm^{-1}. ^{1}H NMR ($CDCl_3$): $\delta = 7.36$–7.21 (m, 10H), 4.15–3.92 (m, 5H, CH_2OPOCH_2 and HCP), 3.84 (d, $J = 13.2$ Hz, 2H, PhHCHN), 3.47 (d, $J = 13.2$ Hz, 2H, PhHCHN), 2.92 (ddAB, $J_{AB} = 13.2$ Hz, $J = 10.8$ Hz, $J = 10.2$ Hz, 1H, H_aCHCP), 2.80 (ddAB, $J_{AB} = 13.2$ Hz, $J = 3.6$ Hz, $J = 2.4$ Hz, 1H, HCH_bCP), 1.24 (t, $J = 7.2$ Hz, 3H, CH_3CH$_2$OPOCH$_2$CH_3), 1.17 (t, $J = 7.2$ Hz, 3H, CH_3CH$_2$OPOCH$_2$CH_3). ^{13}C NMR ($CDCl_3$): $\delta = 137.8$ (brs), 129.0, 128.4, 127.3, 63.7 (d, $J = 167.4$ Hz, C1), 62.8 (d, $J = 7.2$ Hz, CH$_2$OPOCH$_2$), 62.4 (d, $J = 7.2$ Hz, CH$_2$OPOCH$_2$), 58.0 (CH$_2$Ph), 53.4 (d, $J = 3.7$ Hz, C2), 16.4 (d, $J = 5.7$ Hz, CH$_3$CH$_2$OPOCH$_2C$H$_3$), 16.3 (d, $J = 5.7$ Hz, CH$_3$CH$_2$OPOCH$_2C$H$_3$). ^{31}P NMR ($CDCl_3$): $\delta = 23.1$. Anal. Calcd for $C_{20}H_{28}NO_4P$: C, 63.65; H, 7.48; N, 3.71. Found: C, 63.50; H, 7.27; N, 3.63%.

Dimethyl 2-(*N,N*-Dibenzylamino)-1-mesyloxyethylphosphonate 11a

To a solution of the hydroxyphosphonate **10a** (0.21 g, 0.59 mmol) containing triethylamine (0.245 mL, 1.77 mol) in dichloromethane (1.5 mL) cooled to 0°C, mesyl chloride (0.055 mL, 0.71 mmol) was added dropwise. The reaction mixture was stirred at this temperature for 30 min, allowed to warm to 20°C over 20 min, and finally it was diluted with dichloromethane (10 mL). The solution was washed with cold water (10 mL), and the aqueous phase was extracted with

dichloromethane (20 mL). The organic extracts were washed with cold water (15 mL), dried over $MgSO_4$, and all volatiles were removed in vacuo at room temperature to leave crude 1-*O*-mesylate **11a** (0.24 g, 100%) as a colorless oil. ^{1}H NMR ($CDCl_3$): $\delta = 7.42$–7.20 (m, 10H), 5.09 (ddd, $^2J_{PH} = 10.2$ Hz, $^3J_{HH} = 9.6$ Hz, $^3J_{HH} = 2.4$ Hz, 1H, *H*CP), 3.85 (d, $J = 13.5$ Hz, 2H, Ph*H*CHN), 3.76 (d, $J = 10.5$ Hz, 3H, C*H*$_3$OPOC*H*$_3$), 3.73 (d, $J = 10.5$ Hz, 3H, C*H*$_3$OPOC*H*$_3$), 3.50 (d, $J = 13.5$ Hz, 2H, PhHC*H*N), 3.15 (s, 3H, C*H*$_3$SO$_2$), 3.06 (ddAB, $J_{AB} = 15.0$ Hz, $^3J_{HH} = 9.6$ Hz, $^3J_{PH} = 6.0$ Hz, 1H, H_aCHCP),) 2.89 (ddAB, $J_{AB} = 15.0$ Hz, $^3J_{PH} = 4.2$ Hz, $^3J_{HH} = 2.4$ Hz, 1H, HCH_bCP). ^{31}P NMR ($CDCl_3$): $\delta = 20.2$.

Dimethyl 1-(*N,N*-Dibenzylamino)-2-chloroethylphosphonate 12a

A solution of crude 1-*O*-mesylate **11a** (0.61 g, 1.4 mmol) in dichloromethane (5 mL) containing tetraethylammonium chloride (0.20 g, 1.2 mmol) was stirred at room temperature for 10 d. The reaction mixture was diluted with dichloromethane (10 mL), washed with water (10 mL), and the aqueous phase was extracted with dichloromethane (20 mL). The organic extracts were washed with water (15 mL) and dried over $MgSO_4$. The oily residue obtained after evaporation of the solvent (0.43 g) was twice chromatographed on silica gel with ethyl acetate:hexane (2:1, v/v) to give phosphonate **12a** (0.114 g, 22%) as colorless oil. IR (film) $\nu = 2953$, 2924, 2852, 1495, 1455, 1249, 1038 cm^{-1}. ^{1}H NMR ($CDCl_3$): $\delta = 7.45$–7.16 (m, 10H), 3.95 (s, 4H, PhC*H*$_2$N), 3.87 (ddAB, $J_{AB} = 12.0$ Hz, $^3J_{HH} = 9.6$ Hz, $^3J_{PH} = 5.4$ Hz, 1H, H_aCHCP), 3.82 (tAB, $J_{AB} = 12.0$ Hz, $^3J_{HH} =$ $^3J_{PH} = 4.2$ Hz, 1H, HCH_bCP), 3.73 (d, $J = 10.5$ Hz, 3H, C*H*$_3$OPOC*H*$_3$), 3.71 (d, $J = 10.5$ Hz, 3H, C*H*$_3$OPOC*H*$_3$), 3.42 (ddd, $^2J_{PH} = 19.5$ Hz, $^3J_{HH} = 9.6$ Hz, $^3J_{HH} = 4.2$ Hz, 1H, *H*CP). ^{13}C NMR ($CDCl_3$): $\delta = 138.9$ (br s), 129.4, 129.1, 128.3, 127.3, 57.4 (d, $^1J_{PC} = 136.6$ Hz, C1), 55.1 (d, $J = 3.0$ Hz, Ph*C*H$_2$N), 52.9 (d, $J = 7.5$ Hz, *C*H$_3$OPO*C*H$_3$), 52.3 (d, $J = 7.5$ Hz, *C*H$_3$OPO*C*H$_3$), 41.8 (d, $^2J_{PC} = 21.9$ Hz, C2). ^{31}P NMR ($CDCl_3$): $\delta = 26.5$. Anal. Calcd for $C_{18}H_{23}ClNO_3P$: C, 58.78; H, 6.30; N, 3.81. Found: C, 58.68; H, 6.02; N, 3.76%.

Diethyl 1-(*N,N*-Dibenzylamino)-2-(*N*-benzylamino)ethylphosphonate 13b

Crude diethyl 2-(*N,N*-dibenzylamino)-1-mesyloxyethylphosphonate **11b** was obtained as described above from phosphonate **10b** (0.329 g,

0.855 mmol), triethylamine (0.356 mL, 2.56 mmol), and mesyl chloride (0.100 mL, 1.28 mmol). ^{1}H NMR ($CDCl_3$): δ = 7.40–7.19 (m, 10H), 5.08 (dt, J = 9.6 Hz, J = 2.4 Hz, 1H, *H*CP), 4.20–4.00 (m, 4H, C*H*$_2$OPOC*H*$_2$), 3.86 (d, J = 13.5 Hz, 2H, Ph*H*CHN), 3.51 (d, J = 13.5 Hz, 2H, PhHC*H*N), 3.17 (s, 3H, C*H*$_3$SO$_2$), 3.05 (ddAB, J_{AB} = 15.0 Hz, $^3J_{HH}$ = 9.6 Hz, $^3J_{PH}$ = 5.7 Hz, 1H, H_aCHCP), 2.88 (tAB, J_{AB} = 15.0 Hz, $^3J_{HH}$ = $^3J_{PH}$ = 2.4 Hz, 1H, HCH_bCP), 1.27 (t, J = 7.2 Hz, 3H, C*H*$_3$CH$_2$OPOCH$_2$C*H*$_3$), 1.25 (t, J = 7.2 Hz, 3H, C*H*$_3$CH$_2$OPOCH$_2$C*H*$_3$). ^{31}P NMR ($CDCl_3$): δ = 17.7.

A solution of the crude **11b** in toluene (2 mL) containing benzylamine (0.093 mL, 0.86 mmol) and triethylamine (0.12 mL, 0.86 mmol) was kept at 70–75°C for 20 h. All volatiles were evaporated and the residue was twice chromatographed on silica gel with ethyl acetate:hexane (2:1, v/v) to give phosphonate **13b** (0.136 g, 30%) as a colorless oil. IR (film): ν = 3472, 3062, 3028, 2981, 2927, 2907, 2851, 1603, 1495, 1453, 1242, 1051, 1027 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 7.35–7.15 (m, 15H), 4.20–4.05 (m, 4H, C*H*$_2$OPOC*H*$_2$), 3.93 (AB, J_{AB} = 13.2 Hz, 2H, Ph*H*CHN), 3.88 (dAB, J_{AB} = 13.2 Hz, $^4J_{PH}$ = 3.9 Hz, 2H, PhHC*H*N), 3.49 (d, J = 13.5 Hz, 1H, Ph*H*CHN), 3.34 (d, J = 13.5 Hz, 1H, PhHC*H*N), 3.30 (ddd, $^2J_{PH}$ = 16.5 Hz, $^3J_{HH}$ = 9.9 Hz, $^3J_{HH}$ = 3.9 Hz, 1H, *H*CP), 3.02 (ddAB, J_{AB} = 12.9 Hz, $^3J_{HH}$ = 9.9 Hz, $^3J_{PH}$ = 6.3 Hz, 1H, H_aCHCP), 2.81 (tAB, J_{AB} = 12.9 Hz, $^3J_{HH}$ = $^3J_{PH}$ = 3.9 Hz, HCH_bCP), 1.33 (t, J = 7.2 Hz, 3H, C*H*$_3$CH$_2$OPOCH$_2$C*H*$_3$), 1.32 (t, J = 7.2 Hz, 3H, C*H*$_3$CH$_2$OPOCH$_2$C*H*$_3$). ^{13}C NMR ($CDCl_3$): δ = 139.8 (br s), 139.6, 129.3, 128.5, 128.2, 127.3, 127.0, 61.8 (d, J = 6.9 Hz, *C*H$_2$OPO*C*H$_2$), 61.5 (d, J = 6.9 Hz, *C*H$_2$OPO*C*H$_2$), 55.3 (d, J = 2.3 Hz, Ph*C*H$_2$N), 55.1 (d, J = 131.7 Hz, C1), 52.2 (Ph*C*H$_2$N), 46.4 (d, J = 11.2 Hz, C2), 17.0 (d, J = 6.0 Hz, *C*H$_3$CH$_2$OPOCH$_2$*C*H$_3$), 16.9 (d, J = 6.0 Hz, *C*H$_3$CH$_2$OPOCH$_2$*C*H$_3$). ^{31}P NMR ($CDCl_3$): δ = 27.1. Anal. Calcd for $C_{27}H_{35}N_2O_3P$: C, 69.51; H, 7.56; N, 6.00. Found: C, 69.72; H, 7.38; N, 5.83%.

Dimethyl (1*R*,2*S*)-2-(*N*,*N*-Dibenzylamino)-1-hydroxy-3-methyl butylphosphonate (1*R*,2*S*)-15a

To a solution of oxalyl chloride (0.592 mL, 6.92 mmol) in dichloromethane (10 mL) cooled to –70°C, a solution of dimethyl sulfoxide (1.06 mL, 15,0 mmol) in dichloromethane (5 mL) was added dropwise. After stirring for 15 min at this temperature, *N*,*N*-dibenzyl-L-valinol (1.64 g, 5.77 mmol) dissolved in dichloromethane (5 mL) was slowly transferred via cannula to the Swern reagent and the reaction mixture was stirred for another 40 min. Then triethylamine (2.41 mL, 17.3 mmol) was added dropwise and the mixture was stirred at

–70°C for 30 min. A solution of lithium *O*,*O*-dimethyl phosphonate [prepared from dimethyl phosphite (0.635 mL, 6.92 mmol), diisopropylamine (0.970 mL, 6.92 mmol), and 1.6 M BuLi (4.33 mL, 6.92 mmol)] in THF (10 mL) cooled to –70°C was slowly transferred via cannula into the solution of the crude aldehyde at –70°C. After stirring for 1.5 h at this temperature, saturated ammonium chloride (14 mL) was added, and the reaction mixture was allowed to warm up to room temperature. The phases were separated, and the aqueous layer was extracted with dichloromethane (3 × 10 mL). The combined organic extracts were washed with brine (10 mL) and dried over $MgSO_4$. All volatiles were evaporated at room temperature to afford a crude phosphonate **15a**, which was subjected to chromatography on a silica gel column with chloroform:methanol (50:1, v/v). The appropriate fractions were combined and crystallized from a chloroform/hexane mixture to give phosphonate (1*R*,2*S*)-**15a** (1.13 g, 50%) as an amorphous solid. Mp 119.5–120.8°C. $[\alpha]_D^{20} = -36.2$ (*c* 1.5, AcOEt). IR (KBr): $\nu = 3277$, 2953, 1454, 1218, 1057, 1035, 747, 700 cm^{-1}. ^1H NMR ($CDCl_3$): $\delta = 7.40$–7.25 (m, 10H), 4.10 (dd, $^2J_{PH} = 9.6$ Hz, $J_{HH} = 4.2$ Hz, 1H, *H*CP), 3.88 (d, $J = 13.3$ Hz, 2H, Ph*H*CHN), 3.78 (d, $J = 13.3$ Hz, 2H, PhHC*H*N), 3.71 (d, $J = 10.5$ Hz, 3H, C*H*$_3$OPOC*H*$_3$), 3.70 (d, $J = 10.5$ Hz, 3H, C*H*$_3$OPOC*H*$_3$), 2.82 (ddd, $^3J_{PH} = 27.3$ Hz, $J_{HH} = 9.6$ Hz, $^3J_{HH} = 4.2$ Hz, 1H, *H*CCP), 2.45 (dsp, $^3J_{HH} = 9.6$ Hz, $^3J_{HH} = 6.6$ Hz, 1H, *H*CCCP), 1.23 (d, $^3J_{HH} = 6.6$ Hz, 3H, C*H*$_3$CCH$_3$), 0.98 (d, $^3J_{HH} = 6.6$ Hz, 3H, CH$_3$CC*H*$_3$). ^{13}C NMR ($CDCl_3$): $\delta = 139.6$, 129.5, 128.4, 127.2, 66.4 (d, $^1J_{PC} = 154.6$ Hz, C1), 65.7 (d, $J = 4.0$ Hz, C2) 55.3 (Ph*C*H$_2$N), 53.2 (d, $J = 7.4$ Hz, *C*H$_3$OPOCH$_3$), 53.1 (d, $J = 7.4$ Hz, *C*H$_3$OPOCH$_3$), 28.2 (C3), 22.9, 21.7. ^{31}P NMR ($CDCl_3$): $\delta = 26.9$. Anal. Calcd for $C_{21}H_{30}NO_4P$: C, 64.44; H, 7.72; N, 3.58. Found: C, 64.22; H, 7.90; N, 3.66%.

Dimethyl (1*S*,2*R*)-1-(*N*,*N*-Dibenzylamino)-2-chloro-3-methyl butylphosphonate (1*S*,2*R*)-16 and Dimethyl (1*S*,2*S*)-2-(*N*,*N*-Dibenzylamino)-1-chloro-3-methylbutylphosphonate (1*S*,2*S*)-17

To a solution of phosphonate (1*R*,2*S*)-**15a** (0.100 g, 0.255 mmol) in methylene chloride (2 mL) containing triethylamine (0.178 mL, 1.28 mmol) and powdered molecular sieves 4A (0.30 g) cooled to 0°C, mesyl chloride (0.060 mL, 0.77 mmol) was slowly injected followed by the addition of tetraethylammonium chloride (0.085 g, 0.51 mmol). The suspension was stirred at room temperature for 24 h. After filtration through a layer of Celite, the solution was concentrated and subjected

to chromatography on a silica gel column with chloroform:methanol (100:1, v/v) to give several fractions containing various mixtures (from 94:6 to 80:20) of dimethyl (1*S*,2*R*)-1-(*N*,*N*-dibenzylamino)-2-chloro-3-methylbutylphosphonate (1*S*,2*R*)-**16** and dimethyl (1*S*,2*S*)-2-(*N*,*N*-dibenzylamino)-1-chloro-3-methylbutylphosphonate (1*S*,2*S*)-**17** (total 0.075 g, 72%) as colorless oils. Anal. Calcd for $C_{21}H_{29}ClNO_3P$: C, 61.54; H, 7.13; N, 3.42. Found: C, 61.79; H, 7.06; N, 3.34%.

Dimethyl (1*S*,2*R*)-1-(*N*,*N*-Dibenzylamino)-2-chloro-3-methyl butylphosphonate (1*S*,2*R*)-16

^{1}H NMR ($CDCl_3$): $\delta = 7.36$–7.21 (m, 10H), 4.06 (ddd, $J_{H2H1} = 9.9$ Hz, $^3J_{PH2} = 8.1$ Hz, $J_{H2H3} = 2.7$ Hz, 1H, *H*CCP), 3.92 (AB, $J = 13.5$ Hz, 2H, PhCH_2N), 3.88 (AB, $J = 13.5$ Hz, 2H, PhCH_2N), 3.87 (d, $J = 11.0$ Hz, 3H, CH_3OPOCH_3), 3.84 (d, $J = 11.0$ Hz, 3H, CH_3OPOCH_3), 3.31 (dd, $^2J_{PH1} = 15.6$ Hz, $J_{H1H2} = 9.9$ Hz, 1H, *H*CP), 2.55 (spdd, $^3J_{HH} = 6.5$ Hz, $^3J_{H3H2} = 2.7$ Hz, $^4J_{PH3} = 1.5$ Hz, 1H, *H*CCCP), 0.92 (d, $^3J_{HH} = 6.5$ Hz, 3H, CH_3CCH$_3$), 0.26 (d, $^3J_{HH} = 6.5$ Hz, 3H, CH$_3$CCH_3). ^{13}C NMR ($CDCl_3$): $\delta = 138.9$, 129.7, 128.5, 127.5, 66.1 (d, $J = 5.5$ Hz, C2), 59.9 (d, $^1J_{PC} = 137.5$ Hz, C1), 55.8 (d, $J = 1.5$ Hz, Ph*C*H$_2$N), 52.6 (d, $J = 7.5$ Hz, *C*H$_3$OPO*C*H$_3$), 52.0 (d, $J = 7.5$ Hz, *C*H$_3$OPO*C*H$_3$), 29.2 (d, $J = 7.5$ Hz, C3), 20.1, 15.1. ^{31}P NMR ($CDCl_3$): $\delta = 30.7$.

Dimethyl (1*S*,2*S*)-2-(*N*,*N*-Dibenzylamino)-1-chloro-3-methyl butylphosphonate (1*S*,2*S*)-17

^{1}H NMR ($CDCl_3$): $\delta = 7.36$–7.21 (m, 10H), 4.12 (dd, $^2J_{PH1} = 9.6$ Hz, $J_{H1H2} = 4.2$ Hz, 1H, *H*CP), 3.89 (d, $J = 13.5$ Hz, 2H, Ph*H*CHN), 3.78 (d, $J = 13.5$ Hz, 2H, PhHC*H*N), 3.72 (d, $J = 10.5$ Hz, 3H, CH_3OPOCH_3), 3.70 (d, $J = 10.5$ Hz, 3H, CH_3OPOCH_3), 2.82 (ddd, $^3J_{PH2} = 28.8$ Hz, $J_{H2H3} = 10.5$ Hz, $^3J_{H2H1} = 4.2$ Hz, 1H, *H*CCP), 2.46 (dsp, $^3J_{H3H2} = 10.5$ Hz, $^3J_{HH} = 6.5$ Hz, 1H, *H*CCCP), 1.23 (d, $^3J_{HH} = 6.5$ Hz, 3H, CH_3CCH$_3$), 0.98 (d, $^3J_{HH} = 6.5$ Hz, 3H, CH$_3$CCH_3). ^{13}C NMR ($CDCl_3$): $\delta = 139.6$, 129.5, 128.4, 127.3, 65.7 (d, $J = 4.0$ Hz, C2) 55.3 (Ph*C*H$_2$N), 53.2 (d, $J = 7.5$ Hz, *C*H$_3$OPO*C*H$_3$), 53.0 (d, $J = 7.5$ Hz, *C*H$_3$OPO*C*H$_3$), 51.5 (d, $^1J_{PC} = 150.9$ Hz, C1), 28.3 (C3), 23.0, 21.8. ^{31}P NMR ($CDCl_3$): $\delta = 27.4$.

Diethyl (1*R*,2*S*)-and (1*S*,2*S*)-2-(*N*,*N*-Dibenzylamino)-1-hydroxy-3-phenylpropyl-phosphonates (1*R*,2*S*)-19a and (1*S*,2*S*)-19b

A mixture of a crude (*S*)-*N*,*N*-dibenzylphenylalaninal **18** [obtained after Swern oxidation of (*S*)-N,*N*-dibenzylphenylalaninol (1.98 g, 5.97 mmol)], diethyl phosphite (0.769 mL, 5.97 mmol), and triethylamine (0.083 mL, 0.060 mmol) was left at room temperature for 20 h. The residue was chromatographed on a silica gel column with ethyl acetate:hexane (2:1, v/v). The appropriate fractions of the less polar compound were combined to give phosphonate (1*S*,2*S*)-**19b** (0.243 g, 9%) as a colorless oil, which solidified at 5°C.[8] IR (KBr): $\nu = 3215, 2995, 2801, 1495, 1454, 1199, 1053, 1022, 978, 745, 701\ cm^{-1}$. ^1H NMR ($CDCl_3$): $\delta =$ 7.45–7.36 (m, 4H), 7.35–7.29 (m, 1H), 7.29–7.19 (m, 6H), 7.10–7.00 (v br s, 4H), 4.95 (br d, $J = 18.3$ Hz, 1H, HO), 4.22–4.00 (m, 2H, H_2COP), 3.95–3.65 (m, 5H), 3.55–3.25 (m, 4H), 2.99 (dd, $J = 14.7$ Hz, $J = 10.5$ Hz, 1H, HCH_bCCP), 1.28 (t, $J = 6.9$ Hz, 3H, CH_3CH$_2$OP), 1.09 (t, $J = 6.9$ Hz, 3H, POCH$_2$CH_3). ^{13}C NMR ($CDCl_3$): $\delta = 140.2, 138.2, 129.7, 129.4, 129.0, 128.8, 128.7, 128.5, 128.2, 127.5, 126.6, 66.7$ (d, $J = 167.2$ Hz, C1), 63.2 (d, $J = 7.5$ Hz, *C*H$_2$OPO*C*H$_2$), 62.6 (d, $J = 7.5$ Hz, *C*H$_2$OPO*C*H$_2$), 59.8 (d, $J = 4.0$ Hz, C2), 53.6 (s, Ph*C*H$_2$N), 34.5 (s, C3), 16.7 (d, $J = 5.7$ Hz, *C*H$_3$CH$_2$OPOCH$_2$*C*H$_3$), 16.7 (d, $J = 5.7$ Hz, *C*H$_3$CH$_2$OPOCH$_2$*C*H$_3$). ^{31}P NMR ($CDCl_3$): $\delta = 24.5$. Anal. Calcd for $C_{27}H_{34}NO_4P$: C, 69.36; H, 7.33; N, 3.00. Found: C, 69.28; H, 7.08; N, 2.88%.

Further fractions (0.97 g, 36%) contained various mixtures of diastereoisomeric phosphonates (1*R*,2*S*)-**19a** and (1*S*,2*S*)-**19b**. In the final fractions, more polar phosphonate (1.49 g, 54%) was collected and was crystallized from ethyl acetate to afford (1*R*,2*S*)-**19a** (0.79 g, 28%). IR (KBr): $\nu = 3299, 2982, 1454, 1217, 1057, 1026, 976, 745, 698\ cm^{-1}$. ^1H NMR ($CDCl_3$): $\delta =$ 7.30–7.05 (m, 15H), 4.32 (ddd, $J_{PH1} =$ 9.6 Hz, $J_{H1HO} = 7.2$ Hz, $J_{H1H2} = 2.1$ Hz, 1H, *H*CP), 4.17–3.95 (m, 4H, CH_2OPOCH_2), 3.87 (d, $J = 13.8$ Hz, 2H, Ph*H*CHN), 3.57 (d, $J =$ 13.8 Hz, 2H, PhHC*H*N), 3.38 (dddd, 1H, $J_{PH2} = 14.4$ Hz, $J_{H2H3b} = 9.3$ Hz, $J_{H2H3a} = 5.1$ Hz, $J_{H2H1} = 2.1$ Hz, *H*CCP), 3.11 (dAB, $J_{AB} = 14.4$ Hz, $J_{H3aH2} = 5.1$ Hz, 1H, PhH_aCHCCP), 3.05 (dAB, $J_{AB} = 14.4$ Hz, $J_{H3bH2} = 9.3$ Hz, 1H, PhHCH_bCCP), 2.96 (dd, $J_{HOH1} = 7.2$ Hz, $J_{POH} =$ 4.2 Hz, 1H, *H*O), 1.27 (t, $J = 6.9$ Hz, 3H, CH_3CH$_2$OPOCH$_2$CH_3), 1.24 (t, $J = 6.9$ Hz, 3H, CH_3CH$_2$OPOCH$_2$CH_3). ^{13}C NMR ($CDCl_3$): $\delta =$ 140.3, 139.6, 129.8, 128.1, 128.0, 126.8, 125.9, 66.3 (d, $J = 153.8$ Hz, C1), 63.1 (d, $J = 7.2$ Hz, CH$_3$*C*H$_2$OPO*C*H$_2$CH$_3$), 62.6 (d, $J = 7.2$ Hz, CH$_3$*C*H$_2$OPO*C*H$_2$CH$_3$), 59.9 (d, $J = 6.0$ Hz, C2), 54.5 (s, Ph*C*H$_2$N), 32.5 (s, C3), 16.8 (d, $J = 5.5$ Hz, *C*H$_3$CH$_2$OPOCH$_2$*C*H$_3$). ^{31}P NMR ($CDCl_3$): $\delta = 25.1$. Anal. Calcd for $C_{27}H_{34}NO_4P$: C, 69.36; H, 7.33; N, 3.00. Found: C, 69.01; H, 7.23; N, 3.20%.

Diethyl (1*S*,2*R*)-1-(*N*,*N*-Dibenzylamino)-2-chloro-3-phenyl propylphosphonate (1*S*,2*R*)-20 and (1*S*,2*S*)-2-(*N*,*N*-Dibenzyl amino)-1-chloro-3-phenylpropylphosphonate (1*S*,2*S*)-21

To a solution of phosphonate (1*R*,2*S*)-**19a** (0.050 g, 0.11 mmol) in methylene chloride (1 mL) containing triethylamine (0.075 mL, 0.54 mmol) and powdered molecular sieves 4A (0.15 g) cooled to 0°C, mesyl chloride (0.025 mL, 0.32 mmol) was slowly injected followed by the addition of tetraethylammonium chloride (0.035 g, 0.21 mmol). The suspension was stirred at room temperature for 48 h. After filtration through a layer of Celite, the solution was concentrated and subjected to chromatography on a silica gel column with chloroform:methanol (100:1, v/v) to give several fractions containing 1:1 mixtures of diethyl (1*S*,2*R*)-1-(*N*,*N*-dibenzylamino)-2-chloro-3-phenylpropylphosphonate (1*S*,2*R*)-**20** and diethyl (1*S*,2*S*)-2-(*N*,*N*-dibenzylamino)-1-chloro-3-phenylpropylphosphonate (1*S*,2*S*)-**21** (total 0.037 g, 71%) as colorless oils. Anal. Calcd for $C_{27}H_{33}ClNO_3P$: C, 66.73; H, 6.84; N, 2.88. Found: C, 66.83; H, 6.66; N, 2.95%.

Diethyl (1*S*,2*R*)-1-(*N*,*N*-Dibenzylamino)-2-chloro-3-phenyl propylphosphonate (1*S*,2*R*)-20

^{1}H NMR ($CDCl_3$): $\delta = 7.34$–6.95 (m, 15H), 4.39 (dddd, $^3J_{PH2} = 15.6$ Hz, $J_{H2H3b} = 9.3$ Hz, $J_{H2H3a} = 6.0$ Hz, $J_{H2H1} = 5.4$ Hz, 1H, *H*CCP), 4.27–4.11 and 4.09–3.98 (m, 2H, C*H*$_2$OPOC*H*$_2$), 4.14 (AB, $J = 13.5$ Hz, 2H, PhC*H*$_2$N), 3.82 (AB, $J = 13.5$ Hz, 2H, PhC*H*$_2$N), 3.71 (dd, $^2J_{H3aH3b} = 14.1$ Hz, $J_{H3aH2} = 6.0$ Hz, 1H, H_aCHCCP), 3.37 (dd, $^2J_{PH1} = 21.3$ Hz, $J_{H1H2} = 5.4$ Hz, 1H, *H*CP), 2.76 (dd, $^2J_{H3bH3a} = 14.1$ Hz, $J_{H3bH2} = 9.3$ Hz, 1H, HCH_bCCP), 1.30 (t, $J = 7.1$ Hz, 3H, C*H*$_3$CH$_2$OPOCH$_2$C*H*$_3$), 1.21 (t, $J = 7.1$ Hz, 3H, C*H*$_3$CH$_2$OPOCH$_2$C*H*$_3$). ^{13}C NMR ($CDCl_3$): $\delta =$ 139.5, 138.3, 129.5, 128.7, 128.1, 127.3, 126.9, 126.2, 62.1 (d, $J = 7.5$ Hz, *C*H$_2$OPO*C*H$_2$), 61.8 (d, $J = 7.5$ Hz, *C*H$_2$OPO*C*H$_2$), 60.7 (d, $^1J_{PC} =$ 147.5 Hz, C1), 60.4 (d, $J = 7.4$ Hz, C2), 56.1 (d, $J = 4.0$ Hz, Ph*C*H$_2$N), 43.2 (d, $J = 4.0$ Hz, C3), 16.9 (d, $J = 6.0$ Hz, *C*H$_3$CH$_2$OPOCH$_2$*C*H$_3$), 16.8 (d, $J = 6.0$ Hz, *C*H$_3$CH$_2$OPOCH$_2$*C*H$_3$). ^{31}P NMR ($CDCl_3$): $\delta = 24.8$.

Dimethyl (1*S*,2*S*)-2-(*N*,*N*-Dibenzylamino)-1-chloro-3-phenyl propylphosphonate (1*S*,2*S*)-21

^{1}H NMR ($CDCl_3$): $\delta = 7.34$–6.95 (m, 15H), 4.54 (dd, $^2J_{PH1} = 15.6$ Hz, $J_{H1H2} = 0.9$ Hz, 1H, *H*CP), 4.27–4.11 and 4.09–3.98 (m, 4H, C*H*$_2$OPOC*H*$_2$), 4.03 (AB, $J_{AB} = 14.1$ Hz, 2H, PhC*H*$_2$N), 3.43 (AB, $J_{AB} = 14.1$ Hz, 2H, PhC*H*$_2$N), 3.80–3.70 (m, 1H, *H*CCP), 3.16

(dAB, $^2J_{H3aH3b} = 14.4$ Hz, $J_{H3aH2} = 4.2$ Hz, 1H, H_aCHCCP), 3.12 (dAB, $^2J_{H3aH3b} = 14.4$ Hz, $J_{H3bH2} = 9.9$ Hz, 1H, HCH_bCCP), 1.36 (t, $J = 7.1$ Hz, 3H, CH_3CH$_2$OPOCH$_2$CH_3), 1.34 (t, $J = 7.1$ Hz, 3H, CH_3CH$_2$OPOCH$_2$CH_3). ^{13}C NMR ($CDCl_3$): $\delta =$ 139.1, 139.0, 129.9, 129.4, 128.6, 128.4, 128.2, 126.9, 64.1 (d, $J = 7.5$ Hz, *C*H$_2$OPO*C*H$_2$), 63.6 (d, $J = 7.5$ Hz, *C*H$_2$OPO*C*H$_2$), 58.3 (d, $J = 2.6$ Hz, C2), 53.9 (s, Ph*C*H$_2$N), 51.3 (d, $^1J_{PC} = 151.8$ Hz, C1), 34.7 (s, C3), 16.7 (d, $J = 5.3$ Hz, *C*H$_3$CH$_2$OPOCH$_2$*C*H$_3$), 16.6 (d, $J = 5.3$ Hz, *C*H$_3$CH$_2$OPOCH$_2$*C*H$_3$). ^{31}P NMR ($CDCl_3$): $\delta = 20.8$.

Reaction of Crude Diethyl (1*S,2R*)-1-(*N,N*-Dibenzylamino)-2-mesyloxy-3-phenylpropyl-phosphonate (1*S,2R*)-23 with Tetraethylammonium Chloride

To a solution of phosphonate (1*R*,2*S*)-**19a** (0.100 g, 0.214 mmol) in toluene (1 mL) cooled to 0°C, triethylamine (0.090 mL, 0,64 mmol) was added followed by slow injection of mesyl chloride (0.025 mL, 0.32 mmol) at this temperature. After 30 min of stirring at 0°C, toluene (5 mL) was added, the mixture was washed with cold water (2 × 5 mL), dried over $MgSO_4$, and concentrated in vacuo at room temperature. The oily residue was dissolved in chloroform and left at room temperature for 48 h to provide a crude product containing ca. 95% of the 2-mesyloxyphosphonate (1*S*,2*R*)-**23**. ^{1}H NMR ($CDCl_3$): $\delta = 7.40$–7.10 (m, 15H), 5.22 (dtd, $J_{PH2} = 13.5$ Hz, $J_{H2H3a} =$ $J_{H2-H3b} = 6.6$ Hz, $J_{H2H1} = 3.3$ Hz, *H*CCP), 4.20–4.00 (m, 5H, C*H*$_2$OPO*H*CH, Ph*H*CHN), 4.00–3.85 (m, 1H, CH$_2$OPOHC*H*), 3.71 (d, $J = 13.5$ Hz, 2H, PhHC*H*N), 3.50 (dd, $J_{H3aH3b} = 13.5$ Hz, $J_{H3aH2} = 6.6$ Hz, 1H, H_aCHCCP), 3.43 (dd, $J_{PH1} = 24.0$ Hz, $J_{H1H2} = 3.3$ Hz, 1H, *H*CP), 3.16 (dd, $J_{H3bH3a} = 13.5$ Hz, $J_{H3bH2} = 6.6$ Hz, 1H, HCH_bCCP), 2.65 (s, 3H, CH_3SO$_2$), 1.32 (t, $J = 7.1$ Hz, 3H, CH_3CH$_2$OPOCH$_2$CH_3), 1.30 (t, $J = 7.1$ Hz, 3H, CH_3CH$_2$OPOCH$_2$CH_3). ^{13}C NMR ($CDCl_3$): $\delta =$ 138.8, 136.3, 130.0, 129.2, 128.9, 128.3, 127.2, 82.1 (d, $J = 8.6$ Hz, C2), 62.2 (d, $J = 6.8$ Hz, *C*H$_2$OPO*C*H$_2$), 61.9 (d, $J = 6.8$ Hz, *C*H$_2$OPO*C*H$_2$), 57.7 (d, $J = 147.1$ Hz, C1), 56.1 (d, $J = 4.8$ Hz, Ph*C*H$_2$N), 39.3 (s, C3), 39.0 (s, *C*H$_3$SO$_2$), 16.8 (d, $J = 6.0$ Hz, *C*H$_3$CH$_2$OPOCH$_2$*C*H$_3$), 16.7 (d, $J = 6.0$ Hz, *C*H$_3$CH$_2$OPOCH$_2$*C*H$_3$). ^{31}P NMR ($CDCl_3$): δ 23.5.

To a solution of the crude 2-mesyloxyphosphonate (1*S*,2*R*)-**23** (0.100 g, 0.183 mmol) in methylene chloride (1 mL) containing triethylamine (0.077 mL, 0.549 mmol), tetraethylammonium chloride (0.061 g, 0.37 mmol) was added, and the mixture was left at room temperature for 48 h. After dilution with methylene chloride (5 mL), the solution was washed with water (3 × 3 mL), dried over $MgSO_4$, and concentrated.

The oily residue was chromatographed on a silica gel column with chloroform:methanol (100:1, v/v) to give a colorless oil (0.080 g), which was identified as a 1:1 mixture of chlorophosphonates (1*S*,2*R*)-**20** and (1*S*,2*S*)-**21** contaminated with the starting 1-hydroxyphosphonate (1*R*,2*S*)-**19a** (ca. 2%) and the 2-hydroxyphosphonate (1*S*,2*R*)-**24** (ca. 5%).

Reaction of Crude Diethyl (1*S,2R*)-1-(*N,N*-Dibenzylamino) -2-mesyloxy-3-phenylpropyl phosphonate (1*S,2R*)-23 with Water on Silica Gel

A solution of the 2-mesyloxyphosphonate (1*S*,2*R*)-**23** prepared from phosphonate (1*R*,2*S*)-**19a** (0.050 g, 0.11 mmol) in chloroform (1 mL) was left on a silica gel column for 48 h. Elution with chloroform:methanol (20:1, v/v) gave a colorless oil (0.042 g), which was identified as a mixture of five compounds: diethyl (1*S*,2*R*)-1-(*N*,*N*-dibenzylamino)-2-hydroxy-3-phenylpropylphosphonate (1*S*,2*R*)-**24** (ca. 86%), diethyl (1*R*,2S)-2-(*N*,*N*-dibenzylamino)-1-hydroxy-3-phenylpropylphosphonate (1*S*,2*R*)-**19a** (ca. 8%), diethyl (1*S*,2*R*)-1-(*N*,*N*-dibenzylamino)-2-chloro-3-phenylpropylphosphonate (1*S*,2*R*)-**20** (ca. 4%), diethyl (1*S*,2*S*)-2-(*N*,*N*-dibenzylamino)-1-chloro-3-phenylpropylphosphonate (1*S*,2*S*)-**21** (ca. 4%), and ca. 2% of an unidentified phosphonate ($\delta^{31}P = 28.4$ ppm).

Diethyl (1*S,2R*)-1-(*N,N*-Dibenzylamino)-2-hydroxy-3-phenyl propylphosphonate (1*S,2R*)-24

^{1}H NMR ($CDCl_3$): δ = 7.38–7.04 (m, 15H), 4.27–3.98 (m, 5H, $CH_3CH_2OPOCH_2CH_3$, *H*CCP), 3.98 (dd, J = 13.8 Hz, J = 4.2 Hz, 2H, Ph*H*CHN), 3.89 (d, J = 13.8 Hz, 2H, PhHC*H*N), 3.32 (dd, J_{H3aH3b} = 14.1 Hz, J_{H3aH2} = 3.3 Hz, 1H, H_aCHCCP), 3.12 (dd, J_{PH1} = 17.1 Hz, J_{H1H2} = 7.2 Hz, 1H, *H*CP), 2.93 (d, J = 5.7 Hz, 1H, HO), 2.44 (dd, J_{H3bH3a} = 14.1 Hz, J_{H3bH2} = 9.0 Hz, 1H, HCH_bCCP), 1.39 (t, J = 6.9 Hz, 3H, CH_3CH$_2$OPOCH$_2$CH_3), 1.32 (t, J = 6.9 Hz, 3H, CH_3CH$_2$OPOCH$_2$CH_3). ^{13}C NMR ($CDCl_3$): δ = 139.3 (s, C_{ipso}), 138.9 (d, J = 1.7 Hz, NCH$_2C_{ipso}$), 129.5, 129.3, 128.6, 128.4, 127.3, 126.5, 71.8 (d, J = 4.9 Hz, C2), 61.9 (d, J = 7.4 Hz, *C*H$_2$OPO*C*H$_2$), 61.8 (d, J = 7.4 Hz, *C*H$_2$OPO*C*H$_2$), 61.2 (d, J = 132.3 Hz, C1), 56.1 (d, J = 2.9 Hz, N*C*H$_2$Ph), 42.1 (d, J = 8.3 Hz, C3), 17.0 (d, J = 5.7 Hz, *C*H$_3$CH$_2$OPOCH$_2$*C*H$_3$), 16.9 (d, J = 5.7 Hz, *C*H$_3$CH$_2$OPOCH$_2$*C*H$_3$). ^{31}P NMR ($CDCl_3$): δ = 29.7.

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