Diastereoselective Synthesis of Chiral Amidophosphonates by 1,5-Asymmetric Induction

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Dedicated to Professor J.-F. Normant on the occasion of his 65th birthday

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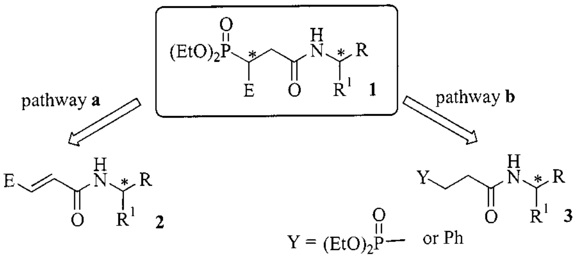
We have investigated two simple diastereoselective syntheses of substituted β-amidophosphonates. The first one involved a Michael addition to α,β-unsaturated amides **6** and **8a–d**, derived from chiral amino alcohols, and permitted the preparation of alkyl-substituted derivatives **7** and **9a–d** with high diastereoselectivities (up to 95%) with the aid of a 1,5-asymmetric induction. The second one, involving 1,5-inductive alkylation of chiral β-amidophosphonates **14a–c**, was promising in terms of the yields, but the diastereoselectivities were disappointing (up to 50%). Finally, removal of the chiral auxiliary afforded phosphonocarboxylic acid, able to provide access to a wide range of compounds of great interest for the synthesis of biologically active products.

Introduction

Phosphonic acids and their derivatives have been prepared and studied as isosteric analogs of carboxylic acids. Phosphorylated amino acids[1] are of particular interest and have found widespread use as enzyme inhibitors,[2] antiviral drugs,[3] antibiotics,[4] and neurodrugs;[5] phaclofen, a γ-aminophosphonic acid, was the first described selective GABA$_B$ antagonist.[6] They are also known to exhibit strong herbicidal activity[7] and are also found as constituents of natural products.[8,9] In general, biological activity is strongly dependent upon the chirality α or β to the phosphorus atom. A number of synthetic routes to α- and β-aminophosphonates have been developed during the past two decades,[10–14] but this is not the case for γ-aminophosphonates. Although some syntheses of these have been reported previously,[15–17] these methods lack versatility and their application to optically active compounds and polysubstituted derivatives seems to be problematic.

We recently decided to develop diastereoselective routes to γ-aminophosphonates with chiral centers α to the phosphorus atom. β-Amidophosphonates were chosen as key intermediates, owing to the high potential of these compounds for conversion into γ-aminophosphonates (by simple reduction or by functionalization of the corresponding phosphonocarboxylic acids). Two approaches, described in Scheme 1, were considered for the synthesis of chiral β-amidophosphonates. In our preliminary paper[18] we described a diastereoselective version of one of the most versatile pathways for the formation of carbon–phosphorus bonds: namely the Pudovik reaction.[19] This reaction involves the addition of compounds containing a labile P–H bond to α,β-unsaturated optically active amides, providing an easy means of access to the potentially biologically interesting α-substituted β-amidophosphonates.



Scheme 1. Route to chiral β-amidophosphonates

Another approach to substituted β-amidophosphonates (pathway **b**) is the diastereoselective metallation/alkylation of β-amidobenzenes or β-amidophosphonates, using amines as chiral auxiliaries. Indeed, Beak[20–24] recently demonstrated that the stereoselective carbon–carbon bond formation in chiral auxiliary-mediated β-lithiation/substitution sequences of β-substituted secondary carboxamides occurred with the involvement of a complex-induced proximity effect. In this report, we present details of these two methods and further application to the preparation of an optically pure β-phosphonocarboxylic acid.

Results and Discussion

In our first study[18] dealing with the asymmetric Michael addition of diethyl phosphite to α,β-unsaturated chiral amides (Scheme 2), we observed that the best results, *de* = 95%, were obtained by using amino alcohols as chiral aux-

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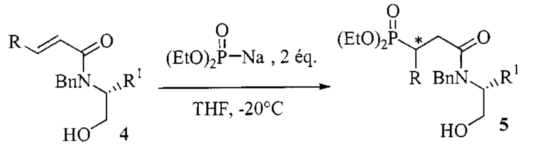


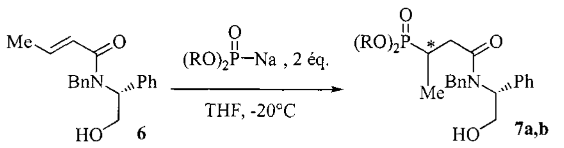
Scheme 2. Diastereoselective addition of diethyl phosphite to α,β-unsaturated chiral amides

iliaries, with 2 equiv. of the sodium salt of the phosphonate in THF at −20 °C.

Diastereoselectivity was also observed to be highly dependent on the nature of the olefinic substituent, with the highest *de* values (> 90%) furnished by alkyl groups (R = Me, Et, *i*Pr), while a phenyl substituent produced a lower *de* value (45%). The same excellent diastereoselectivities (92% for R = Me) were observed with either aminobutyl alcohol, valinol, or phenylglycinol derivatives, demonstrating the relative unimportance of the nature of the group α to the nitrogen atom. Introduction of a substituent α to the oxygen atom of the amino alcohol, however, produced dramatically decreased diastereoselectivity.

To complete these preliminary results, we then turned our attention to the influence of the nature of the phosphonate substituents and the N-substituent (Table 1).

Table 1. Influence of the size of the nucleophile



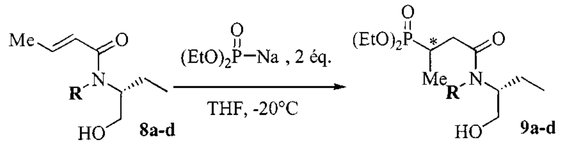
Entry	Product	R	Yield (%)	d.e. (%)[a]
1	**7a**	Et	50	92
2	**7b**	*i*Pr	65	92
3	–	*t*Bu	0	–

[a] Measured on the crude product by ^{31}P NMR or by HPLC.

It appeared that the use of diisopropyl phosphite as a nucleophile (Entry 2) not only preserved diastereoselectivity (92%), but also increased the yield to 65%. In order to increase steric hindrance, we also used di-*tert*-butyl phosphite (Entry 3), but whatever the conditions, we were unable to detect any formation of the desired product.

We then studied the effect of nitrogen substitution (Table 2). *N*-Monoalkylated derivatives of aminobutyl alcohol were prepared in good yields by treatment of the primary amine with the corresponding aldehydes, followed by reduction of the imine with $NaBH_4$. After condensation with crotonyl chloride, amides **8** were treated with diethyl phosphite anion. The best diastereoselectivity was obtained with the *N*-benzylated amino alcohol (Entry 4), a lower diastereoselectivity was obtained with the *N*-methyl derivative (Entry 2). Surprisingly, use of a more hindered substituent such as isopropyl (Entry 3) resulted in a complete loss of selectivity (*de*: 22%). We also performed the addition with the secondary amide **8a**, affording **9a** in good yield (55%) and with excellent *de* (82%). To the best of our knowledge, this is the first example of diastereoselective addition with secondary chiral amide.

Table 2. Influence of the substituent of the nitrogen

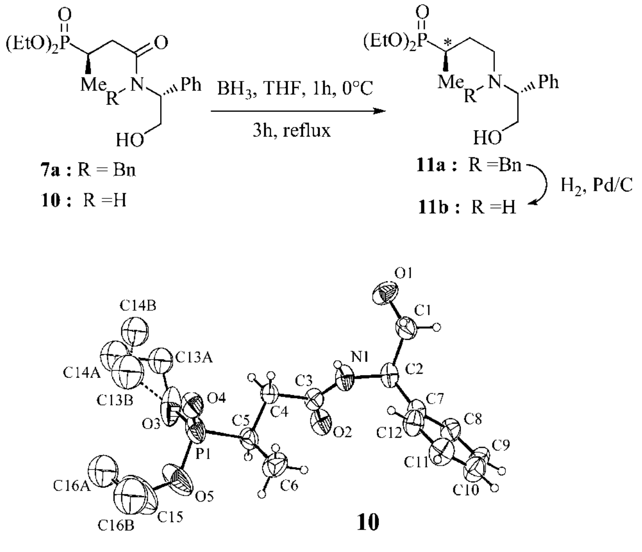


Entry	Substrate	R	Product	Yield (%)	d.e. (%)[a]
1	**8a**	H	**9a**	55	82
2	**8b**	Me	**9b**	60	76
3	**8c**	*i*Pr	**9c**	45	22
4	**8d**	Bn	**9d**	50	92

[a] Measured on the crude product by ^{31}P NMR or by HPLC.

None of the products synthesized during this study furnished sought-after crystals for X-ray analysis, suitable for determination of the absolute configuration of the newly created chiral center. Fortunately, however, during an experiment conducted on unsubstituted phenylglycinol, we obtained compound **10** (Scheme 3) on addition of diethyl phosphite to the corresponding crotonamide. After separation of the isomers, we were pleased to obtain the major product as a crystalline product. An X-ray analysis performed on this compound[25] indicated the (*R*) configuration at the chiral center α to the phosphorus atom (Scheme 3). It was possible, using ^{31}P NMR, to correlate the reduced product **11b** obtained from **10** with the major isomer obtained by reduction of **7a** and subsequent selective hydrogenolysis of the benzyl group. The same major isomer of **11b** was obtained in each case, confirming the same (*R*) configuration in the major product.

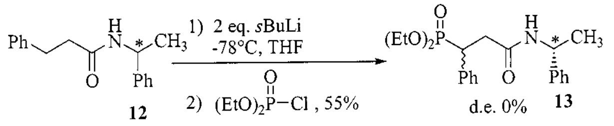
At this stage of our study, it was very difficult to propose a mechanism to explain the observed results, because of the existence of various deprotonated species in the course of



Scheme 3. Determination of the absolute configuration of the newly created chiral center

the reaction and also the possible retro-Michael reaction. Moreover, the observed configuration of the major isomer was the opposite of that predicted by Mukaiyama[26] and Brown[27] for the Michael addition of alkyl Grignard reagents to various α,β-unsaturated chiral tertiary amides. Even the introduction of trimethylsilyl chloride at the end of the reaction, in order to identify the intermediate species, produced a mixture of different compounds and did not clarify the mechanism.

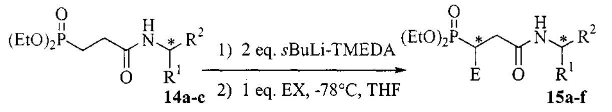
In order to develop another route to chiral β-amidophosphonates, one that would allow the synthesis of different substituted products, we experimented with the diastereoselective introduction of an electrophile by means of the deprotonation/alkylation sequence described in Scheme 1 (pathway **b**). We first tried to functionalize β-amidobenzene (Scheme 4), using diethyl chlorophosphite as an electrophile, following the experimental conditions described by Beak. We were never able to observe any diastereoselection in the formation of the substituted compound **13**.



Scheme 4. Alkylation of β-amidobenzene

We then reasoned that the phosphonate group could be used as an acidity activator for the α-proton in place of the phenyl group used by Beak. The same mechanism might thus permit the preparation of functionalized derivatives (Table 3).

Table 3. Alkylation of β-amidophosphonates



Entry	Substrate	R^1	R^2	Product	E	Yield (%)	d.e. (%)[a]
1	**14a**	Me	Ph	**15a**	Me	80	20
2	**14a**	Me	Ph	**15b**	Bn	55	5
3	**14a**	Me	Ph	**15c**	TMS	85	5
4	**14b**	Et	CH_2OBn	**15d**	Me	60	30
5	**14b**	Et	CH_2OBn	**15e**	Bn	70	50
6	**14b**	Et	CH_2OBn	**15f**	TMS	50	10
7	**14c**	Et	CH_2OH	–	Me	–	–

[a] Measured on the crude product by ^{31}P NMR or by HPLC.

β-Amidophosphonates **14a−c** were easily obtained by 1,4-addition of diethyl phosphite to ethyl acrylate, using a catalytic amount of NaH in THF. The esters were then saponified and transformed into acyl chlorides,[28] which were capable of reaction with different amines [(*R*)-(+)-α-methylbenzylamine, (*R*)-(−)-2-aminobutan-1-ol, and *O*-benzylated (*R*)-2-aminobutan-1-ol] in the presence of sodium carbonate to afford desired compounds **14a−c** in 76, 35, and 65% overall yields, respectively.

The alkylation step was then optimized (solvent, base, temperature, number of equiv.); the best conditions appeared to be *s*BuLi (2 equiv.) in the presence of added TMEDA (2 equiv.) in THF at −78 °C, followed by the addition of the electrophile (1 equiv.). Alkylation yields were always high, but the diastereoselectivities were disappointingly low (Table 3). The results obtained with α-methylbenzylamine (*de* < 20%, Entries 1−3) showed that adoption of Beak's method was not helpful for our substrates. The best diastereoselectivity, up to 50%, was obtained using *O*-benzylated aminobutyl alcohol as a chiral auxiliary and benzyl bromide as an electrophile (Entry 5), but the results were highly dependent on the electrophile. We never obtained the alkylated product when unprotected aminobutyl alcohol was used as a chiral auxiliary (Entry 7); indeed, we observed a mixture of products − methylated oxazoline derivatives in particular − with no regioselectivity in methylation (α or β to the phosphorus atom).

To explain that disappointing results, we have to consider the rigid intermediate **16** proposed by Beak to explain very high diastereoselectivities. In our case, the system is perhaps disturbed by the phosphonate oxygen atoms, which might also chelate the lithium ion of the intermediate,[29] as shown for compound **17** (Figure 1). Nevertheless, these results represent the first application of this method to nonaromatic substrates.

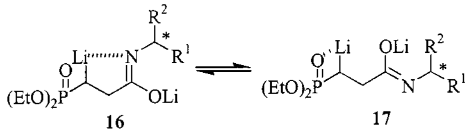
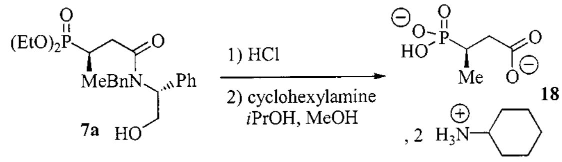


Figure 1. Lithium intermediates in the alkylation step

The practical use of this methodology for the synthesis of functionalized α-substituted phosphonic acid is illustrated by the preparation of acid **18**,[30] for which no asymmetric synthesis has been described. Hydrolysis of amide **7a** or **7b** was accomplished by treatment with acid (HCl, 8 M). Compound **18** was isolated in 45% and 65% yields, respectively, as its cyclohexylammonium salt (Scheme 5).



Scheme 5. Deprotection of the chiral β-amidophosphonate

Conclusion

In summary, we have investigated two simple diastereoselective syntheses of substituted β-amidophosphonates. The first involved a Michael addition and enabled alkyl-substituted derivatives to be prepared with high diastereoselectivities (up to 95%) by means of a 1,5-asymmetric induction. The second one, involving a 1,5-inductive alkylation, is promising in terms of the yields. It could be applied to other phosphorus derivatives without heteroatoms such as phosphanes that disturb the reactive intermediates. Finally, removal of the chiral auxiliary made it possible to prepare a wide range of compounds that can be used for the synthesis of biologically active products.

Experimental Section

General Remarks: Solvents were purified by conventional methods prior to use. − TLC was performed on Merck 60F 250 silica gel plates and column chromatography on silica gel SI 60 (230−240 mesh). − Melting points were taken with a Kofler apparatus and are uncorrected. − Elemental analyses were carried out with a Carlo Erba EA 1100 analyzer. − NMR spectra were recorded with a Bruker DPX 300 spectrometer operating at 300 MHz for ^{1}H, 75.4 MHz for ^{13}C, and 121.5 MHz for ^{31}P. This probe was equipped for pulsed-field (*z*) gradients. Chemical shifts (δ) are expressed in ppm relative to TMS for ^{1}H and ^{13}C nuclei and to H$_3$PO$_4$ for ^{31}P nuclei; coupling constants (*J*) are given in Hertz; coupling multiplicities are reported using conventional abbreviations. − IR spectra were recorded with a Perkin−Elmer Paragon 500 FT-IR spectrometer.

Compound 6: Crotonyl chloride (900 mg, 8.6 mmol) was slowly added to a solution of *N*-benzyl(phenyl)glycinol[31] (1.77 g, 7.8 mmol) in CH$_2$Cl$_2$ (30 mL). NaOH (345 mg, 8.6 mmol), dissolved in the minimum amount of water, was then added. After the mixture had been stirred for 3 h at room temperature, water (10 mL) was added, and the mixture was extracted with dichloromethane (3 × 20 mL). The combined organic layers were dried with magnesium sulfate, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (EtOAc/cyclohexane, 30:70) to provide **6** (1.89 g) in 82% yield (presence of rotamers). − ^{1}H NMR (CDCl$_3$): δ = 1.76 (d, *J* = 6.4 Hz, 3 H, =CH−C*H*$_3$), 4.02 (m, 2 H, C*H*$_2$−OH), 4.31 and 4.44 (2 d, *J* = 17.6 Hz, N−C*H*$_2$−C$_6$H$_5$), 5.38 (m, 1 H, N−C*H*), 6.11 (d, *J* = 14.7 Hz, 1 H, C*H*=CH−CH$_3$), 6.95−7.10 (m, 1 H, CH=C*H*−CH$_3$), 7.23 (m, 10 H, *H*$_{\mathrm{ar}}$). − ^{13}C NMR (CDCl$_3$): δ = 18.7 (*C*H$_3$−CH=), 50.1 (N−*C*H$_2$−Ph), 62.8 (N−*C*H), 63.9 (*C*H$_2$−OH), 122.9 (*C*H=CH−CH$_3$), 126.6, 127.9, 128.3, 128.7, 129.1, 129.2 (*C*$_{\mathrm{ar}}$), 137.5, 137.8 (*C*$_{\mathrm{ar\ quat}}$), 144.2 (CH=*C*H−CH$_3$), 169.5 (*C*=O). − IR (neat): $\tilde{\nu}$ = 3275, 1654, 1589 cm^{-1}. − $[\alpha]_{\mathrm{D}}^{20}$ = −31.7 (*c* = 1, CHCl$_3$). − C$_{19}$H$_{21}$NO$_2$ (295.38): calcd. C 77.26, H 7.17, N 4.74; found C 77.15, H 7.32, N 4.88.

Compound 7a: Diethyl phosphite (1.16 mL, 9 mmol) was added to a suspension of NaH (206 mg, 8.6 mmol) in anhydrous THF (20 mL) under an inert gas at room temperature. After stirring for 1 h, the mixture was cooled to −20 °C, and a solution of amide **6** (1 g, 4.29 mmol) in THF (10 mL) was added. After the mixture had been stirred for 5 h at −20 °C, water (10 mL) was added, and the compound was extracted with dichloromethane (3 × 20 mL). The combined organic layers were dried with magnesium sulfate, filtered, and concentrated. The crude mixture was purified by column chromatography on silica gel (EtOAc/MeOH, 95:5) to provide **7a** (0.8 g) in 50% yield and with a *de* of 92%. Description of the major diastereoisomer (presence of rotamers). − ^{31}P NMR (CDCl$_3$): δ = 34.52 and 35.75. − ^{1}H NMR (CDCl$_3$): δ = 1.09 (dd, *J* = 6.9 and 17.9 Hz, 3 H, P−CH−C*H*$_3$), 1.16−1.24 (m, 6 H, C*H*$_3$−CH$_2$−O), 2.14−2.22 (m, 1 H, P−CH−C*H*$_2$), 2.22 (s, 1 H, O*H*), 2.59−2.68 (m, 2 H, P−CH−C*H*$_2$, P−C*H*−CH$_2$), 3.93−4.09 (m, 6 H, CH$_3$−C*H*$_2$−O, C*H*$_2$−OH), 4.41 and 4.6 (2 d, *J* = 17.7 Hz, N−C*H*$_2$−C$_6$H$_5$), 5.65 and 5.62 (2 d, *J* = 4.4 Hz, 1 H, N−C*H*), 6.94−7.28 (m, 10 H, *H*$_{\mathrm{ar}}$). − ^{13}C NMR (CDCl$_3$): δ = 14.9 (d, *J* = 5.2 Hz, P−CH−*C*H$_3$), 16.8 and 16.9 [2 d, *J* = 5.7 Hz, (*C*H$_3$−CH$_2$−O)$_2$], 28.7 (d, *J* = 142.6 Hz, P−*C*H−CH$_2$), 35.9 (P−CH−*C*H$_2$), 49.5 (N−*C*H$_2$−C$_6$H$_5$), 61.9 (N−*C*H), 62.0−62.4 [m, (CH$_3$−*C*H$_2$−O)$_2$], 63.3 (*C*H$_2$−OH), 126.4−129.3 (m, *C*$_{\mathrm{ar}}$), 137.6 and 137.8 (*C*$_{\mathrm{ar\ quat}}$), 173.8 (d, *J* = 12.5 Hz, *C*=O). − IR (neat): $\tilde{\nu}$ = 3310, 1650, 1240, 1026, 740, 699 cm^{-1}. − MS (IC): *m*/*z* = 434 [M + 1]$^{+}$, 403 (2.5), 326 (2.5), 314 (10), 209 (1). − HRMS [MH]$^{+}$: calcd. 434.2096, found 434.2098

Compound 7b: This compound was prepared in the same manner as **7a**, but with diisopropyl phosphite. Column chromatography on silica gel (eluent AcOEt/MeOH, 90:10), yielded **7b** (270 mg, 65%, *de* 92%) as a colorless oil. Description of the major diastereoisomer (presence of rotamers). − ^{31}P NMR (CDCl$_3$): δ = 32.14 and 33.46. − ^{1}H NMR (CDCl$_3$): δ = 1.06 (dd, *J* = 7.0 and 17.8 Hz, 3 H, P−CH−C*H*$_3$), 1.15−1.28 (m, 12 H, (C*H*$_3$)$_2$−CH−O), 1.9 (s, 1 H, O*H*), 2.05−2.20 (m, 1 H, P−CH−C*H*$_2$), 2.55−2.70 (m, 2 H, P−CH−C*H*$_2$, P−C*H*−CH$_2$), 4.00−4.12 (m, 2 H, C*H*$_2$−OH), 4.35 and 4.57 (2 d, *J* = 17.7 Hz, N−C*H*$_2$−C$_6$H$_5$), 4.55−4.61 (m, 2 H, (CH$_3$)$_2$−C*H*−O), 5.60 (m, 1 H, N−C*H*), 7.13−7.21 (m, 10 H, *H*$_{\mathrm{ar}}$). − ^{13}C NMR (CDCl$_3$): δ = 14.4 and 14.9 (2 d, *J* = 5.5 Hz, P−CH−*C*H$_3$), 24.2−24.6 (m, (*C*H$_3$)$_2$−CH−O), 28.8 and 29.7 (2 d, *J* = 143 Hz, P−*C*H−CH$_2$), 34.8 and 35.8 (P−CH−*C*H$_2$), 49 (N−*C*H$_2$−Ph), 61.2 and 61.4 (2 s, N−*C*H), 63.0 (*C*H$_2$−OH), 70.4, 70.9, 70.6 and 70.7 [4d, *J* = 6.6 Hz, (CH$_3$)$_2$−*C*H−O], 126.5, 127.5, 127.7, 127.8, 129.1, 129.3 (*C*$_{\mathrm{ar}}$),138.2, 139.9 (*C*$_{\mathrm{ar\ quat}}$), 172.7 and 174.0 (2 d, *J* = 13 Hz, *C*=O). − IR (neat): $\tilde{\nu}$ = 3390, 2979, 1644, 1454, 1222, 1000, 700 cm^{-1}.

Compound 8a: This compound was prepared in the same manner as **6**, but starting from 2-aminobutanol, yielding **8a** (220 mg, 70%) as a white powder after column chromatography on silica gel (eluent AcOEt). − ^{1}H NMR (CDCl$_3$): δ = 0.88 (t, *J* = 7.5 Hz, 3 H, C*H*$_3$−CH$_2$−CH), 1.42−1.59 (m, 2 H, CH$_3$−C*H*$_2$−CH), 1.78 (dd, *J* = 6.9 and 1.6 Hz, 3 H, =CH−C*H*$_3$), 3.10 (s, 1 H, OH), 3.50−3.65 (m, 2 H, C*H*$_2$−OH), 3.9 (m, 1 H, N−C*H*), 5.78 (dd, *J* = 15.2 and 1.6 Hz, 1 H, C*H*=CH−CH$_3$), 6.11 (d, *J* = 7.7 Hz, 1 H, NH), 6.72−6.84 (m, 1 H, CH=C*H*−CH$_3$). − ^{13}C NMR (CDCl$_3$): δ = 10.5 (*C*H$_3$−CH$_2$−CH), 17.5 (*C*H$_3$−CH=), 24.0 (CH$_3$−*C*H$_2$−CH), 53.0 (N−*C*H), 64.4 (*C*H$_2$−OH), 125.0 (*C*H=CH−CH$_3$), 139.8 (=*C*H−CH$_3$), 166.8 (*C*=O). − IR (neat): $\tilde{\nu}$ = 3276, 1660, 1630 cm^{-1}. − MS (IC): *m*/*z* = 158 (100) [M + 1]$^{+}$. − $[\alpha]_{\mathrm{D}}^{20}$ = −50.1 (*c* = 1, CHCl$_3$). − C$_8$H$_{15}$NO$_2$ (157.21): calcd. C 61.12, H 9.62, N 8.91; found C 59.92, H 10.13, N 9.07.

Compound 8b: This compound was prepared in the same manner as **6**, but starting from *N*-methylaminobutyl alcohol,[31] yielding **8b** (246 mg, 72%) as a yellow oil after column chromatography (eluent EtOAc/cyclohexane, 1:1) on silica gel. Rotamers in evidence. − ^{1}H NMR (CDCl$_3$): δ = 0.79 and 0.81 (2 t, *J* = 7.2 Hz, 3 H, C*H*$_3$−CH$_2$−CH), 1.35−1.54 (m, 2 H, CH$_3$−C*H*$_2$−CH), 1.79 and 1.83 (2 dd, *J* = 6.8 and 1.4 Hz, 3 H, =CH−C*H*$_3$), 2.72 and 2.86 (2 s, 3 H, N−C*H*$_3$), 3.45−3.63 (m, 2 H, C*H*$_2$−OH), 3.83−3.9 and 4.38−4.44 (2 m, 1 H, N−C*H*), 6.22 and 6.32 (2 d, *J* = 15.1 Hz, 1 H, C*H*=CH−CH$_3$), 6.68−6.88 (m, 1 H, CH=C*H*−CH$_3$). − ^{13}C NMR (CDCl$_3$): δ = 10.9 and 11.1 (*C*H$_3$−CH$_2$−CH), 18.7 (*C*H$_3$−CH=), 21.4 and 22.1 (CH$_3$−*C*H$_2$−CH), 26.7 and 30.7 (*C*H$_3$−N), 58.5 and 61.2 (N−*C*H), 62.9 and 63.6 (*C*H$_2$−OH), 122.7 and 123.2 (*C*H=CH−CH$_3$), 141.0 and 142.6 (=*C*H−CH$_3$), 169.1 and 169.4 (*C*=O). − IR (neat): $\tilde{\nu}$ = 3390, 1660, 1600, 1454, 1100, 1068 cm^{-1}.

Compound 8c: This compound was prepared in the same manner as **6**, but starting from *N*-isopropylaminobutyl alcohol,[31] yielding **8c** (259 mg, 65%) as a colorless oil, after column chromatography (eluent EtOAc/cyclohexane, 1:1) on silica gel. Rotamers in evidence. − ^{1}H NMR (CDCl$_3$): δ = 0.87 (t, *J* = 7.5 Hz, 3 H, C*H*$_3$−CH$_2$−CH), 1.07−1.16 (m, 6 H, (C*H*$_3$)$_2$−CH−N), 1.54−1.57 (m, 1 H, CH$_3$−C*H*$_2$−CH), 2.06−2.20 (m, 1 H, CH$_3$−C*H*$_2$−CH), 1.81 (d, *J* = 6.8 Hz, 3 H, =CH−C*H*$_3$), 3.07 (m, 1 H, N−C*H*), 3.66 (d, *J* = 11.7 Hz, 1 H, C*H*$_2$−OH), 3.81 (dd, *J* = 11.7 and 4.9 Hz, 1 H, C*H*$_2$−OH), 4.05−4.12 (m, 1 H, (CH$_3$)$_2$−C*H*−N), 6.17 (d, *J* = 15.2 Hz, 1 H, C*H*=CH−CH$_3$), 6.70−6.82 (m, 1 H, CH=C*H*−CH$_3$). − ^{13}C NMR (CDCl$_3$): δ = 11.9 (*C*H$_3$−CH$_2$−CH), 18.4 and 18.7 ($\mathit{C}H_3-CH=$), 21.4 and 21.5 [$(\mathit{C}H_3)_2-CH-N$], 21.6 ($CH_3-\mathit{C}H_2-CH$), 50.0 [$(CH_3)_2-\mathit{C}H-N$], 58.3 ($N-\mathit{C}H$), 65.1 ($\mathit{C}H_2-OH$), 123.6 ($\mathit{C}H=CH-CH_3$), 142.2 ($=\mathit{C}H-CH_3$), 168.8 ($\mathit{C}=O$). − IR (neat): $\tilde{\nu}$ = 3372, 1659, 1600, 1156, 1100 cm^{-1}. − $[\alpha]_D^{20}$ = −18.0 (*c* = 1, $CHCl_3$).

Compound 8d: This compound was prepared in the same manner as **6**, but starting from *N*-benzyl-2-aminobutanol,[31] yielding **8d** (366 mg, 74%) as a white powder after column chromatography (eluent EtOAc/cyclohexane, 30:70) on silica gel. Rotamers in evidence. − ^1H NMR ($CDCl_3$): δ = 0.81 (t, *J* = 7.3 Hz, 3 H, $C\mathit{H}_3-CH_2-CH$), 1.44−1.57 (m, 2 H, $CH_3-C\mathit{H}_2-CH$), 1.75−1.80 (2 d, *J* = 6.9 Hz, 3 H, $=CH-C\mathit{H}_3$), 3.40−3.70 (m, 3 H, $N-C\mathit{H}$, $C\mathit{H}_2-OH$), 4.50 and 4.65 (2 d, *J* = 17.5 Hz, 2 H, $N-C\mathit{H}_2-C_6H_5$), 6.10 and 6.40 (2 d, *J* = 14.8 Hz, 1 H, $C\mathit{H}=CH-CH_3$), 6.80−7.00 (m, 1 H, $CH=C\mathit{H}-CH_3$), 7.20−7.35 (m, 5 H, H_{ar}). − ^{13}C NMR ($CDCl_3$): δ = 11.7 ($\mathit{C}H_3-CH_2-CH$), 18.7 ($\mathit{C}H_3-CH=$), 21.8 ($CH_3-\mathit{C}H_2-CH$), 51.3 ($N-\mathit{C}H_2-Ph$), 62.7 ($N-\mathit{C}H$), 64.2 ($\mathit{C}H_2-OH$), 123.0 ($\mathit{C}H=CH-CH_3$), 127.0, 128.0, 129.2 (C_{ar}), 138.0 ($\mathit{C}_{ar\ quat}$), 141.9 ($=\mathit{C}H-CH_3$), 169.6 ($\mathit{C}=O$). − IR (neat): $\tilde{\nu}$ = 3303, 1656, 1588 cm^{-1}. − $[\alpha]_D^{20}$ = +5.5 (*c* = 1, $CHCl_3$). − $C_{15}H_{21}NO_2$ (247.33): calcd. C 72.84, H 8.56, N 5.66; found C 72.82, H 8.59, N 5.45.

Compound 9a: This compound was prepared in the same manner as **7a**, but starting from **8a**, yielding **9a** (162 mg, 55%, *de* 82%) as a colorless oil after column chromatography (eluent AcOEt/MeOH, 90:10) on silica gel. Description of the major diastereoisomer. − ^{31}P NMR ($CDCl_3$): δ = 34.83. − ^1H NMR ($CDCl_3$): δ = 0.88 (t, *J* = 7.4 Hz, 3 H, $C\mathit{H}_3-CH_2-CH$), 1.06 (dd, *J* = 7.2 and 18.1 Hz, 3 H, $P-CH-C\mathit{H}_3$), 1.26 (t, *J* = 7.0 Hz, 6 H, $C\mathit{H}_3-CH_2-O$), 1.33−1.58 (m, 2 H, $CH_3-C\mathit{H}_2-CH$), 2.10−2.30 (m, 1 H, $P-CH-C\mathit{H}_2$), 2.38−2.55 (m, 2 H, $P-CH-C\mathit{H}_2$, $P-C\mathit{H}-CH_2$), 3.45−3.70 (m, 2 H, $C\mathit{H}_2-OH$), 3.80 (m, 1 H, $N-C\mathit{H}$), 3.96−4.07 (m, 4 H, $CH_3-C\mathit{H}_2-O$), 6.51 (d, *J* = 8.2 Hz, 1 H, $N\mathit{H}$). − ^{13}C NMR ($CDCl_3$): δ = 11.0 ($\mathit{C}H_3-CH_2-CH$), 14.4 (d, *J* = 5 Hz, $P-CH-\mathit{C}H_3$), 16.8 (d, $\mathit{C}H_3-CH_2-O$), 24.4 ($CH_3-\mathit{C}H_2-CH$), 28.1 (d, *J* = 143.1 Hz, $P-\mathit{C}H-CH_2$), 38.0 ($P-CH-\mathit{C}H_2$), 53.8 ($N-\mathit{C}H$), 62.5 (d, *J* = 7 Hz, $CH_3-\mathit{C}H_2-O$), 64.7 ($\mathit{C}H_2-OH$), 171.4 (d, *J* = 13 Hz, $\mathit{C}=O$). − IR (neat): $\tilde{\nu}$ = 3401, 3288, 1648, 1553, 1219, 1026 cm^{-1}.

Compound 9b: This compound was prepared in the same manner as **7a**, but starting from **8b**, yielding **9b** (186 mg, 60%, *de* 76%) as a yellowish oil after column chromatography (eluent AcOEt/MeOH, 90:10) on silica gel. Description of the major diastereoisomer (presence of rotamers). − ^{31}P NMR ($CDCl_3$): δ = 34.98 and 36.07. − ^1H NMR ($CDCl_3$): δ = 0.73 and 0.75 (t, *J* = 7.1 Hz, 3 H, $C\mathit{H}_3-CH_2-CH$), 1.06 (dd, *J* = 7.0 and 18.0 Hz, 3 H, $P-CH-C\mathit{H}_3$), 1.16−1.21 (m, 6 H, $C\mathit{H}_3-CH_2-O$), 1.30−1.50 (m, 2 H, $CH_3-C\mathit{H}_2-CH$), 2.10−2.25 (m, 1 H, $P-CH-C\mathit{H}_2$), 2.40−2.58 (m, 1 H, $P-C\mathit{H}-CH_2$), 2.58−2.69 (m, 1 H, $P-CH-C\mathit{H}_2$), 2.63 and 2.76 (2 s, 3 H, $N-CH_3$), 3.43−3.45 (2 d, *J* = 3.7 Hz, 2 H, $C\mathit{H}_2-OH$), 3.92−4.00 (m, 5 H, $N-C\mathit{H}$, $CH_3-C\mathit{H}_2-O$). − ^{13}C NMR ($CDCl_3$): δ = 11.2 and 11.7 (2 s, $\mathit{C}H_3-CH_2-CH$), 14.3 and 14.7 (2 d, *J* = 5 Hz, $P-CH-\mathit{C}H_3$), 16.7 and 16.8 (2 d, $\mathit{C}H_3-CH_2-O$), 21.9 and 22.7 (2 s, $CH_3-\mathit{C}H_2-CH$), 26.5 and 29.3 (2 s, $N-\mathit{C}H_3$), 28.5 (d, *J* = 143 Hz, $P-\mathit{C}H-CH_2$), 34.7 and 35.6 (2 s, $P-CH-\mathit{C}H_2$), 61.5 and 61.7 (2 s, $N-\mathit{C}H$), 62.0−62.3 (m, $CH_3-\mathit{C}H_2-O$), 63.4 and 63.6 (2 s, $\mathit{C}H_2-OH$), 173.6 (d, *J* = 13.4 Hz, $\mathit{C}=O$). − IR (neat): $\tilde{\nu}$ = 3401, 2925, 1644, 1207, 1052, 1030 cm^{-1}.

Compound 9c: This compound was prepared in the same manner as **7a**, but starting from **8c**, yielding **9c** (152 mg, 45%, *de* 22%) as a colorless oil after column chromatography (eluent AcOEt/MeOH, 90:10) on silica gel. Description of the major diastereoisomer. − ^{31}P NMR ($CDCl_3$): δ = 35.11. − ^1H NMR ($CDCl_3$): δ = 0.70−0.78 (m, 3 H, $C\mathit{H}_3-CH_2-CH$), 1.01−1.15 [m, 9 H, $N-CH-(C\mathit{H}_3)_2$, $P-CH-C\mathit{H}_3$], 1.16−1.20 (m, 6 H, $C\mathit{H}_3-CH_2-O$), 1.30−1.50 (m, 2 H, $CH_3-C\mathit{H}_2-CH$), 2.10−2.25 (m, 1 H, $P-CH-C\mathit{H}_2$), 2.40−2.52 (m, 1 H, $P-C\mathit{H}-CH_2$), 2.52−2.60 (m, 1 H, $P-CH-C\mathit{H}_2$), 3.43−3.45 (2 d, *J* = 3.7 Hz, 2 H, $C\mathit{H}_2-OH$), 3.80−3.90 [m, 1 H, $N-C\mathit{H}-(CH_3)_2$], 4.00−4.30 (m, 5 H, $CH_3-CH_2-C\mathit{H}$, $CH_3-C\mathit{H}_2-O$). − IR (neat): $\tilde{\nu}$ = 3410, 2977, 1630, 1216, 1053, 1030 cm^{-1}.

Compound 9d: This compound was prepared in the same manner as **7a**, but starting from **8d**, yielding **9c** (193 mg, 50%, *de* 92%) as a colorless oil after column chromatography (eluent AcOEt) on silica gel. Description of the major diastereoisomer. − ^{31}P NMR ($CDCl_3$): δ = 34.57 and 35.99. − ^1H NMR ($CDCl_3$): δ = 0.83 (m, 3 H, $C\mathit{H}_3-CH_2-CH$), 1.14 (dd, *J* = 6.7 and 17.0 Hz, 3 H, $P-CH-C\mathit{H}_3$), 1.18−1.28 (m, 6 H, $C\mathit{H}_3-CH_2-O$), 1.48−1.58 (m, 2 H, $CH_3-C\mathit{H}_2-CH$), 2.10−2.30 (m, 1 H, $P-CH-C\mathit{H}_2$), 2.50−2.80 (m, 2 H, $P-CH-C\mathit{H}_2$, $P-C\mathit{H}-CH_2$), 3.30−3.78 (m, 2 H, $C\mathit{H}_2-OH$), 3.80−4.15 (m, 5 H, $CH_3-C\mathit{H}_2-O$, $N-C\mathit{H}$), 4.34−4.84 (m, $N-C\mathit{H}_2-C_6H_5$), 7.14−7.31 (m, 5 H, H_{ar}). − ^{13}C NMR ($CDCl_3$): δ = 11.2 and 11.7 ($\mathit{C}H_3-CH_2-CH$), 14.3 and 14.7 (2 d, *J* = 5 Hz, $P-CH-\mathit{C}H_3$), 16.8 (2 d, $\mathit{C}H_3-CH_2-O$), 21.9 and 22.7 (2 s, $CH_3-\mathit{C}H_2-CH$), 28.5 (d, *J* = 143 Hz, $P-\mathit{C}H-CH_2$), 34.7 and 35.6 (2 s, $P-CH-\mathit{C}H_2$), 50.2 and 52.0 (2 s, $N-\mathit{C}H_2-Ph$), 61.5 and 61.7 (2 s, $N-\mathit{C}H$), 62.0−62.3 (m, $CH_3-\mathit{C}H_2-O$), 63.4 and 63.6 (2 s, $\mathit{C}H_2-OH$), 126.5, 126.9, 127.5, 127.6, 127.9, 129.0, 129.3 (C_{ar}), 138.0, 139.8 ($\mathit{C}_{ar\ quat}$), 173.6 (d, *J* = 13.4 Hz, $\mathit{C}=O$). − IR (neat): $\tilde{\nu}$ = 3312, 1650, 1240, 1026 cm^{-1}. − MS (IC): *m*/*z* = 408.4 (27) $[M + Na]^+$, 386.4 (22) $[M + H]^+$, 368.4 (100), 230.2 (50).

Compound 10: This compound was prepared in the same manner as **7a**, yielding **10** (338 mg, 50%, *de* 82%) as a white solid. Description of the major diastereoisomer after separation by column chromatography on silica gel (eluent AcOEt/MeOH, 90:10). − ^{31}P NMR ($CDCl_3$): δ = 35.02. − ^1H NMR ($CDCl_3$): δ = 1.12 (dd, *J* = 7.0 and 18.0 Hz, 3 H, $P-CH-C\mathit{H}_3$), 1.16−1.28 (m, 6 H, $C\mathit{H}_3-CH_2-O$), 2.18−2.39 (m, 1 H, $P-CH-C\mathit{H}_2$), 2.39−2.55 (m, 1 H, $P-C\mathit{H}-CH_2$), 2.55−2.70 (m, 1 H, $P-CH-C\mathit{H}_2$), 2.81 (s, 1 H, $O\mathit{H}$), 3.70−3.82 (m, 2 H, $C\mathit{H}_2-OH$), 3.90−4.06 (m, 4 H, $CH_3-C\mathit{H}_2-O$), 5.00 (m, 1 H, $N-C\mathit{H}$), 7.25 (m, 5 H, H_{ar}), 7.33 (d, *J* = 7.2 Hz, $N\mathit{H}$). − ^{13}C NMR ($CDCl_3$): δ = 14.1 (d, *J* = 5 Hz, $P-CH-\mathit{C}H_3$), 16.3 (d, *J* = 6 Hz, $\mathit{C}H_3-CH_2-O$), 27.7 (d, *J* = 143 Hz, $P-\mathit{C}H-CH_2$), 37.5 ($P-CH-\mathit{C}H_2$), 55.9 ($N-\mathit{C}H$), 62.0 (d, *J* = 7 Hz, $CH_3-\mathit{C}H_2-O$), 65.8 ($\mathit{C}H_2-OH$), 126.7, 127.4, 128.5 (C_{ar}), 139.3 ($\mathit{C}_{ar\ quat}$), 170.7 (d, *J* = 12.8 Hz, $\mathit{C}=O$). − IR (neat): $\tilde{\nu}$ = 3341, 3285, 1648, 1568, 1220, 1024, 758, 704 cm^{-1}. − $[\alpha]_D^{20}$= −19.2 (*c* = 0.75, $CHCl_3$)

Compound 11a: $BH_3 \cdot THF$ (1 M, 130 μL, 0.13 mmol) was added at 0 °C to a solution of *N*-benzylphosphonoamide **7a** (48 mg, 0.11 mmol) in anhydrous THF (2 mL) under an inert gas. After stirring at 0 °C for 1 h, the mixture was heated at reflux for 3 h. The solution was then again cooled to 0 °C, and a solution of HCl (6 N, 300μL) was slowly added. After addition of water (10 mL), the side products were extracted with dichloromethane (2 × 10 mL). After addition of saturated $NaHCO_3$ solution (10 mL) to the aqueous phase, the compound was extracted with dichloromethane (3 × 20 mL). The combined organic layers were dried with magnesium sulfate, filtered, and concentrated, affording compound **11a** (35 mg, 75%, *de* 92%). Description of the major diastereoisomer. − ^{31}P NMR ($CDCl_3$): δ = 35.70. − ^1H NMR ($CDCl_3$):

δ = 0.98 (dd, *J* = 7.2 and 18.4 Hz, 3 H, P−CH−C*H*$_3$), 1.21 (t, *J* = 7.1 Hz, 6 H, C*H*$_3$−CH$_2$−O), 1.35−1.43 (m, 1 H, P−CH−C*H*$_2$), 1.77−1.83 (m, 1 H, P−C*H*−CH$_2$), 1.93−1.98 (m, 1 H, P−CH−C*H*$_2$), 2.23−2.3 (m, 1 H, P−CH−CH$_2$−C*H*$_2$), 2.81−2.87 (m, 1 H, P−CH−CH$_2$−C*H*$_2$), 3.2 (d, *J* = 13.9 Hz, 1 H, N−C*H*$_2$−Ph), 3.57 (dd, *J* = 5.1 and 10.8 Hz, 1 H, C*H*$_2$−OH), 3.76 (d, *J* = 13.9 Hz, 1 H, N−C*H*$_2$−Ph), 3.86 (dd, *J* = 4.9 and 10.8 Hz, 1 H, C*H*$_2$−OH), 3.94−4.04 (m, 5 H, CH$_3$−C*H*$_2$−O, N−C*H*), 7.25 (m, 10 H, *H*$_{ar}$). − ^{13}C NMR (CDCl$_3$): δ = 14.7 (d, *J* = 5.2 Hz, P−CH−*C*H$_3$), 16.8 (d, *J* = 5.7 Hz, *C*H$_3$−CH$_2$−O), 29.7 (d, *J* = 143 Hz, P−*C*H−CH$_2$−CH$_2$), 29.9 (d, *J* = 3.4 Hz, P−CH−*C*H$_2$−CH$_2$), 47.5 (d, *J* = 11 Hz, P−CH−CH$_2$−*C*H$_2$), 54.5 (N−*C*H$_2$−Ph), 61.0 (*C*H$_2$−OH), 65.0 (N−*C*H), 62.2 (d, CH$_3$−*C*H$_2$−O), 127.5, 128.2, 128.7, 128.9, 129.0, 129.2 (*C*$_{ar}$), 136.6, 139.9 (*C*$_{ar\ quat}$). − IR (neat): ṽ = 3393, 2980, 1220, 1026, 701 cm^{-1}.

Compound 11b. − Method A: The compound was prepared in the same manner as **11a**, but starting from enantiopure (*R*)-**10** to yield enantiopure (*R*)-**11b** (121 mg, 75%) as a colorless oil. − ^{31}P NMR (CDCl$_3$): δ = 35.73. − **Method B:** Hydrogenolysis of **11a** with palladium on charcoal in EtOH over 24 h and filtration through Celite afforded **11b** (19 mg, 75%, *de* 92%). − ^{31}P NMR (CDCl$_3$): δ = 35.73 (major diastereomer) and 35.93 (minor diastereomer).

Compound 13: *s*BuLi (104 μL, 1.67 mmol) was added at −78 °C to a solution of β-amidobenzene **12** (0.2 g, 0.79 mmol) in anhydrous THF (4 mL) under an inert gas. After the mixture had been stirred at −78 °C for 5 h, diethyl chlorophosphite (125 μL, 0.87 mmol) was then added and the system was stirred at −78° for an additional 12 h. The solution was then quenched with water (10 mL) and the mixture was extracted with dichloromethane (3 × 20 mL). The combined organic layers were dried with magnesium sulfate, filtered, and concentrated, affording compound **13** as a 1:1 mixture of isomers (169 mg, 55%) after column chromatography on silica gel (eluent AcOEt/MeOH, 95:5). − ^{31}P NMR (CDCl$_3$): δ = 29.13 and 29.17. − ^{1}H NMR (CDCl$_3$): δ = 1.07 and 1.25 (2 d, *J* = 6.9 Hz, 3 H, N−CH−C*H*$_3$), 1.14 and 1.28 (2 t, *J* = 6.9 Hz, 6 H, C*H*$_3$−CH$_2$−O), 2.86 (m, 2 H, P−CH−C*H*$_2$), 3.85−3.92 and 4.00−4.10 (2m, 4 H, CH$_3$−C*H*$_2$−O), 3.62−3.68 (m, 1 H, P−C*H*−CH$_2$), 4.84−4.90 (2 quint, 1 H, *J* = 6.9 Hz, N−C*H*), 7.04−7.40 (m, 10 H, *H*$_{ar}$). − ^{13}C NMR (CDCl$_3$): δ = 15.1 and 15.4 (2 d, *J* = 5.7 Hz, *C*H$_3$−CH$_2$−O), 20.5 (N−CH−*C*H$_3$), 36.1 and 36.3 (2 s, P−CH−*C*H$_2$), 37.4 and 37.5 (2 d, *J* = 140.5 Hz, P−*C*H−CH$_2$), 47.5 and 47.6 (2 s, N−*C*H), 60.9 and 62.0 (3 d, *J* = 7.5 Hz, CH$_3$−*C*H$_2$−O), 124.7−128.4 (m, *C*$_{ar}$), 134.3 and 134.4 (2 d, *J* = 6.3 Hz, *C*$_{ar\ quat}$), 142.0 and 142.3 (2 s, *C*$_{ar\ quat}$), 167.9 (d, *J* = 17.2 Hz, *C*=O). − IR (neat): ṽ = 3280, 1650, 1548, 1240, 1025 cm^{-1}.

Compound 14a: Diethylphosphonopropionyl chloride[28] (4.80 g, 21.9 mmol) was slowly added to a solution of the α-methylbenzylamine (2.65 g, 21.9 mmol) in CH$_2$Cl$_2$ (100 mL). Na$_2$CO$_3$ (2.55 g, 24 mmol), dissolved in the minimum amount of water, was then added. After the mixture had been stirred for 2 h at room temperature, brine (10 mL) was added, and the compound was extracted with dichloromethane (3 × 20 mL). The combined organic layers were dried with magnesium sulfate, filtered, and concentrated. The crude mixture was purified by column chromatography on silica gel (EtOAc/MeOH, 90:10) to provide **14a** (5.21 g, 76%). − ^{31}P NMR (CDCl$_3$): δ = 32.70. − ^{1}H NMR (CDCl$_3$): δ = 1.21−1.34 (t, *J* = 7.2 Hz, 6 H, C*H*$_3$−CH$_2$−O), 1.46 (d, *J* = 6.9 Hz, 3 H, N−CH−C*H*$_3$), 2.00−2.15 (m, 2 H, P−C*H*$_2$), 2.42−2.56 (m, 2 H, P−CH$_2$−C*H*$_2$), 3.90−4.12 (q, *J* = 7.2 Hz, 4 H, CH$_3$−C*H*$_2$−O), 5.02−5.13 (quint, 1 H, *J* = 7.3 Hz, N−C*H*), 7.00 (d, *J* = 7.3 Hz, 1 H, N*H*), 7.23 (m, 5 H, *H*$_{ar}$). − ^{13}C NMR (CDCl$_3$): δ = 16.2 (d, *J* = 4 Hz, *C*H$_3$−CH$_2$−O), 20.7 (d, *J* = 143.2 Hz, P−*C*H$_2$−CH$_2$), 21.8 (N−CH−*C*H$_3$), 28.5 (d, *J* = 3 Hz, P−CH$_2$−*C*H$_2$), 48.6 (N−*C*H), 61.6 (d, *J* = 5.7 Hz, CH$_3$−*C*H$_2$−O), 126.0, 126.9, 128.3 (*C* ar), 143.6 (*C*$_{ar\ quat}$), 170.0 (d, *J* = 16.9 Hz, *C*=O). − IR (neat): ṽ = 3285, 1650, 1550, 1240, 1026 cm^{-1}. − $[\alpha]^{20}_{D}$ = +55.9 (*c* = 1, CHCl$_3$). − MS (EI, 70eV): *m*/*z* (%) = 313 (1), 193 (11), 165 (8), 137 (15), 120 (100), 91 (5), 77 (8), 55 (8), 42 (4).

Compound 14b: This compound was prepared in the same manner as **14a**, but starting from *O*-benzyl-2-aminobutanol alcohol to yield **14b** (2.41 g, 65%) as a yellow oil, after column chromatography (eluent EtOAc/MeOH, 90:10) on silica gel. Rotamers in evidence. − ^{31}P NMR (CDCl$_3$): δ = 32.62. − ^{1}H NMR (CDCl$_3$): δ = 0.83 (t, *J* = 7.4 Hz, 3 H, C*H*$_3$−CH$_2$−CH), 1.22 (t, *J* = 7.1 Hz, 6 H, C*H*$_3$−CH$_2$−O), 1.30−1.65 (m, 2 H, CH$_3$−C*H*$_2$−CH), 1.92−2.09 (m, 2 H, P−C*H*$_2$−CH$_2$), 2.19−2.50 (m, 2 H, P−CH$_2$−C*H*$_2$), 3.35 (dd, *J* = 9.5 and 4.3 Hz, 1 H, C*H*$_2$−OBn), 3.43 (dd, *J* = 9.5 and 3.8 Hz, 1 H, C*H*$_2$−OBn), 3.85−4.09 (m, 5 H, N−C*H*, CH$_3$−C*H*$_2$−O), 4.40 (d, *J* = 4.0 Hz, 2 H, O−C*H*$_2$−Ph), 6.55 (d, *J* = 8.5 Hz, 1 H, N*H*), 7.2−7.28 (m, 5 H, *H*ar). − ^{13}C NMR (CDCl$_3$): δ = 10.2 (*C*H$_3$−CH$_2$−CH), 16.1 (d, *J* = 5.9 Hz, *C*H$_3$−CH$_2$−O), 20.8 (d, *J* = 143.4 Hz, P−*C*H$_2$−CH$_2$), 24.3 (CH$_3$−*C*H$_2$−CH), 28.7 (d, *J* = 3.3 Hz, P−CH$_2$−*C*H$_2$) 50.3 (N−*C*H), 61.4 (d, *J* = 6.4 Hz, CH$_3$−*C*H$_2$−O), 71.0 (*C*H$_2$−OBn), 72.8 (O−*C*H$_2$−Ph), 127.3−128.1 (m, *C*$_{ar}$), 137.9 (*C*$_{ar\ quat}$), 170.5 (*C*=O). − IR (neat): ṽ = 3287, 1650, 1240, 1100, 1026 cm^{-1}. − $[\alpha]^{20}_{D}$ = +29.2 (*c* = 1, CHCl$_3$). − MS (EI, 70 eV): *m*/*z* (%) = 372 (1), 343 (2), 326 (3), 280 (6), 250 (34), 193 (100), 165 (25), 137 (57), 109 (14), 91 (75), 65 (11).

Compound 14c: This compound was prepared in the same manner as **14a**, but starting from 2-aminobutanol to yield **14c** (197 mg, 35%) as a yellow oil after column chromatography (eluent EtOAc/MeOH, 90:10) on silica gel. Rotamers in evidence. − ^{31}P NMR (CDCl$_3$): δ = 32.90. − ^{1}H NMR (CDCl$_3$): δ = 0.76 (t, *J* = 7.7 Hz, 3 H, C*H*$_3$−CH$_2$−CH), 1.14 (t, *J* = 7.0 Hz, 6 H, C*H*$_3$−CH$_2$−O), 1.40 (m, 2 H, CH$_3$−C*H*$_2$−CH), 1.83−2.06 (m, 2 H, P−C*H*$_2$−CH$_2$), 2.24−2.50 (m, 2 H, P−CH$_2$−C*H*$_2$), 3.33−3.53 (m, 2 H, C*H*$_2$−OH), 3.69 (m, 1 H, N−C*H*), 3.80−4.06 (m, 4 H, CH$_3$−C*H*$_2$−O), 7.00 (d, *J* = 7.4 Hz, 1 H, N*H*). − ^{13}C NMR (CDCl$_3$): δ = 10.5 (*C*H$_3$−CH$_2$−CH), 16.2 (d, *J* = 5.8 Hz, *C*H$_3$−CH$_2$−O), 20.9 (d, *J* = 143 Hz, P−*C*H$_2$−CH$_2$), 23.8 (CH$_3$−*C*H$_2$−CH), 28.9 (d, *J* = 3.8 Hz, P−CH$_2$−*C*H$_2$), 53.2 (N−*C*H), 61.8 (d, *J* = 6.6 Hz, CH$_3$−*C*H$_2$−O), 64.1 (*C*H$_2$−OH), 171.4 (d, *J* = 14.3 Hz, *C*=O). − IR (neat): ṽ = 3412, 3290, 1652, 1556, 1230, 1026 cm^{-1}. − $[\alpha]^{20}_{D}$ = +27.4 (*c* = 1, CHCl$_3$).

Compound 15a: *s*BuLi (42 μL, 0.67 mmol) was added at −78 °C to a solution of β-amidophosphonate **14a** (100 mg, 0.32 mmol) and TMEDA (81 mg, 0.7 mmol) in anhydrous THF (2 mL) under an inert gas. After the mixture had been stirred at −78 °C for 1 h, iodomethane (113 mg, 0.80 mmol) was then added and the system was stirred at −78 °C for an additional 5 h. The reaction was then quenched with brine (10 mL), and the mixture was extracted with diethyl ether (2 × 10 mL) and then with dichloromethane (2 × 10 mL). The combined organic layers were dried with magnesium sulfate, filtered and concentrated, affording compound **15a** (83 mg, 80%, *de* 20%) after column chromatography on silica gel (eluent AcOEt/MeOH, 95:5). − ^{31}P NMR (CDCl$_3$): δ = 35.18 and 35.20. − ^{1}H NMR (CDCl$_3$): δ = 1.10 and 1.15 (2 dd, *J* = 7.1 and 18.1 Hz, 3 H, P−CH−C*H*$_3$), 1.16−1.32 (m, 6 H, C*H*$_3$−CH$_2$−O), 1.43 and 1.44 (2 d, *J* = 7.0 Hz, 3 H, N−CH−C*H*$_3$), 2.15−2.25 (m, 1 H, P−CH−C*H*$_2$), 2.37−2.50 (m, 1 H, P−C*H*−CH$_2$), 2.55−2.70 (m, 1 H, P−CH−C*H*$_2$), 3.91−4.06 (m, 4 H, CH$_3$−C*H*$_2$−O), 5.05−5.12

(quint, 1 H, *J* = 7.0 Hz, N−C*H*), 7.06 and 7.12 (2 d, *J* = 7.4 Hz, 1 H, N*H*), 7.25 (m, 5 H, *H*$_{ar}$). − ^{13}C NMR (CDCl$_3$): δ = 13.1 (d, *J* = 4.1 Hz, CH$_3$−CH−P), 16.27 (d, *J* = 5.1 Hz, *C*H$_3$−CH$_2$−O), 21.9 (d, *J* = 4.2 Hz, N−CH−*C*H$_3$), 27.0 (2 d, *J* = 144 Hz, P−*C*H−CH$_2$), 36.4 (P−CH−*C*H$_2$), 49.3 (N−*C*H), 61.6 (d, *J* = 4.7 Hz, CH$_3$−*C*H$_2$−O), 126.0, 126.1, 126.8, 128.2 (*C*$_{ar}$), 143.6 (2 s, *C*$_{ar\ quat}$), 169.5 (2 d, *J* = 17.7 Hz, *C*=O). − MS (EI, 70eV): *m*/*z* (%) = 327 (2), 299 (2), 207 (9), 179 (8), 151 (18), 120 (100), 105 (16), 69 (14).

Compound 15b: This compound was prepared in the same manner as **15a**, but with benzyl bromide as electrophile to yield **15b** (222 mg, 55%, *de* 5%) as a colorless oil after column chromatography on silica gel (eluent cyclohexane/AcOEt, 1:1). − ^{31}P NMR (CDCl$_3$): δ = 33.66 and 33.68. − ^{1}H NMR (CDCl$_3$): δ = 1.12−1.30 (m, 6 H, C*H*$_3$−CH$_2$−O), 1.40 and 1.47 (2 d, *J* = 6.8 Hz, 3 H, N−CH−C*H*$_3$), 2.00−3.20 (m, 5 H, P−CH−C*H*$_2$−Ph, P−CH−C*H*$_2$, P−C*H*−CH$_2$), 3.90−4.10 (m, 4 H, CH$_3$−C*H*$_2$−O), 4.50−5.10 (2 quint, 1 H, *J* = 7.2 Hz, N−C*H*), 6.48−6.58 (2 d, *J* = 6.7 Hz, 1 H, N*H*), 7.18−7.33 (m, 10 H, *H*$_{ar}$). − ^{13}C NMR (CDCl$_3$): δ = 16.2 (d, *J* = 5.3 Hz, *C*H$_3$−CH$_2$−O), 21.8 (d, *J* = 7.9 Hz, N−CH−*C*H$_3$), 33.8 and 34.0 (2 d, *J* = 140.5 Hz, P−*C*H−CH$_2$), 34.5 (P−CH−*C*H$_2$), 34.8 (P−CH−*C*H$_2$−Ph), 48.8 (N−*C*H), 61.8 (2 d, *J* = 6.1 Hz, CH$_3$−*C*H$_2$−O), 126.1, 126.4, 127.1, 128.2, 128.4, 129.1 (*C*$_{ar}$), 138.4 (2 d, *J* = 9.5 Hz, *C*$_{ar\ quat}$. P−CH−CH$_2$−*C*$_6$H$_5$), 143.2 (2 s, *C*$_{ar\ quat}$. CH−*C*$_6$H$_5$), 169.3 (2 d, *J* = 9.3 Hz, *C*=O). − MS (EI, 70eV): *m*/*z* (%) = 403 (7), 283 (4), 266 (6), 241 (100), 213 (7), 162 (14), 145 (17), 120 (51), 91 (15).

Compound 15c: This compound was prepared in the same manner as **15a**, but with trimethylsilyl chloride as electrophile, to yield **15c** (164 mg, 85%, *de* 5%) as a yellow powder after column chromatography on silica gel (eluent cyclohexane/AcOEt, 1:1). − ^{31}P NMR (CDCl$_3$): δ = 36.76 and 36.91. − ^{1}H NMR (CDCl$_3$): δ = 0.00 and 0.05 (2 s, 9 H, (CH$_3$)$_3$Si), 1.03−1.33 (m, 6 H, C*H*$_3$−CH$_2$−O), 1.43 (d, *J* = 6.7 Hz, 3 H, N−CH−C*H*$_3$), 1.73−2.00 (m, 1 H, P−C*H*−CH$_2$), 2.20−2.47 (m, 1 H, P−CH−C*H*$_2$), 2.47−2.70 (m, 1 H, P−CH−C*H*$_2$), 3.80−4.10 (m, 4 H, CH$_3$−C*H*$_2$−O), 5.05 (quint, 1 H, *J* = 7.3 Hz, N−C*H*), 7.27 (m, 5 H, *H*$_{ar}$), 7.48 and 7.63 (2 d, *J* = 7.3 Hz, 1 H, N*H*). − ^{13}C NMR (CDCl$_3$): δ −1.7 [(*C*H$_3$)$_3$−Si), 16.2 (*C*H$_3$−CH$_2$−O), 20.4 (d, *J* = 126.3 Hz, P−*C*H−CH$_2$), 22.0 (d, *J* = 9.7 Hz, N−CH−*C*H$_3$), 31.3 (d, *J* = 4.4 Hz, P−CH−*C*H$_2$), 48.9 (N−*C*H), 61.1 and 61.4 (2 d, *J* = 6.6 Hz, CH$_3$−*C*H$_2$−O), 126.1, 126.8, 128.3 (*C*$_{ar}$), 143.7 (2 s, *C*$_{ar\ quat}$), 170.5 (d, *J* = 6.3 Hz, *C*=O).

Compound 15d: This compound was prepared in the same manner as **15a**, but starting from β-amidophosphonate **14b** derived from 2-aminobutanol, to yield **15d** (231 mg, 60%, *de* 30%) as a colorless oil after column chromatography on silica gel (eluent AcOEt/MeOH, 90:10). − ^{31}P NMR (CDCl$_3$): δ = 35.00 and 35.03. − ^{1}H NMR (CDCl$_3$): δ = 0.83 (2 t, *J* = 7.4 Hz, 3 H, C*H*$_3$−CH$_2$−CH), 1.08−1.14 (2 dd, *J* = 7.2 and 18.1 Hz, 3 H, P−CH−C*H*$_3$), 1.20−1.30 (t, *J* = 7.0 Hz, 6 H, C*H*$_3$−CH$_2$−O), 1.40−1.60 (m, 2 H, CH$_3$−C*H*$_2$−CH), 2.02−2.11 (m, 1 H, P−CH−C*H*$_2$), 2.35−2.41 (m, 1 H, P−C*H*−CH$_2$), 2.53−2.63 (m, 1 H, P−CH−C*H*$_2$), 3.20−3.45 (m, 2 H, C*H*$_2$−OBn), 4.00−4.10 (m, 5 H, N−C*H*, CH$_3$−C*H*$_2$−O), 4.40 (d, *J* = 2.6 Hz, 2 H, O−C*H*$_2$−Ph), 5.90−6.05 (m, 1 H, N*H*), 7.2−7.27 (m, 5 H, *H*$_{ar}$). − ^{13}C NMR (CDCl$_3$): δ = 10.9 (2 s, *C*H$_3$−CH$_2$−CH), 13.7 and 13.8 (2 d, *J* = 5 Hz, *C*H$_3$−CH−P), 16.9 (d, *J* = 5.8 Hz, *C*H$_3$−CH$_2$−O), 25.1 and 25.2 (2 s, CH$_3$−*C*H$_2$−CH), 28.0 and 28.1 (2 d, *J* = 144 Hz, P−*C*H−CH$_2$), 37.7 (P−CH−*C*H$_2$), 51.0 (N−*C*H), 62.2 (2 d, *J* = 7.1 Hz, CH$_3$−*C*H$_2$−O), 71.5 (*C*H$_2$−OBn), 73.6 (O−*C*H$_2$−Ph), 126.5, 128.0, 128.8 (*C*$_{ar}$), 138.5 (*C*$_{ar\ quat}$), 169.0 and 170.7 (2 d, *J* = 14.5 Hz, *C*=O).

Compound 15e: This compound was prepared in the same manner as **15d**, but with benzyl bromide as electrophile, to yield **15e** (161 mg, 70%, *de* 50%) as a colorless oil after column chromatography on silica gel (eluent AcOEt/MeOH, 95:5). − ^{31}P NMR (CDCl$_3$): δ = 33.64 and 33.67. − ^{1}H NMR (CDCl$_3$): δ = 0.75−0.84 (2 t, *J* = 7.5 Hz, 3 H, C*H*$_3$−CH$_2$−CH), 1.10−1.19 (m, 6 H, C*H*$_3$−CH$_2$−O), 1.40−1.52 (m, 2 H, CH$_3$−C*H*$_2$−CH), 2.10−2.25 (m, 1 H, P−C*H*−CH$_2$), 2.40−2.55 (m, 1 H, P−CH−C*H*$_2$), 2.65−3.05 (m, 3 H, CH−C*H*$_2$−Ph, P−CH−C*H*$_2$), 3.25−3.45 (m, 2 H, C*H*$_2$−OBn), 3.88−4.00 (m, 5 H, N−C*H*, CH$_3$−C*H*$_2$−O), 4.37−4.47 (m, 2 H, O−C*H*$_2$−Ph), 5.85−5.95 (2 d, *J* = 7.3 Hz, 1 H, N*H*), 7.10−7.40 (m, 10 H, *H*ar). − ^{13}C NMR (CDCl$_3$): δ = 10.9 (2 s, *C*H$_3$−CH$_2$−CH), 16.7 and 16.8 (2 d, *J* = 6 Hz, *C*H$_3$−CH$_2$−O), 25.1 (CH$_3$−*C*H$_2$−CH), 34.4 and 34.5 (2 d, *J* = 141 Hz, P−*C*H−CH$_2$), 35.1 (P−CH−*C*H$_2$−Ph), 35.6 (P−CH−*C*H$_2$), 51.0 (2 s, N−*C*H), 62.1−62.4 (m, CH$_3$−*C*H$_2$−O), 71.3 (*C*H$_2$−OBn), 73.6 (O−*C*H$_2$−Ph), 126.8, 128.0, 128.1, 128.7, 128.8, 129.9 (*C*$_{ar}$), 138.5, 139.1 (*C*$_{ar\ quat}$), 169.0 and 170.7 (2 d, *J* = 11 Hz, *C*=O), MS (EI, 70eV): *m*/*z* (%) = 461 (3), 415 (1), 405 (2), 370 (16), 340 (43), 283 (80), 241 (78), 207 (42), 185 (10), 145 (90), 139 (39), 91 (100), 58 (15), 44 (32).

Compound 15f: This compound was prepared in the same manner as **15d**, but with trimethylsilyl chloride as electrophile, to yield **15f** (111 mg, 50%, *de* 10%) as a colorless oil after column chromatography on silica gel (eluent AcOEt/MeOH, 95:5). − ^{31}P NMR (CDCl$_3$): δ = 36.50 and 36.60. − ^{1}H NMR (CDCl$_3$): δ = 0.00 (s, 9 H, (CH$_3$)$_3$Si) 0.76 and 0.78 (2 t, *J* = 7.5 Hz, 3 H, C*H*$_3$−CH$_2$−CH), 1.08−1.28 (m, 6 H, C*H*$_3$−CH$_2$−O), 1.40−1.51 (m, 2 H, CH$_3$−C*H*$_2$−CH), 1.63−1.79 (m, 1 H, P−C*H*−CH$_2$), 2.05−2.25 (m, 1 H, P−CH−C*H*$_2$), 2.32−2.50 (m, 1 H, P−CH−C*H*$_2$), 3.29−3.40 (m, 2 H, C*H*$_2$−OBn), 3.81−3.94 (m, 5 H, N−C*H*, CH$_3$−C*H*$_2$−O), 4.25−4.35 (m, 2 H, O−C*H*$_2$−Ph), 6.10 and 6.30 (2 d, *J* = 8.7 Hz, 1 H, N*H*), 7.20 (m, 5 H, *H*ar). − ^{13}C NMR (CDCl$_3$): δ = 0 [(*C*H$_3$)$_3$−Si], 12.1 (*C*H$_3$−CH$_2$−CH), 17.8 (*C*H$_3$−CH$_2$−O), 22.5 and 23.3 (2 d, *J* = 127 Hz, P−*C*H−CH$_2$), 26.3 (CH$_3$−*C*H$_2$−CH), 33.3 (P−CH−*C*H$_2$), 52.2 (N−*C*H), 62.9 (CH$_3$−*C*H$_2$−O), 72.7 (*C*H$_2$−OBn), 74.7 (O−*C*H$_2$−Ph), 127.2, 129.3, 129.9 (*C*$_{ar}$), 138.8 (2 s, *C*$_{ar\ quat}$), 171.8 and 172.2 (2 d, *J* = 14 Hz, *C*=O).

Compound 18: A solution of β-amidophosphonate **7a** or **7b** (0.46 mmol) in HCl (8 M) was heated under reflux for 4 h. The reaction mixture was then concentrated under vacuum. This residue was taken up in 2-propanol/methanol (1:1), and cyclohexylamine was added dropwise. The precipitate was filtered off, affording white crystals of compound **18** in 45% yield from **7a** and 65% yield from **7b**. − ^{31}P NMR (D$_2$O): δ = 26.10. − ^{1}H NMR (D$_2$O): δ = 0.90 (dd, *J* = 6.8 and 16.1 Hz, 3 H, P−CH−C*H*$_3$), 1.10−1.30 [m, 12 H, (C*H*$_2$)$_3$], 1.60−1.75 (m, 4 H, C*H*$_2$−CH−N), 1.81−1.93 (m, 6 H, C*H*$_2$−CH−N, P−CH−C*H*$_2$, P−C*H*−CH$_2$), 2.47 (m, 1 H, P−CH−C*H*$_2$,), 3.11 (m, 2 H, CH$_2$−C*H*−N). − ^{13}C NMR (D$_2$O): δ = 14.5 (d, *J* = 3.7 Hz, P−CH−*C*H$_3$), 24.1 [(*C*H$_2$)$_3$], 30.7 (*C*H$_2$−CH−N), 31.2 (d, *J* = 134 Hz, P−*C*H−CH$_2$), 40.6 (d, *J* = 2.3 Hz, P−CH−*C*H$_2$), 50.6 (N−*C*H).

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