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Chemoenzymatic Synthesis of Phosphonic Acid Analogues of L-Lysine, L-Proline, L-Ornithine, and L-Pipecolic Acid of 99% *ee* – Assignment of Absolute Configuration to (–)-Proline

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(±)-ω-Halo-α-(chloroacetoxy)phosphonates were kinetically resolved by use of a protease (Chirazyme® P-2). The esters recovered at levels of conversion between 56 and 72% furnished (*S*)-alcohols of 99% *ee*. These were converted via azides into the phosphonic acid analogues of L-lysine, L-proline, L-ornithine and L-pipecolic acid. (–)-Phosphaproline was transformed into crystalline ureas derived from (*R*)- and (*S*)-1-phenylethyl isocyanate. X-ray structure analyses revealed that the levorotary phosphaproline has the *R* configuration, contrary to earlier reports.

Introduction

α-Aminophosphonic acids are structural analogues of α-amino carboxylic acids and have diverse biological effects.[1,2] To give just a few examples, they and their derivatives inhibit various enzymes of medical[3] and agricultural[4] importance. Many methods for the synthesis of racemic[5] and chiral, nonracemic[6] α-aminophosphonic acids have been developed, especially those with alkyl side chains. However, the number of approaches to cyclic α-aminophosphonic acids and those with functionalized side chains is rather limited. Representatives of these groups caught our imagination. Here we present our results on the chemoenzymatic syntheses of the phosphonic acid analogues of two proteinogenic examples [L-lysine (**1**, L-phosphalysine, Figure 1) and L-proline (**2**, L-phosphaproline)] and of two nonproteinogenic ones [L-ornithine (**3**, L-phosphaornithine) and L-pipecolic acid (**4**, L-phosphapipecolic acid)], all of 99% *ee*. All four aminophosphonic acids have been prepared in racemic[7–10] form, but only the cyclic ones also in homochiral[11,12] form. Dipeptides containing (±)-phosphaproline or (±)-phosphapipecolic acid and L-Ala or L-Leu display plant-growth-regulating activity,[13] whereas (±)-phosphaornithine shows antitumour[9b] activity. (*S*)-Phosphaproline and its diethyl ester were recently used as efficient organocatalysts.[11d] Phosphalysine and phosphaornithine have never been prepared in chiral, nonracemic form. Additionally, we determined the absolute configuration of levorotary phosphaproline, because this had not previously been done rigorously.

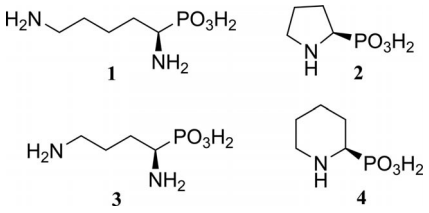

Figure 1. Phosphonic acid analogues of L-lysine (**1**), L-proline (**2**), L-ornithine (**3**), and L-pipecolic acid (**4**).

Results and Discussion

In preceding publications we demonstrated that various chiral, nonracemic α-aminophosphonic acids can be prepared from α-hydroxyphosphonates[14] by an approach comprising a Mitsunobu reaction with HN_3, reduction of the azide to the amine, deprotection and purification by ion exchange chromatography. The starting α-hydroxyphosphonates were obtained by lipase-[15] or protease-catalysed[16] kinetic resolution of the corresponding acetates or chloroacetates. This methodology was extended to prepare the four aminophosphonic acids **1**–**4**.

The envisaged starting materials – the α-hydroxyphosphonates (±)-**6a**–**c** (Scheme 1), each with an ω-haloalkyl side chain – were not accessed by the standard method, base-catalysed addition of diisopropyl phosphite to the corresponding aldehydes, but were easily accessible through one-pot reactions starting from the commercially available esters **5a**–**c**.[15a]

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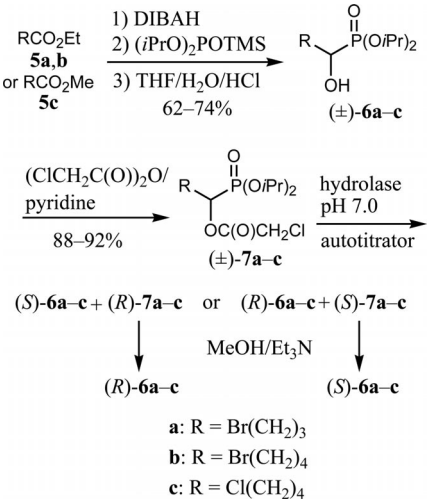


Scheme 1. Preparation of the chiral, nonracemic α-hydroxyphosphonates **6**.

These were reduced with DIBAH at 78 °C in dry toluene. After two hours diisopropyl trimethylsilyl phosphite was added and the mixtures were allowed to warm slowly to 15 °C in the cooling bath, whereupon the tetrahedral intermediates collapsed with the formation of *i*Bu$_2$AlOR (R = Me or Et) and aldehydes. The latter were intercepted by the silylated phosphite to give α-silyloxyphosphonates, which were converted on workup into the desired α-hydroxyphosphonates (±)-**6a**–**c**. They were chloroacetylated[14b] to give the esters (±)-**7a**–**c**, which displayed much higher reactivities than the corresponding acetates with hydrolases.

From our experience in the use of lipases and proteases in kinetic resolutions of α-acetoxy- and α-(chloroacetoxy)-phosphonates, we decided first to test lipase AP 6 (from *Aspergillus niger*)[15b] and protease Chirazyme® P-2 (an alkaline serine-type endoprotease)[16] on an analytical scale. The substrates (±)-**7a**–**c** (1 mmol) were thus hydrolysed at room temperature at pH 7.0 in a biphasic system (50 mM phosphate buffer and hexanes/*tert*-butyl methyl ether (1:1) with an autotitrator.[15b] The reaction was stopped at a degree of conversion of 45% by addition of HCl to bring the pH to 4.0. Extractive workup and flash chromatography furnished the chiral, nonracemic α-hydroxyphosphonates (*S*)-**6a**–**c** together with the unreacted chloroacetates (*R*)-**7a**–**c** or vice versa, depending on the hydrolase used. The chloroacetates were transesterified (MeOH/Et$_3$N) to give α-hydroxyphosphonates enantiomeric to those formed by enzymatic hydrolyses. The configurations and the enantiomeric excesses of the α-hydroxyphosphonates were determined by preparation of their (*R*)-Mosher esters and recording of ^{1}H and ^{31}P NMR spectra.[17,18] The data are compiled in Table 1.

Table 1. Chemical shifts (δ, ppm) of ^{31}P NMR signals of (*R*)-Mosher esters derived from α-hydroxyphosphonates **6**.

Entry	**6**	(*R*)-Mosher ester derived from (*S*)-**6**	(*R*)-**6**	$\Delta\delta$ (ppm)[a]
1	**6a**	13.59	12.95	0.64
2	**6b**	13.01	12.39	0.62
3	**6c**	13.35	12.74	0.61

[a] $\Delta\delta = \delta(S) - \delta(R)$.

In summary, lipase AP 6 preferentially hydrolysed the (*S*)-α-chloroacetates **7** whereas the protease preferentially hydrolysed the (*R*)-α-chloroacetates, to give the (*S*)- and (*R*)-α-hydroxyphosphonates, respectively (Table 2). The increase in the length of the side chain on going from Br(CH$_2$)$_3$ to Br(CH$_2$)$_4$ had more influence on the reaction rate of the protease than on that of the lipase, which was also used in larger amounts. The *ee* values of the α-hydroxyphosphonates formed on enzymatic hydrolysis are very similar for both enzymes, although the results might be somewhat better for the protease, which was therefore selected to prepare the chiral, nonracemic (*S*)-α-hydroxyphosphonates needed as starting materials on a preparative scale (Table 2, Entries 6–8). To obtain high *ee* values for (*S*)-**7a**–**c**, the enzymatic hydrolyses were stopped at degrees of conversion of 56%, 68% and 72%, respectively. The (*R*)-α-hydroxyphosphonates had low *ee* values at this point, but the α-(chloroacetoxy)phosphonates (*S*)-**7** had very high ones (99%). Chemical hydrolysis of the esters (*S*)-**7a**–**c** furnished the α-hydroxyphosphonates (*S*)-**6a**–**c** with the same *ee* values.

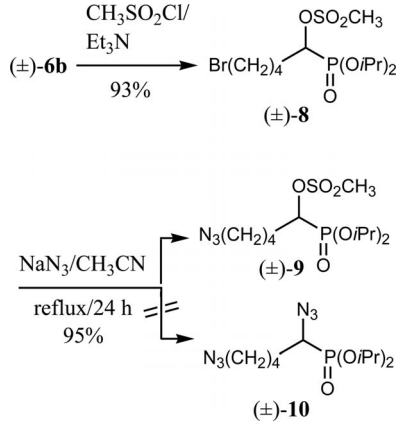
Table 2. Enantioselective hydrolysis of α-(chloroacetoxy)phosphonates (±)-**7** at room temp. (22–24 °C).

Entry	(±)-**7** [mmol]	Enzyme/ amount[a]	Time [h]	Conv.[b] [%]	Alcohol Yield [%]	Alcohol $[\alpha]_D^{20}$ (*c*)[c]	Alcohol *ee*[d] [%]	Alcohol Conf.	Ester Yield [%]	Ester $[\alpha]_D^{20}$ (*c*)[c]	Alcohol obtained from ester by chemical hydrolysis Yield [%]	Alcohol obtained from ester by chemical hydrolysis $[\alpha]_D^{20}$ (*c*)[c]	Alcohol obtained from ester by chemical hydrolysis *ee*[d] [%]	Alcohol obtained from ester by chemical hydrolysis Conf.
1	**7a**/1	AP6/10 mg	4.3	45	40	+12.1 (1.1)	86	*S*	38	–16.7 (1.0)	68	–4.3 (1.1)	–	*R*
2	**7a**/1	P2/10 μL	4.2	45	36	–14.1 (1.1)	95	*R*	45	+15.3 (1.0)	73	+9.4 (1.1)	78	*S*
3	**7b**/1	AP6/21 mg	3.8	45	38	+10.3 (1.3)	85	*S*	49	–16.5 (1.1)	98	–9.6 (1.1)	69	*R*
4	**7b**/1	P2/60 μL	20	47	38	–10.7 (1.1)	82	*R*	49	+15.7 (1.2)	–	–	–	–
5	**7c**/1	P2/60 μL	21	45	37	–12.9 (1.0)	84	*R*	50	+13.1 (1.0)	90	+6.6 (1.0)	82	*S*
6[e]	**7a**/18	P2/50 μL	20	56	37	–13.6 (1.4)	–	*R*	38	+17.0 (1.0)	84	+15.4 (1.0)	99	*S*
7[e]	**7b**/13	P2/0.5 mL	44	68	54	–6.0 (1.0)	–	*R*	30	+22.5 (1.3)	93	+12.8 (1.0)	99	*S*
8[e]	**7c**/7.6	P2/0.5 mL	21	72	50	–6.1 (1.0)	–	*R*	25	+26.0 (1.1)	99	+14.9 (1.1)	99	*S*

[a] For Chirazyme® P-2: lyophilisate or solution (600 mg of lyophilisate with protein content of 80% in 5 mL of solution). [b] Conv. = mean value of conversion determined from 0.5 M NaOH consumed and conversion determined by ^{1}H NMR of crude product. [c] In acetone solution (2 mL), rounded to the nearest tenth. [d] Mean value of *ee* determined by ^{1}H and ^{31}P NMR of (*R*)-Mosher ester. [e] The reaction was usually performed in phosphate buffer (50 mL) without organic solvent.

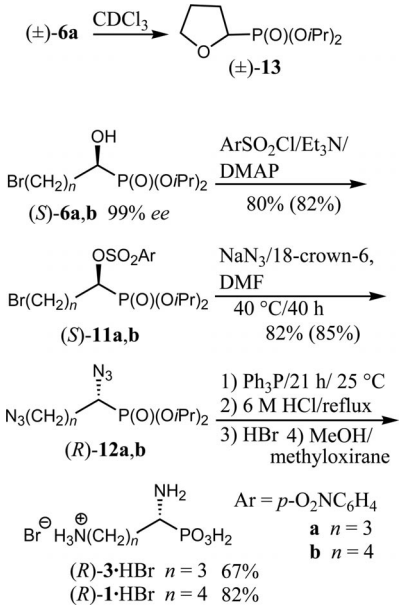
Preparation of L-Phosphalysine and L-Phosphaornithine

L-Lysine is a basic proteinogenic amino acid. L-Ornithine is an intermediate of the urea cycle and on decarboxylation yields putrescine (1,4-diaminobutane),[19] required for the biosynthesis of spermidine and spermine, two essential components for cell growth. The phosphonic acid analogues of these two amino acids were prepared similarly, from the starting (*S*)-α-hydroxyphosphonates (*S*)-**6a** and (*S*)-**6b**. We reasoned that diazidophosphonates should be easily accessible from the α-hydroxyphosphonates **6** and convertible into the corresponding α-aminophosphonic acids. In an exploratory experiment, we activated the OH group of (±)-**6b** by mesylation (Scheme 2).



Scheme 2. Attempted preparation of the 1,5-diazidophosphonate (±)-**10**.

The substitution of the bromide in the bromomesylate (±)-**8** (NaN_3/18-crown-6 in CH_3CN at reflux) was a smooth reaction, but unfortunately that of the mesyloxy group, to give the diazide (±)-**10**, did not take place. To substitute the mesyloxy group as well, DMF at 70 °C was required as solvent, but then dealkylation at phosphorus occurred as a side reaction. The (*S*)-1-hydroxyphosphonates (*S*)-**6a** and (*S*)-**6b** were therefore converted into the more reactive *p*-nitrobenzenesulfonates (*S*)-**11a** and (*S*)-**11b** (Scheme 3) in high yields (80% and 82%). These were treated with NaN_3 and 18-crown-6 in DMF – but not in CH_3CN – at 40 °C for 40 h to effect smooth substitution of both leaving groups to furnish the diazides (*R*)-**12a** and (*R*)-**12b**. Reduction with Ph_3P[20] (Staudinger reaction) and deblocking with HCl (6 M, reflux) furnished the diaminophosphonic acids L-phosphaornithine [(*R*)-**3**] and L-phosphalysine [(*R*)-**1**], which were isolated as their hydrobromides. Crystals of the latter compound contained a substoichiometric amount (0.17 equiv.) of HBr. The *ee* value of the phosphaornithine was determined by HPLC with a chiral anion exchanger to be 99%, in agreement with that the of starting material.[21]



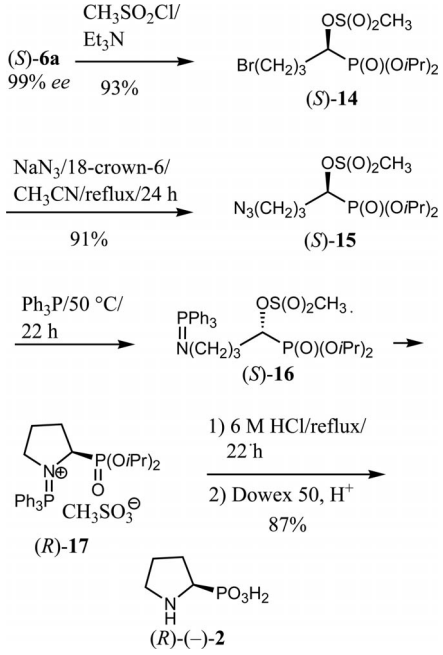
Scheme 3. Preparation of L-phosphaornithine [(*R*)-**3**] and L-phosphalysine [(*R*)-**1**].

Preparation of L-Phosphaproline

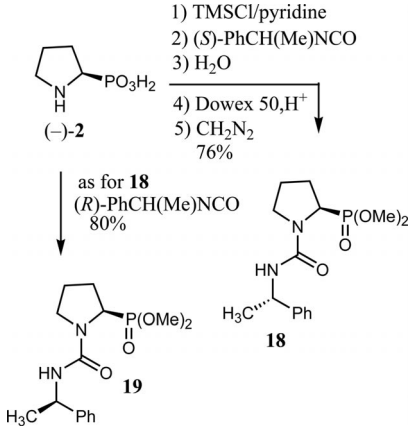
The starting material for the preparation of L-phosphaproline was the bromo-hydroxy-phosphonate (*S*)-**6a**, a chemically unstable compound, as already established for the racemate. When a NMR sample in $CDCl_3$ was left for one week at room temperature, evidently a proportion of the compound cyclized to give diisopropyl (tetrahydrofuran-2-yl)phosphonate [(±)-**13**, ratio of **6a**/(±)-**13** 1.6:1]. This slow cyclization reduced the yields relative to **6b** whenever a reaction that produced or consumed **6a** was performed.

The α-hydroxyphosphonate (*S*)-**6a** was mesylated in 93% yield and then selectively converted (NaN_3/18-crown-6/MeCN/24 h/reflux) into the monoazide (*S*)-**15** in 91% yield (Scheme 4). A Staudinger reaction with Ph_3P in DMF furnished the intermediate iminophosphorane (*S*)-**16**, which cyclized to the protected L-phosphaproline (*R*)-**17**. This was deprotected and purified by the standard procedure to yield L-phosphaproline [(–)-**2**] in 87% yield. If it is assumed that the starting (+)-**6a** has the *S* configuration, on the basis of the ^1H and ^{31}P NMR spectra of the (*R*)-Mosher ester and the plausible assumption of inversion of its configuration upon cyclization, the levorotary proline should have the *R* configuration. However, the *S* configuration had been assigned to it some years ago on the basis of analogy of the migration properties on TLC of dipeptides consisting of various α-aminophosphonic and α-aminocarboxylic acids.[11b] This assignment was later used to deduce the configurations of the enantiomers of piperidazin-3-ylphosphonic acids.[11b] The diethyl ester of (*S*)-phosphaproline[11c] was prepared by Katritzky et al., but they did not deblock it and correlate it with the first assignment. (*S*)-Phosphaproline was recently prepared by deprotection of the diethyl ester of (*S*)-phosphaproline accessed by the method of Katritzky et al. Unfortunately, the specific rotation was not given.[11d] To resolve the discrepancies relating to the absolute configuration, we decided to derivatize

(–)-phosphaproline and to perform X-ray structure analyses (Scheme 5). Phosphaproline [(–)-**2**] was silylated with TMSCl in dry pyridine and then treated with (*S*)-1-phenylethyl isocyanate to form a urea derivative. The phosphonic acid group was esterified with diazomethane to give the derivative **18** in an overall yield of 76%. Because it initially could not be induced to crystallize, we also derivatized the same phosphaproline similarly with (*R*)-1-phenylethyl isocyanate. Luckily, we ended up with suitable crystals of both derivatives for X-ray structure analyses, although the latter crystals were more suited (see Figures 2 and 3). The figures show that the levorotary phosphaproline indeed has the *R* configuration and consequently that the dextrorotary form has the *S* one. The previous assignment[11b] based on R_f values thus requires revision, as do the configurations of the (piperidazin-3-yl)phosphonic acids. Additionally, this result lends credence to the determination of the configurations of α-hydroxyphosphonates by NMR spectroscopic investigation of their Mosher esters.



Scheme 4. Preparation of L-phosphaproline [(*R*)-**2**].



Scheme 5. Derivatization of (–)-phosphaproline with both (*S*)- and (*R*)-1-phenylethyl isocyanate.

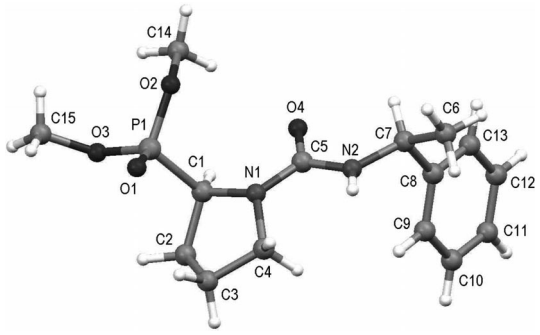


Figure 2. X-ray structure of the (–)-proline derivative **18**. Selected interatomic distances and angles [Å (°)]: P1–C1 1.812(2), P1–O1 1.4677(13), P1–O2 1.5711(16), P1–O3 1.5861(12), C5–O4 1.232(2), C5–N1 1.382(2), C5–N2 1.362(2), O1–P1–C1–N1 56.87(17), C5–N2–C7–C6 156.2(2), C5–N2–C7–C8 –79.7(3), intermolecular hydrogen bond N2···O1 2.857(2).

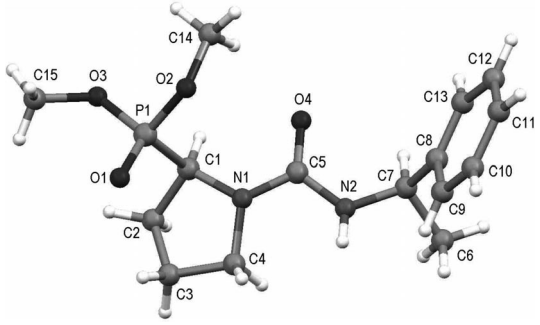


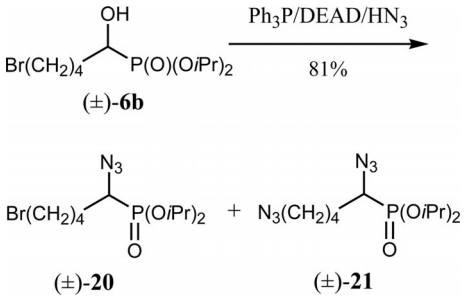
Figure 3. X-ray structure of the (–)-proline derivative **19**. Selected interatomic distances and angles [Å (°)]: P1–C1 1.8145(9), P1–O1 1.4751(6), P1–O2 1.5751(7), P1–O3 1.5853(7), C5–O4 1.2371(10), C5–N1 1.3845(11), C5–N2 1.3574(10), O1–P1–C1–N1 –64.84(7), C5–N2–C7–C6 –143.96(8), C5–N2–C7–C8 93.24(9), intermolecular hydrogen bond N2···O1 2.9368(9).

Preparation of L-Phosphapipecolic Acid

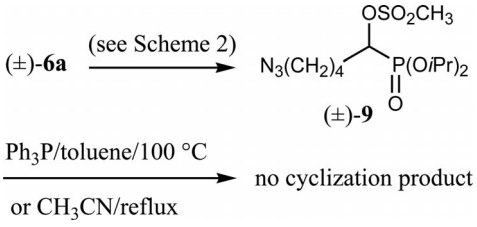
L-Pipecolic acid is on one of two alternative biodegradative routes from lysine to L-α-aminoadipic semialdehyde ultimately leading to acetoacetyl-CoA. Here we prepared the phosphonic acid analogue of this important intermediate.

We first tried to access racemic phosphapipecolic acid from the α-hydroxyphosphonate (±)-**6b** by a very short route as shown in Scheme 6. A Mitsunobu reaction with HN_3 furnished a mixture of the monazide (±)-**20** and the diazide (±)-**21** in a ratio of 1:0.9. It was hoped that the former might be converted into phosphapipecolic acid by a method similar to that depicted in Scheme 3. The selectivity of the Mitsunobu reaction could not be improved significantly, however, so we resorted to the method used for the preparation of L-phosphaproline (Scheme 7). The azidomesylate (±)-**9**, accessed from the α-hydroxyphosphonate (±)-**6a** as in Scheme 2, was treated with Ph_3P to induce a

Staudinger reaction, very probably giving an iminophosphorane. Surprisingly, though, this could not be forced to cyclize, either in acetonitrile at reflux or in toluene at 100 °C. However, the analogous cyclization worked smoothly for phosphaproline.

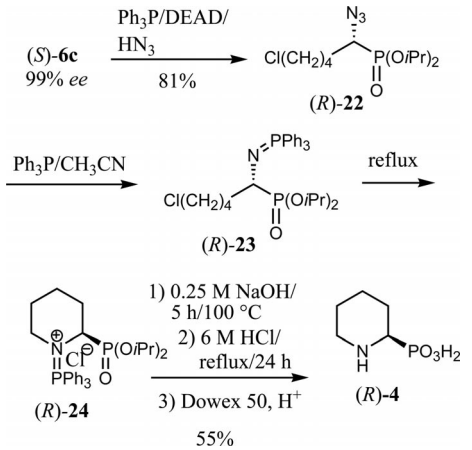


Scheme 6. Attempted preparation of the bromo azide (±)-**20**.



Scheme 7. Attempted preparation of (±)-phosphapipecolic acid.

The failure of the sequence detailed in Scheme 7 was attributed to sluggish intramolecular substitution of the mesyloxy group α to the phosphonate group by the nitrogen atom of the iminophosphorane as nucleophile. To circumvent this difficulty, the ω-chloro-α-hydroxyphosphonate (*S*)-**6c** with 99% *ee* was transformed into the chloroazide (*R*)-**22** by means of a Mitsunobu reaction (Scheme 8). Unlike the bromide in (±)-**6b**, however, the chloride was not replaced by azide. The ensuing Staudinger reaction and the subsequent cyclization with substitution at a primary position were effected in acetonitrile at reflux. The P–N bond in the cyclized product (*R*)-**24** was very stable and could not be cleaved under the acidic conditions used for the removal of the isopropyl groups as in the case of the phosphaproline derivative, but had to be done under mildly basic conditions. The isopropyl groups were removed by treatment with HCl (6 M, reflux). The hydrochloride of L-phosphapipecolic acid was converted into the free acid by ion-exchange chromatography (Dowex 50, H^+). Its overall yield from the starting chloroazide (*R*)-**22** was 55%.



Scheme 8. Preparation of L-phosphapipecolic acid [(*R*)-**4**].

Conclusions

In summary, we have demonstrated that (*S*)-ω-halo-α-hydroxyphosphonates are versatile starting materials for the preparation of phosphonic acid analogues of naturally occurring amino acids. The former compounds were obtained with *ee* values of 99% by protease-catalysed kinetic resolution of the corresponding chloroacetates and were then converted into the corresponding α-aminophosphonic acids by combinations of simple chemical reactions.

Experimental Section

General: All starting materials and enzymes were obtained from commercial suppliers and were generally used without further purification. ^1H and ^{13}C NMR (*J*-modulated) spectra were recorded at 300 K in $CDCl_3$, unless stated otherwise, with use of tetramethylsilane as internal standard with a Bruker AM 400 WB instrument at 400.13 and 100.61 MHz, respectively. ^{31}P NMR spectra were recorded with the same spectrometer at 161.97 MHz and with H_3PO_4 (85%) as external standard. In order to provide undistorted ^{31}P signal intensities for accurate integration, suitable relaxation times were used without irradiation during this period to avoid NOE enhancements. Chemical shifts (δ) are given in ppm and coupling constants (*J*) in Hz. IR spectra were run with a Perkin–Elmer 1600 FT-IR spectrometer; liquid samples were measured as films between NaCl plates or on a silicon disc,[22] solids as Nujol mulls between NaCl plates.

Optical rotations were measured at 20 °C with a Perkin–Elmer 341 polarimeter in a 1 dm cell. TLC was carried out with Merck plates (0.25 mm, silica gel 60 F_{254}). Flash (column) chromatography was performed with Merck silica gel 60 (230–400 mesh). Spots were visualized by dipping the plate into a solution of $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ (24 g) and $Ce(SO_4)_2\cdot 4H_2O$ (1 g) in H_2SO_4 in water (10%, 500 mL), followed by heating with a heat gun. TLC (*i*PrOH/H_2O/NH_3 6:3:1) of aminophosphonic acids was also performed on silica gel plates. Spots were visualized by dipping the plate into a solution of ninhydrin [0.2% in ethanol (96%) or a 0.2% solution of ninhydrin in EtOH (96%)/AcOH/collidine, 16:3:1], followed by heating with a heat gun. A Metrohm 702 SM Titrino instrument was used as an autotitrator. (*S*)-(+)-α-Methoxy-α-(trifluoromethyl)phenylacetyl chloride {JPS Chimie. $[a]_D^{20}$ = +136.5 (*c* = 5.2, CCl_4), *ee* > 99.5%} was used for derivatization of α-hydroxyphosphonates. Enzymes [lyophilized preparations of lipase AP 6 and protease Chirazyme® P-2 or a solution of it (5 mL of solution contained 600 mg of lyophilisate with a protein content of 80%)] were stored at +4 °C and used as supplied.

The α-hydroxyphosphonates (±)-**6a**–**c** were prepared by a literature procedure[15a] and esterified[14b] with chloroacetic anhydride/pyridine.

Enzymatic Hydrolysis of the α-(Chloroacetoxy)phosphonates (±)-7a–c (General Procedure A): A chloroacetate (±)-**7** (1 mmol) was

hydrolysed in a biphasic system [phosphate buffer (pH 7.0, 50 mM, 17 mL) and a hexanes/*tert*-butyl methyl ether mixture (1:1, 4 mL)] at room temp. When the level of conversion had reached 45%, the hydrolysis was stopped and the mixture was worked up as reported (for results see Table 2).[15b] Enzymatic hydrolyses performed on a preparative scale were performed in a 100 mL three-necked flask with use of phosphate (50 mL) but without organic solvent (for results see Table 2).

The Mosher esters **6**·MTPA-(*R*) were prepared by a literature procedure[16] except that the α-hydroxyphosphonates **6** (approximately 0.05 mmol) were esterified with (*S*)-(+)-MTPACl (2.5 equiv.) and dry pyridine (10 equiv.) in dry CH_2Cl_2 (0.5 mL). The solutions were allowed to stand overnight (TLC: hexanes/EtOAc 1:4 or hexanes/EtOAc 1:2) at room temp. and worked up as reported after the addition of a few drops of water.

Chemical Hydrolysis of the α-(Chloroacetoxy)phosphonates 7 (General Procedure B): A stirred solution of an α-chloroacetoxyphosphonate **7** in methanol (10 mL for each mmol of **7**) was treated with Et_3N (2 mL for each mmol of **7**) at room temp. Stirring was continued until no starting material could be detected by TLC. After evaporation of the solvent, the crude product was purified by flash chromatography.

Preparation of the α-Azidophosphonates (General Procedure C): Diethyl azodicarboxylate (1.5 equiv.) and a solution of HN_3 in toluene (1.5 equiv.) were added at 0 °C under argon to a stirred mixture of an α-hydroxyphosphonate **6** and Ph_3P (1.5 equiv.) in dry toluene (15 mL for 2 mmol of **6**) and dry CH_2Cl_2 (3 mL for 2 mmol of **6**).[14b] Stirring was continued for 30 min at 0 °C and for 1 h at room temperature. MeOH (0.2 mL for 2 mmol of **6**) was added, and 30 min later the solvent was removed under reduced pressure. Hexanes were added to the residue and the mixture was allowed to stand overnight at 4 °C. The crystals were removed and the filtrate was concentrated under reduced pressure. The crude product was purified by flash chromatography.

Preparation of the α-Aminophosphonic Acids (General Procedure D): An azide (1 mmol) was dissolved in EtOH (30 mL) containing concd. HCl (0.5 mL), and after the addition of Pd on charcoal (50 mg, 10%) the azide was hydrogenated in a Parr apparatus (3.4 bar) at room temp. for 4 h.[14b] The catalyst was filtered off and the solvent was removed under reduced pressure. The residue was dissolved in HCl (6 M, 10 mL) and heated at reflux for 5 h. After evaporation of the solvent under reduced pressure and drying of the residue over KOH in a desiccator, the crude product was purified by ion exchange chromatography on Dowex 50 WX8 or 50 WX4, H^+ (50–100 mesh) with water as eluent. Ninhydrin-positive fractions were collected, concentrated under reduced pressure and finally lyophilized.

(±)-Diisopropyl (4-Bromo-1-hydroxybutyl)phosphonate [(±)-6a]: This compound was prepared in 74% yield from ethyl 4-bromobutanoate (**5a**, 5.85 g, 30 mmol), as a viscous colourless oil, which crystallized at –5 °C and should be stored at this temperature; R_f = 0.41 (EtOAc). ^{1}H NMR: δ = 1.27 (d, J = 6.0 Hz, 6 H), 1.280 and 1.285 (d, J = 6.0 Hz, 3 H), 1.73 (m, 1 H), 1.91 (m, 2 H), 2.11 (m, 1 H), 2.83 (s, 1 H), 3.40 (m, 2 H), 3.74 (ddd, J = 3.5, 4.7, 10.3 Hz, 1 H), 4.68 (m, 2 H) ppm. ^{13}C NMR: δ = 23.95 (d, J = 2.6 Hz), 23.99 (d, J = 3.1 Hz), 24.07 (d, J = 3.8 Hz), 24.13 (d, J = 3.1 Hz), 29.00 (d, J = 13.8 Hz), 29.8 and 33.4, 67.2 (d, J = 162.9 Hz), 71.2 (d, J = 6.9 Hz), 71.4 (d, J = 7.6 Hz) ppm. IR (NaCl): $\tilde{\nu}$ = 3298, 2979, 2935, 1452, 1386, 1375, 1217, 1178, 1142, 1106, 1078, 990 cm^{-1}. $C_{10}H_{22}BrO_4P$ (317.17): calcd. C 37.87, H 6.99; found C 37.82, H 6.73.

(±)-Diisopropyl (5-Bromo-1-hydroxypentyl)phosphonate [(±)-27i]: This compound was prepared in 68% yield from ethyl 5-bromopentanoate (**5b**, 2.51 g, 12 mmol) as a viscous colourless oil, which crystallized at –5 °C; R_f = 0.38 (EtOAc), 0.24 (hexanes/EtOAc 1:4). ^{1}H NMR: δ = 1.302 [d, J = 6.4 Hz, 6 H, OCH(CH_3)$_2$], 1.306 [d, J = 6.4 Hz, 3 H, OCH(CH_3)$_2$], 1.312 [d, J = 5.9 Hz, 3 H, OCH(CH_3)$_2$], 1.53 (m, 1 H, CH_2), 1.70 (m, 3 H, CH_2), 1.88 (m, 2 H, CH_2), 3.38 (br. s, 1 H, OH), 3.39 (t, J = 6.9 Hz, 2 H, CH_2Br), 3.74 (m, 1 H, CHP), 4.71 [m, 2 H, OCH(CH$_3$)$_2$] ppm. ^{13}C NMR: δ = 24.0 (d, J = 4.4 Hz), 24.08 (d, J = 3.9 Hz), 24.12 (d, J = 3.6 Hz), 24.6 (d, J = 13.6 Hz), 30.4, 32.5 and 33.4, 67.8 (d, J = 161.9 Hz), 71.1 (d, J = 7.4 Hz), 71.3 (d, J = 7.2 Hz) ppm. IR (NaCl): $\tilde{\nu}$ = 3299, 2978, 2937, 2870, 1454, 1386, 1375, 1227, 1178, 1142, 1106, 990 cm^{-1}. $C_{11}H_{24}BrO_4P$ (331.19): calcd. C 39.89, H 7.30; found C 40.17, H 7.19.

(±)-Diisopropyl (5-Chloro-1-hydroxypentyl)phosphonate [(±)-6c]: This compound was prepared in 62% yield from methyl 5-chloropentanoate (**5c**, 3.01 g, 20 mmol) as a viscous colourless oil, which crystallized at –5 °C; R_f = 0.51 (EtOAc). ^{1}H NMR: δ = 1.26 (d, J = 6.0 Hz, 6 H), 1.265 (d, J = 6.0 Hz, 3 H), 1.27 (d, J = 6.0 Hz, 3 H), 1.49 (m, 1 H), 1.71 (m, 5 H), 3.48 (t, J = 6.5 Hz, 2 H), 3.56 (dd, J = 3.5, 6.0 Hz, 1 H), 3.70 (m, 1 H), 4.67 (m, 2 H) ppm. ^{13}C NMR: δ = 23.3 (d, J = 13.8 Hz), 24.0 (d, J = 6.1 Hz), 24.07 and 24.11 (d, J = 3.8 Hz), 30.6 and 32.3, 44.8, 67.8 (d, J = 162.1 Hz), 71.0 and 71.2 (d, J = 7.6 Hz) ppm. IR (Si): $\tilde{\nu}$ = 3300, 2980, 2938, 2872, 1454, 1386, 1375, 1313, 1287, 1221, 1179, 1142, 1106, 990 cm^{-1}. $C_{11}H_{24}ClO_4P$ (286.74): calcd. C 46.08, H 8.44; found C 46.31, H 8.28.

(±)-Diisopropyl [4-Bromo-1-(chloroacetoxy)butyl]phosphonate [(±)-7a]: R_f = 0.69 (hexanes/EtOAc 1:4); yield 82%; viscous oil. ^{1}H NMR: δ = 1.30 (d, J = 6.4 Hz, 3 H), 1.31 (d, J = 5.9 Hz, 3 H), 1.32 (d, J = 6.4 Hz, 6 H, 6 H), 1.92 (m, 3 H), 2.10 (m, 3 H), 3.39 (t, J = 6.2 Hz, 2 H), 4.09 (AB system, J_{AB} = 15.0 Hz, 2 H), 4.74 (oct, J = 6.4 Hz, 2 H), 5.23 (dt, J = 3.8, 9.2 Hz, 1 H) ppm. ^{13}C NMR: δ = 23.8 (d, J = 4.9 Hz), 23.99 (d, J = 4.5 Hz), 24.02 and 24.2 (d, J = 3.5 Hz), 28.1 and 32.5, 28.5 (d, J = 11.8 Hz), 40.6, 69.5 (d, J = 171.1 Hz), 71.8 (d, J = 7.2 Hz), 72.0 (d, J = 6.7 Hz), 166.5 (d, J = 5.8 Hz) ppm. IR (NaCl): $\tilde{\nu}$ = 2981, 2936, 1766, 1452, 1386, 1376, 1254, 1164, 1105, 991 cm^{-1}. $C_{12}H_{23}BrClO_5P$ (393.65): calcd. C 36.61, H 5.89; found C 36.88, H 6.00.

(±)-Diisopropyl [5-Bromo-1-(chloroacetoxy)pentyl]phosphonate [(±)-7b]: R_f = 0.47 (hexanes/EtOAc 1:2); yield 88%; viscous oil. ^{1}H NMR: δ = 1.28 and 1.30 (d, J = 5.9 Hz, 3 H), 1.31 (d, J = 5.9 Hz, 6 H), 1.51 (m, 2 H), 1.85 (m, 4 H), 3.36 (t, J = 6.6 Hz, 2 H), 4.09 (AB system, J_{AB} = 14.8 Hz, 2 H), 4.72 (m, 2 H), 5.21 (dt, J = 4.4, 9.3 Hz, 1 H) ppm. ^{13}C NMR: δ = 23.8 (d, J = 4.9 Hz), 23.99 (d, J = 5.4 Hz), 24.00 (d, J = 3.3 Hz), 24.12 (d, J = 12.2 Hz), 24.14 (d, J = 3.4 Hz), 28.6, 32.0 and 33.0, 40.6, 70.0 (d, J = 170.5 Hz), 71.7 (d, J = 7.3 Hz), 71.9 (d, J = 6.7 Hz), 166.5 (d, J = 5.6 Hz) ppm. IR (NaCl): $\tilde{\nu}$ = 2981, 1767, 1454, 1386, 1256, 1164, 1105, 991 cm^{-1}. $C_{13}H_{25}BrClO_5P$ (407.68): calcd. C 38.30, H 6.18; found C 38.54, H 6.09.

(±)-Diisopropyl [5-Chloro-1-(chloroacetoxy)pentyl]phosphonate [(±)-7c]: R_f = 0.62 (EtOAc); yield 92%; viscous oil. ^{1}H NMR: δ = 1.33 (d, J = 6.0 Hz, 3 H), 1.34 (d, J = 5.9 Hz, 3 H), 1.35 (d, J = 6.0 Hz, 6 H), 3.54 (t, J = 6.5 Hz, 2 H), 4.13 (AB system, J_{AB} = 15.1 Hz, 2 H), 4.76 (m, 2 H), 5.25 (dt, J = 4.3, 9.3 Hz, 1 H) ppm. ^{13}C NMR: δ = 22.9 (d, J = 12.2 Hz), 23.8 and 23.98 (d, J = 5.3 Hz), 24.00 (d, J = 3.8 Hz), 24.1 (d, J = 3.1 Hz), 28.7 and 31.8, 40.6, 43.4, 70.1 (d, J = 170.4 Hz), 71.7 (d, J = 7.1 Hz), 71.9 (d, J = 6.6 Hz) ppm. IR (NaCl): $\tilde{\nu}$ = 2981, 1767, 1454, 1386, 1376, 1253,

1165, 1105, 991, 889 cm^{-1}. $C_{13}H_{25}Cl_2O_5P$ (363.22): calcd. C 42.99, H 6.94; found C 42.78, H 6.66.

(±)-Diisopropyl (5-Bromo-1-mesyloxypentyl)phosphonate [(±)-8b]: $MeSO_2Cl$ (485 mg, 4.23 mmol, 0.33 mL) and dry Et_3N (4.23 mmol, 0.59 mL) were added under argon at 0 °C to a stirred solution of the α-hydroxyphosphonate (±)-**6b** (934 mg, 2.82 mmol) in dry CH_2Cl_2 (15 mL). After the mixture had been stirred for 30 min at 0 °C (TLC: hexanes/EtOAc 1:4), water (10 mL) and concd. HCl (1 mL) were added. The organic phase was separated and the aqueous one was extracted twice with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure, and the residue was purified by flash chromatography (hexanes/EtOAc 1:4, R_f = 0.53); yield 93%, viscous oil. ^{1}H NMR: δ = 1.29 (d, J = 5.5 Hz, 6 H), 1.31 (d, J = 6.0 Hz, 6 H), 1.55 (m, 1 H), 1.68 (m, 1 H), 1.83 (m, 4 H), 3.14 (s, 3 H), 3.34 (t, J = 6.8 Hz, 2 H), 4.71 (m, 3 H) ppm. ^{13}C NMR: δ = 23.8 (d, J = 5.3 Hz), 24.0 (d, J = 5.3 Hz, 2 C), 24.1 (d, J = 10.7 Hz), 24.2 (d, J = 3.8 Hz), 29.7, 31.5 and 32.9, 39.2, 72.1 and 72.4 (d, J = 6.9 Hz), 77.0 (d, J = 171.3 Hz) ppm. IR (NaCl): $\tilde{\nu}$ = 2981, 2936, 2874, 1454, 1414, 1387, 1360, 1255, 1225, 1175, 1143, 1104, 990 cm^{-1}. $C_{12}H_{26}BrO_6PS$ (409.27): calcd. C 35.22, H 6.40; found C 35.21, H 6.12.

(±)-Diisopropyl (5-Azido-1-mesyloxypentyl)phosphonate [(±)-9b]: NaN_3 (343 mg, 5.28 mmol) and 18-crown-6 (140 mg, 0.53 mmol) were added under argon to a stirred solution of the mesylate (±)-**8** (1.08 g, 2.64 mmol) in dry CH_3CN (25 mL). The mixture was heated at reflux for 24 h. The solvent was evaporated under reduced pressure and the residue was taken up in water (20 mL). The aq. mixture was extracted three times with EtOAc. The combined organic layers were dried ($MgSO_4$) and after removal of the solvent the crude product was purified by flash chromatography. R_f = 0.65 (hexanes/EtOAc 1:4); yield 95%, colourless oil. ^{1}H NMR: δ = 1.29 (d, J = 6.0 Hz, 6 H), 1.31 (d, J = 5.5 Hz, 6 H), 1.38–1.65 (m, 4 H), 1.81 (m, 2 H), 3.14 (s, 3 H), 3.23 (t, J = 6.3 Hz, 2 H), 4.70 (m, 3 H) ppm. ^{13}C NMR: δ = 22.7 (d, J = 12.2 Hz), 23.8 (d, J = 4.6 Hz), 24.0 (d, J = 4.6 Hz, 2 C), 24.1 (d, J = 3.8 Hz), 28.2 and 30.1, 39.2, 51.0, 72.1 and 72.5 (d, J = 6.9 Hz), 77.0 (d, J = 170.6 Hz) ppm. IR (NaCl): $\tilde{\nu}$ = 2982, 2937, 2875, 2098, 1455, 1360, 1253, 1176, 1143, 1105, 991 cm^{-1}. $C_{11}H_{26}N_3O_6PS$ (371.39): calcd. C 38.81, H 7.06, N 11.31; found C 38.88, H 6.94, N 11.39.

(*S*)-(+)-Diisopropyl [4-Bromo-1-(4-nitrophenylsulfonyloxy)butyl]-phosphonate [(*S*)-(+)-11a]: The α-hydroxyphosphonate (*S*)-(+)-**6a** {650 mg 2.05 mmol, $[\alpha]_D^{20}$ = +15.4 (c = 1.0, acetone), *ee* 99%} was transformed into the 4-nitrobenzenesulfonate (*S*)-(+)-**11a** by the procedure used for the preparation of the 4-nitrobenzenesulfonate (*S*)-(+)-**11b**; R_f = 0.54 (hexanes/EtOAc 1:1). $[\alpha]_D^{20}$ = +5.7 (c = 1.0, acetone); yield 80%; viscous oil. ^{1}H NMR: δ = 1.19 (d, J = 6.5 Hz, 3 H), 1.21 (d, J = 6.0 Hz, 3 H), 1.24 (d, J = 6.5 Hz, 6 H), 1.93 (m, 2 H), 2.05 (m, 2 H), 3.37 (t, J = 5.8 Hz, 2 H), 4.57 (oct, J = 6.5 Hz, 1 H), 4.65 (oct, J = 6.3 Hz, 1 H), 4.83 (m, 1 H), 8.22 (J = 9.0 Hz, 4 H, AA′BB′-system) ppm. ^{13}C NMR: δ = 23.7 and 23.9 (d, J = 5.4 Hz), 23.98 and 24.04 (d, J = 3.8 Hz), 28.2 (d, J = 10.0 Hz), 29.1 and 32.5, 72.4 and 72.5 (d, J = 7.6 Hz), 77.2 (d, J = 172.1 Hz), 124.2 and 129.4 (each 2 C), 142.5 and 150.8 ppm. IR (NaCl): $\tilde{\nu}$ = 3107, 2982, 2936, 1535, 1453, 1404, 1376, 1351, 1313, 1256, 1187, 1143, 1104, 993 cm^{-1}. $C_{16}H_{25}BrNO_8PS$ (502.31): calcd. C 38.26, H 5.02, N 2.79; found C 38.55, H 4.86, N 2.76.

(*S*)-(+)-Diisopropyl [5-Bromo-1-(4-nitrophenylsulfonyloxy)pentyl]-phosphonate [(S)-(+)-11b]: A solution of 4-nitrobenzenesulfonyl chloride (926 mg, 4.18 mmol) in dry CH_2Cl_2 (5 mL), dry Et_3N (847 mg, 8.37 mmol, 1.16 mL) and DMAP (30 mg) were added under argon at 0 °C to a stirred solution of (*S*)-(+)-**6b** {1.15 g, 3.47 mmol, $[\alpha]_D^{20}$ = +12.8 (c = 1.0, acetone), *ee* 99%} in dry CH_2Cl_2 (20 mL). After the mixture had been stirred for 30 min at 0 °C and for 2 h at room temp. (TLC: hexanes/EtOAc 1:4), water (10 mL) and concd. HCl (1 mL) were added. The organic phase was separated and the aqueous one was extracted twice with CH_2Cl_2. The combined organic layers were washed with a sat. aq. solution of $NaHCO_3$, dried ($MgSO_4$) and then concentrated under reduced pressure. The residue was purified by flash chromatography (hexanes/EtOAc 1:1, R_f = 0.51). $[\alpha]_D^{20}$ = +2.8 (c = 1.1, acetone); yield 82%; viscous oil. ^{1}H NMR: δ = 1.19 (d, J = 6.0 Hz, 3 H), 1.21 (d, J = 6.5 Hz, 3 H), 1.24 (d, J = 6.0 Hz, 6 H), 1.55 (m, 2 H), 1.82 (m, 4 H), 3.31 (t, J = 6.5 Hz, 2 H), 4.61 (m, 2 H), 4.81 (dt, J = 4.5, 9.0 Hz, 1 H), 8.22 (J = 9.0 Hz, 4 H, AA′BB′ system) ppm. ^{13}C NMR: δ = 23.7 and 23.9 (d, J = 4.6 Hz), 23.98 and 24.03 (d, J = 3.8 Hz), 24.2 (d, J = 10.0 Hz), 29.7, 31.93 and 32.90, 72.3 and 72.4 (d, J = 6.9 Hz), 77.9 (d, J = 172.9 Hz), 124.2 and 129.3 (each 2 C), 142.6 and 150.7 ppm. IR (NaCl): $\tilde{\nu}$ = 3107, 2981, 2937, 1608, 1534, 1454, 1404, 1375, 1351, 1313, 1257, 1187, 1143, 1105, 991 cm^{-1}. $C_{17}H_{27}BrNO_8PS$ (516.35): calcd. C 39.54, H 5.27, N 2.71; found C 39.79, H 5.19, N 2.64.

(*R*)-(–)-Diisopropyl (1,4-Diazidobutyl)phosphonate [(*R*)-(–)-12a]: The 4-nitrobenzenesulfonate (*S*)-(+)-**11a** {751 mg, 1.50 mmol, $[\alpha]_D^{20}$ = +5.7 (c = 1.0, acetone), *ee* 99%} was transformed into the diazide (*R*)-(–)-**12a** by the procedure used for the preparation of the diazide (*R*)-(–)-**12b**. R_f = 0.21 (hexanes/EtOAc 1:2). $[\alpha]_D^{20}$ = –53.8 (c = 1.0, acetone); yield 82%; oil. ^{1}H NMR: δ = 1.300 (d, J = 6.5 Hz, 3 H), 1.305 (d, J = 6.0 Hz, 9 H), 1.64 (m, 2 H), 1.84 (m, 2 H), 3.29 (m, 3 H), 4.72 (m, 2 H) ppm. ^{13}C NMR: δ = 24.0 (d, J = 5.3 Hz, 2 C), 24.10 and 24.13 (d, J = 3.8 Hz), 26.07, 26.10 (d, J = 13.8 Hz), 50.8, 57.4 (d, J = 157.6 Hz), 71.88 and 71.91 (d, J = 6.9 Hz) ppm. IR (NaCl): $\tilde{\nu}$ = 2982, 2936, 2875, 2100, 1454, 1387, 1376, 1353, 1254, 1178, 1142, 1105, 990 cm^{-1}. $C_{10}H_{21}N_6O_3P$ (304.29): calcd. C 39.47, H 6.96, N 27.62; found C 39.69, H 6.67, N 27.37.

(*R*)-(–)-Diisopropyl (1,5-Diazidopentyl)phosphonate [(*R*)-(–)-12b]: NaN_3 (608 mg, 9.35 mmol) and 18-crown-6 (247 mg, 0.935 mmol) were added under argon to a stirred solution of (*S*)-(+)-**11b** {1.207 g, 2.34 mmol, $[\alpha]_D^{20}$ = +2.8 (c = 1.1, acetone)} in dry DMF (25 mL). The mixture was stirred for 40 h at 40 °C. Water (20 mL) was added and the mixture was extracted three times with EtOAc. The combined organic layers were dried ($MgSO_4$) and after the evaporation of the solvent residual DMF was removed by bulb-to-bulb distillation (bath temperature below 70 °C). The crude product was purified by flash chromatography. R_f = 0.60 (hexanes/EtOAc 1:2). $[\alpha]_D^{20}$ = –49.3 (c = 1.7, acetone); yield 85%; oil. ^{1}H NMR: δ = 1.29 (d, J = 6.0 Hz, 3 H), 1.30 (d, J = 6.0 Hz, 9 H), 1.43 (m, 1 H), 1.60 (m, 4 H), 1.80 (m, 1 H), 3.25 (m, 3 H), 4.72 (m, 2 H) ppm. ^{13}C NMR: δ = 24.0 (d, J = 13.0 Hz), 24.1 (d, J = 3.8 Hz, 2 C), 24.4 (d, J = 4.6 Hz, 2 C), 28.2 and 28.3, 51.1, 57.7 (d, J = 156.8 Hz), 71.76 and 71.83 (d, J = 6.9 Hz) ppm. IR (NaCl): $\tilde{\nu}$ = 2981, 2936, 2871, 2100, 1455, 1386, 1376, 1350, 1253, 1178, 1142, 1106, 989 cm^{-1}. $C_{11}H_{23}N_6O_3P$ (318.31): calcd. C 41.50, H 7.28, N 26.40; found C 41.71, H 7.11, N 26.35.

(*R*)-(–)-(1,4-Diaminobutyl)phosphonic Acid Hydrobromide [(*R*)-Phosphaornithine·HBr, (*R*)-(–)-3·HBr]: The diazide (*R*)-(–)-**12a** {301 mg, 0.99 mmol, $[\alpha]_D^{20}$ = –53.8 (c = 1.0, acetone)} was transformed into (*R*)-(–)-**3**·HBr by the procedure used for the preparation of (*R*)-(–)-**1**·HBr. Melting range 110–160 °C, 274–278 °C (dec.). $[\alpha]_D^{20}$ = –1.3 (c = 0.65, H_2O); yield 67%; colourless crystals. ^{1}H NMR (D_2O): δ = 1.68–2.02 (m, 4 H), 3.01 (t, J = 7.0 Hz, 2 H), 3.23 (dt, J = 6.6, 13.2 Hz, 1 H) ppm. ^{13}C NMR (D_2O): δ = 24.3 (d, J = 7.6 Hz), 26.1, 39.3, 49.0 (d, J = 141.5 Hz) ppm. ^{31}P NMR (D_2O): δ = 13.7 ppm. IR (Nujol): $\tilde{\nu}$ = 3583, 1614, 1154, 1045,

917 cm^{-1}. $C_4H_{14}BrN_2O_3P$ (249.05): calcd. C 19.29, H 5.66, N 11.25, Br 32.08; found C 19.60, H 5.39, N 11.09, Br 29.82.

(*R*)-(–)-(1,5-Diaminopentyl)phosphonic Acid [(*R*)-Phosphalysine·0.17 HBr, (*R*)-(–)-1·0.17 HBr]: A solution of the diazide (*R*)-(–)-**12b** (170 mg, 0.534 mmol) and Ph_3P (336 mg, 1.28 mmol) in dry toluene (3 mL) was stirred under argon for 1 h at room temp. and for 21 h at 30–40 °C.[20] The solvent was evaporated under reduced pressure and the viscous residue was heated at reflux with HCl (6 M, 10 mL) for 23 h. Water (20 mL) was added and the aq. suspension was extracted three times with Et_2O. After removal of the solvent under reduced pressure the hydrochloride of (*R*)-**1a** was transformed into the hydrobromide by treatment of the solid residue with HBr (5 mL, 48%) and evaporation of the solvent under reduced pressure. This process was repeated twice. The residue was dissolved several times in water and concentrated under reduced pressure, and was then repeatedly admixed with EtOH and concentrated again. The crude product, which was carefully dried under reduced pressure, was dissolved in MeOH (2 mL), and afterwards propene oxide (0.1 mL) was added dropwise to the stirred solution. After 3 h the crystals were collected, washed with a small portion of cold MeOH and dried under reduced pressure; m.p. 269–273 °C (dec.). $[\alpha]_D^{20}$ = –9.7 (*c* = 0.66, H_2O); yield (calculated with a formula weight $C_5H_{16}BrN_2O_3P$·0.17 HBr): 82%; colourless crystals. ^1H NMR (D_2O): δ = 1.48 (m, 2 H), 1.64 (m, 3 H), 1.85 (m, 1 H), 2.94 (t, *J* = 7.3 Hz, 2 H), overlapping with 2.99 (m, 1 H) ppm. ^{13}C NMR (D_2O): δ = 23.2 (d, *J* = 8.4 Hz), 26.7 and 28.8, 39.4, 50.4 (d, *J* = 135.4 Hz) ppm. ^{31}P NMR (D_2O): δ = 13.1 ppm. IR (Nujol): $\tilde{\nu}$ = 3583, 2193, 1626, 1557, 1112, 1065, 974 cm^{-1}. $C_5H_{15}N_2O_3P$·0.17 HBr (assumed, 195.91): calcd. C 30.65, H 7.74, N 14.30, Br 6.93; found C 30.45, H 7.52, N 13.67, Br 6.99.

(±)-Diisopropyl (Tetrahydrofuran-2-yl)phosphonate [(±)-13)]: Assignable signals for compound (±)-**13** were obtained from the NMR spectra of a 1 to 1.6 mixture of (±)-**13** and the α-hydroxyphosphonate (±)-**6a**. ^1H NMR: δ = 4.01 (dt, *J* = 2.3, 7.8 Hz, 1 H) ppm. ^{13}C NMR: δ = 26.1 (d, *J* = 6.0 Hz), 27.3, 69.7 (d, *J* = 7.6 Hz), 70.9 (d, *J* = 7.0 Hz), 71.2 (d, *J* = 7.2 Hz), 73.7 (d, *J* = 173.0 Hz) ppm.

(*S*)-(+)-Diisopropyl (4-Bromo-1-mesyloxybutyl)phosphonate [(*S*)-(+)-14]: Compound (*S*)-(+)-**6a** {1.05 g, 3.31 mmol, $[\alpha]_D^{20}$ = +15.4 (*c* = 1.0, acetone) *ee* 99%} was transformed into the mesylate (*S*)-(+)-**69** by the procedure used for the preparation of the mesylate (±)-**8**. R_f = 0.62 (hexanes/EtOAc 1:4). $[\alpha]_D^{20}$ = +13.9 (*c* = 1.2, acetone); yield 93%; viscous oil. ^1H NMR: δ = 1.30 (d, *J* = 5.7 Hz, 3 H), 1.305 (d, *J* = 6.0 Hz, 3 H), 1.31 (d, *J* = 6.0 Hz, 6 H), 1.92 (m, 2 H), 2.06 (m, 2 H), 3.15 (s, 3 H), 3.41 (m, 2 H), 4.72 (m, 3 H) ppm. ^{13}C NMR: δ = 23.9 (d, *J* = 5.3 Hz), 24.0 (d, *J* = 3.8 Hz, 2 C), 24.2 (d, *J* = 3.8 Hz), 28.2 (d, *J* = 12.2 Hz), 29.0 and 32.7, 39.2, 72.3 (d, *J* = 6.0 Hz), 72.6 (d, *J* = 6.9 Hz), 76.4 (d, *J* = 171.3 Hz) ppm. IR (NaCl): $\tilde{\nu}$ = 2981, 2936, 2877, 1467, 1454, 1414, 1387, 1360, 1255, 1234, 1175, 1143, 1104, 990 cm^{-1}. $C_{11}H_{24}BrO_6PS$ (395.25): calcd. C 33.43, H 6.12; found C 33.14, H 5.90.

(*S*)-(+)-Diisopropyl (4-Azido-1-mesyloxybutyl)phosphonate [(*S*)-(+)-15]: The mesylate (*S*)-(+)-**14** {1.18 g, 2.98 mmol), $[\alpha]_D^{20}$ = +13.9 (*c* = 1.2, acetone), *ee* 99%} was transformed into the azidomesylate (*S*)-(+)-**15** by the procedure used for the preparation of the mesylate (±)-**9**. R_f = 0.60 (hexanes/EtOAc 1:4). $[\alpha]_D^{20}$ = +13.1 (*c* = 1.0, acetone); yield 91%; viscous oil. ^1H NMR: δ = 1.30 (d, *J* = 6.0 Hz, 6 H), 1.31 (d, *J* = 6.5 Hz, 6 H), 1.68 (m, 1 H), 1.76–2.00 (m, 3 H), 3.15 (s), 3.30 (m, 2 H), 4.72 (m, 3 H) ppm. ^{13}C NMR: δ = 23.8 (d, *J* = 5.3 Hz), 24.0 (d, *J* = 3.8 Hz, 2 C), 24.2 (d, *J* = 3.8 Hz), 24.9 (d, *J* = 11.5 Hz), 27.7, 39.2, 50.6, 72.2 (d, *J* = 7.6 Hz), 72.6 (d, *J* = 6.9 Hz), 76.7 (d, *J* = 157.6 Hz) ppm. IR (NaCl): $\tilde{\nu}$ = 2982, 2937, 2877, 2100, 1641, 1454, 1360, 1255, 1175, 1143, 1105, 990 cm^{-1}. $C_{11}H_{24}N_3O_6PS$ (357.36): calcd. C 36.97, H 6.77, N 11.76; found C 36.80, H 6.52, N 11.53.

(*R*)-(–)-(Pyrrolidin-2-yl)phosphonic Acid [(*R*)-Phosphaproline, (*R*)-(–)-2]: A solution of the azidomesylate (*R*)-(+)-**15** {929 mg, 2.60 mmol, $[\alpha]_D^{20}$: = +13.9 (*c* = 1.2, acetone), = 99%} and Ph_3P (818 mg, 3.12 mmol) in dry DMF (20 mL) was stirred under argon for 22 h. The solvent was removed by bulb-to-bulb distillation. The cyclic intermediate (*R*)-**17** {assignable signals of the NMR spectra of crude **17** are given: ^1H NMR (CD_3OD): δ = 0.95, 1.10, 1.18 and 1.25 (d, *J* = 6.0 Hz, 3 H), 3.32 and 3.52 (m, 1 H), 3.75 (m, 1 H), 4.34 and 4.60 (m, 1 H) ppm. ^{13}C NMR: δ = 24.4, 24.58 and 24.62 (d, *J* = 3.8), 24.79 (d, *J* = 4.6), 26.53 and 28.49 (d, *J* = 5.4), 52.40 (d, *J* = 3.1), 59.4 (dd, *J* = 3.1, 165.2), 74.27 and 74.30 (d, *J* = 6.6) ppm} was dried under reduced pressure and then heated at reflux with HCl (6 M, 25 mL) for 22 h. Water (50 mL) was added and the aq. solution was extracted with Et_2O (3 × 40 mL). The aq. phase was concentrated under reduced pressure and the crude product was purified by ion-exchange chromatography on Dowex 50, H^+ with water as eluent; m.p. 265–270 °C (dec.) (ref. 272–273 °C[11b]). $[\alpha]_D^{20}$ = –49.1, $[\alpha]_{578}^{20}$ = –51.6 (*c* = 1.1, 1 M NaOH) (ref. $[\alpha]_{578}^{20}$ = +64 (*c* = 1.0, 1 M NaOH), *ee* 100%[11b]); yield 87%; crystalline solid. ^1H NMR (D_2O): δ = 2.01 (m, 3 H), 2.24 (m, 1 H), 3.32 (m, 1 H), 3.51 (q, *J* = 9.2 Hz, 1 H) ppm. ^{13}C NMR (D_2O): δ = 24.3 (d, *J* = 8.4 Hz), 26.8, 47.2 (d, *J* = 6.1 Hz), 56.20 (d, *J* = 143.8 Hz) ppm. ^{31}P NMR (D_2O): δ = 13.6 ppm. IR (Nujol): $\tilde{\nu}$ = 1694, 1622, 1556, 1401, 1339, 1311, 1242, 1167, 1066, 1030 cm^{-1}. $C_4H_{10}NO_3P$ (151.10): calcd. C 31.80, H 6.67, N 9.27; found C 31.74, H 6.42, N 9.10.

Derivatization of (–)-Phosphaproline with (*S*)-(–)- and (*R*)-(+)-1-Phenylethyl Isocyanate to Give the Derivatives 18 and 19

Derivative 18: A mixture of (–)-phosphaproline {51 mg, 0.338 mmol, $[\alpha]_D^{20}$ = –49.1 (*c* = 1.1, 1 M NaOH)}, TMSCl (110 mg, 1.01 mmol, 0.128 mL, 3 equiv.) and dry pyridine (2 mL) was heated at 60 °C until the substrate had dissolved (10 min.). The solution was allowed to cool to room temp., (*S*)-(–)-1-phenylethyl isocyanate (0.150 g, 1.014 mmol, 0.145 mL, 3 equiv.) was then added, and stirring was continued for 18 h, after which a crystalline precipitate had formed. Water (0.5 mL) was added and volatile components were removed under reduced pressure (0.5 mbar, 30 °C). Water (5 mL) was added to the residue. The mixture was filtered and the filtrate was applied to Dowex 50, H^+ (column: 1 cm i.d. × 12 cm, elution with water, fractions of 25 mL). Product-containing fractions (TLC: *i*PrOH/H_2O/25% NH_3 6:3:1; Ce(IV)/ammonium molybdate) number 1 and 2 were pooled and concentrated under reduced pressure. The residue was dissolved in dry MeOH and esterified with freshly distilled ethereal CH_2N_2. The solution was concentrated under reduced pressure and the residue was flash chromatographed (AcOEt/MeOH 5:1, R_f = 0.68) to give the derivative **18** (083 mg, 76%) as a colourless oil; needles were obtained by allowing the solvent to evaporate slowly from a solution in CH_2Cl_2/hexanes; m.p. 107–108 °C. $[\alpha]_D^{20}$ = –37.69 (*c* = 0.65, acetone). ^1H NMR: δ = 1.44 (d, *J* = 6.8 Hz, 3 H), 1.77–1.87 (m, 1 H), 1.92–2.03 (m, 1 H), 2.06–2.22 (m, 2 H), 3.25 (ddd, *J* = 10.4, 7.6, 3.9 Hz, 1 H), 3.60–3.69 (m, 1 H), 3.73 (d, *J* = 10.1 Hz, 3 H), 3.74 (d, *J* = 10.6 Hz, 3 H), 4.07 (dd, *J* = 8.7, 4.0 Hz, 1 H), 4.89 (≈quint, *J* = 7.2 Hz, 1 H), 6.43 (br. s, 1 H), 7.16–7.39 (m, 5 H) ppm. ^{13}C NMR: δ = 23.4, 23.9 (d, *J* = 1.6 Hz), 28.0 (d, *J* = 1.4 Hz), 47.2 (d, *J* = 2.3 Hz), 50.6, 52.7 (d, *J* = 7.7 Hz), 54.2 (d, *J* = 166.0 Hz), 54.2 (d, *J* = 6.9 Hz), 126.0 (2 C), 126.8, 128.4 (2 C), 145.1, 157.7 ppm. ^{31}P NMR: δ = 28.9 ppm. IR (Si): $\tilde{\nu}$ = 3316, 2957, 1645, 1538, 1375, 1223, 1182, 1030 cm^{-1}. $C_{15}H_{23}N_2O_4P$ (326.32): calcd. C 55.21, H 7.10, N 8.58; found C 55.34, H 6.95, N 8.55.

Derivative 19: (–)-Phosphaproline (66 mg, 0.437 mmol, was converted into **19** (0.114 g, 80%), as a colourless oil, by use of the procedure for the preparation of **18** except that (*S*)-(–)-1-phenylethyl isocyanate was replaced by the *R* (+) enantiomer. The crude derivative was flash chromatographed (AcOEt/EtOH 10:1, R_f = 0.35). Colourless needles were obtained by allowing the solvent to evaporate slowly from a solution in CH_2Cl_2/hexanes; m.p. 97–98 °C. $[a]_D^{20}$ = –108.71 (*c* = 1.24, acetone). ^{1}H NMR: δ = 1.48 (d, *J* = 6.5 Hz, 3 H), 1,76–1.86 (m, 1 H), 1.91–2.22 (m, 3 H), 3.29 (ddd, *J* = 10.6, 7.8, 4.0 Hz, 1 H), 3.62–3.70 (m, 1 H), 3.74 (d, *J* = 10.6 Hz, 3 H), 3.80 (d, *J* = 10.4 Hz, 3 H), 4.01 (dd, *J* = 8.9, 3.8 Hz, 1 H), 4.95 (quint, *J* = 6.5 Hz, 1 H), 7.17–7.22 (m, 1 H), 6.50 (br. s, 1 H), 7.26–7.36 (m, 4 H) ppm. ^{13}C NMR: δ = 22.9, 23.8, 28.0 (d, *J* = 1.4 Hz), 47.2 (d, *J* = 2.3 Hz), 50.4, 52.7 (d, *J* = 7.7 Hz), 54.18 (d, *J* = 6.5 Hz), 54.19 (d, *J* = 166.0 Hz), 126.1 (2 C), 126.8, 128.4 (2 C), 145.0, 157.9 ppm. ^{31}P NMR: δ = 28.8 ppm. IR (Si): $\tilde{\nu}$ = 3306, 2956, 1636, 1540, 1375, 1223, 1031 cm^{-1}. $C_{15}H_{23}N_2O_4P$ (326.32): calcd. C 55.21, H 7.10, N 8.58; found C 55.60, H 6.95, N 8.61.

(*R*)-(–)-Diisopropyl (1-Azido-5-chloropentyl)phosphonate [(*R*)-(–)-22]: This compound was prepared by General Procedure C from (*S*)-(+)-**6c** {500 mg, 1.74 mmol, $[a]_D^{20}$ = +14.9 (*c* = 1.1, acetone)}; R_f = 0.26 (hexanes/acetone 5:1). $[a]_D^{20}$ = –53.8 (*c* = 1.0. acetone); yield 81%; oil. ^{1}H NMR: δ = 1.29 (d, *J* = 6.0 Hz, 3 H), 1.30 (d, *J* = 6.0 Hz, 9 H), 1.44–1.88 (m, 6 H), 3.26 (ddd, *J* = 3.0, 10.5, 12.0 Hz, 1 H), 3.48 (t, *J* = 6.5 Hz, 2 H), 4.72 (m, 2 H) ppm. ^{13}C NMR: δ = 24.0 (d, *J* = 4.6 Hz, 2 C) 24.11 (d, *J* = 3.8 Hz, 2 C), 24.14 (d, *J* = 13.8 Hz), 27.9 and 31.9, 44.4, 57.7 (d, *J* = 157.6 Hz), 71.75 and 71.82 (d, *J* = 6.9 Hz) ppm. IR (NaCl): $\tilde{\nu}$ = 2981, 2936, 2872, 2103, 1454, 1386, 1376, 1353, 1254, 1178, 1142, 1106, 989 cm^{-1}. $C_{11}H_{23}ClN_3O_3P$ (318.32): calcd. C 42.38, H 7.44, N 13.48; found C 42.68, H 7.23, N 13.53.

(*R*)-(–)-(Piperidin-2-yl)phosphonic Acid [(*R*)-Phosphapipecolic Acid, (*R*)-(–)-4]: A solution of (*R*)-(–)-**22** {408 mg, 1.309 mmol, $[a]_D^{20}$ = –53.8, (*c* = 1.0, acetone)}, Ph_3P (412 mg, 1.57 mmol) and dry CH_3CN (18 mL) was stirred under argon for 1 h at 40 °C and for 24 h at reflux. Evaporation of the solvent yielded the cyclic intermediate (*R*)-**24**. [Assignable signals of the NMR spectra of the crude product are given: ^{1}H NMR (CD_3OD): δ = 0.94, 1.12 and 1.30 [d, *J* = 6.0, 3 H, OCH(C*H*$_3$)$_2$], 1.25 [d, *J* = 6.5, 3 H, OCH(C*H*$_3$)$_2$], 3.28 (m, 2 H, CH_2N), 3.90 (m, 1 H, CHP), 4.39 and 4.70 [m, 1 H, OC*H*(CH$_3$)$_2$] ppm. ^{13}C NMR (CD_3OD): δ = 24.5 and 24.9 (d, *J* = 3.8), 24.7 (d, *J* = 4.6), 24.8 (d, *J* = 5.3), 20.6 and 25.0, 26.7 (t, *J* = 3.1), 47.8, 53.01 (d, *J* = 156.8), 74.2 and 74.8 (d, *J* = 7.6) ppm.] The crude product was heated with aq. NaOH (15 mL, 0.25 M) for 5 h at 100 °C. The solvent was evaporated under reduced pressure and the residue was taken up in HCl (6 M, 15 mL), which was then heated at reflux for 24 h. After evaporation of the solvent under reduced pressure and drying (KOH) of the residue in a vacuum desiccator, the crude product was purified by ion-exchange chromatography on Dowex 50, H^+ (150 mL) with water as eluent. Ninhydrin-positive fractions were pooled, concentrated under reduced pressure and finally lyophilized; m.p. 254–257 °C (dec.) (ref.[12] 230 °C). $[a]_D^{20}$ = –4.3 (*c* = 0.7, 1 M NaOH), {ref. $[a]_D^{20}$ = –4.5 (*c* = 1.0, 1 M NaOH), *ee* > 95%[12]}; yield 55%; crystalline solid. ^{1}H NMR (D_2O): δ = 1.46 and 2.04 (m, 1 H), 1.62 and 1.84 (m, 2 H), 2.95 (dt, *J* = 3.0, 12.8 Hz, 1 H), 3.13 (dt, *J* = 2.7, 12.9 Hz, 1 H), 3.36 (m, 1 H) ppm. ^{13}C NMR (D_2O): δ = 22.0 (d, *J* = 11.5 Hz), 22.1, 24.3 (d, *J* = 2.3 Hz), 46.2 (d, *J* = 6.9 Hz), 54.7 (d, *J* = 143.0 Hz) ppm. ^{31}P NMR (D_2O): δ = 12.8 ppm. IR (Nujol): $\tilde{\nu}$ = 3147, 2523, 1626, 1405, 1352, 1309, 1237, 1228, 1164, 1133, 1069, 1026, 982 cm^{-1}. $C_5H_{12}NO_3P$ (165.13): calcd. C 36.37, H 7.32, N 8.48; found C 36.15, H 7.09, N 8.35.

X-ray Structure Determination of the (–)-Phosphaproline Derivatives 18 and 19: X-ray data were collected with a Bruker Kappa APEX-2 CCD area detector diffractometer and use of graphite-monochromated Mo-K_α radiation (λ = 0.71073 Å) and 0.5° ϕ- and ω-scan frames. Corrections for absorption and $\lambda/2$ effects were applied.[23] After structure solution with the SHELXS97 program and direct methods, refinement on F^2 was carried out with the SHELXL97 program.[24] Non-hydrogen atoms were refined anisotropically. H atoms were placed in calculated positions and thereafter treated as riding. The absolute structures could be unambiguously determined by anomalous dispersion effects and the Flack absolute structure parameter (*FASP*). Important crystallographic data are:

Compound 18: $C_{15}H_{23}N_2O_4P$, M_r = 326.32, colourless prism from CH_2Cl_2/hexanes, 0.60 × 0.35 × 0.30 mm, monoclinic, space group $P2_1$ (no. 14), *a* = 10.7745(8) Å, *b* = 7.1982(5) Å, *c* = 10.8448(8) Å, β = 92.538(1)°, *V* = 840.27(11) Å^3, *Z* = 2, μ = 0.182 mm^{-1}, d_x = 1.290 g cm^{-3}, *T* = 100 K. 17050 reflections collected (θ_{max} = 30.0°) and merged to 4246 independent data (R_{int} = 0.029); final *R* indices (all data): R_1 = 0.0447, wR_2 = 0.1113, 202 parameters, *FASP* = –0.01(9). This solid showed weak superstructure reflections at low Bragg angles and *T* = 100 K consistent with a *C*-centred unit cell with *a*-axis doubled and *c*-axis sextupled. This superstructure was neglected for this work and only the substructure given above is reported. The feature essentially affects the phenyl C atoms, which exhibit anomalously anisotropic displacement ellipsoids in the $P2_1$ substructure.

Compound 19: $C_{15}H_{23}N_2O_4P$, M_r = 326.32, colourless block from CH_2Cl_2/hexanes, 0.49 × 0.44 × 0.23 mm, orthorhombic, space group $P2_12_12_1$ (no. 19), *a* = 6.9309(6) Å, *b* = 10.5631(9) Å, *c* = 22.774(2) Å, *V* = 1667.3(2) Å^3, *Z* = 4, μ = 0.184 mm^{-1}, d_x = 1.300 g cm^{-3}, *T* = 100 K. 36029 reflections collected (θ_{max} = 30.0°) and merged to 4865 independent data (R_{int} = 0.023); final *R* indices (all data): R_1 = 0.0238, wR_2 = 0.0644, 206 parameters, *FASP* = 0.01(4).

CCDC-780395 (for **18**) and -780396 (for **19**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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