133. Dipeptide Derivatives with a Phosphonate Instead of Carboxylate Terminus by *C*-Alkylation of Protected (Decarboxy-dipeptidyl)phosphonates

by **Christian Gerber**[1]) and **Dieter Seebach***

Laboratorium für Organische Chemie der Eidgenössischen Technischen Hochschule, ETH-Zentrum, Universitätstrasse 16, CH-8092 Zürich

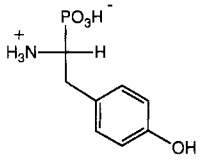
Dedicated to Prof. *Horst Prinzbach* on the occasion of his 60th birthday

(10.V.91)

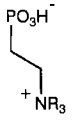
Z-Protected diphenyl (decarboxy-dipeptidyl)phosphonates **5a–c** with a (decarboxysarcosinyl)phosphonate moiety are prepared from Z-L-alanine (**1a**), Z-L-valine (**1b**), and Z-L-phenylalanine (**1c**) by the following series of steps: coupling with methyl sarcosinate (→ **2a–c**), saponification (→ **3a–c**), *Hofer-Moest* oxidative decarboxylation by electrolysis in MeOH (→ **4a–c**), and *Arbuzov* reaction with $P(OPh)_3/TiCl_4$ (*Scheme 3*). Double deprotonation and alkylation lead to non-stereoselective incorporation of side chains next to the phosphonate group (products of type **6–8**, nine examples, see *Scheme 4*). In the cases of **6a–c** and **8c**, the diastereoisomers could be separated and the configuration of the newly formed stereogenic center deduced. We assign the L,D-configuration to the diastereoisomers for which the ^{31}P-NMR signal appears at higher field.

Aminophosphonic acids with the amino group in the α-, β-, γ-, or δ-position [1–4] are natural products (*Scheme 1*); they are employed as pesticides [5], and they have been incorporated into peptides to mimic the tetrahedral intermediate of hydrolysis of an

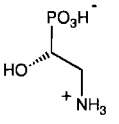
Scheme 1. *Some Naturally Occurring Aminophosphonic Acids*



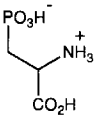
Component of K-4 (an ACE Inhibitor) [1]



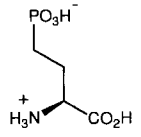
(2-Aminoethyl)-phosphonic acid (AEP), Ciliatin [2a]



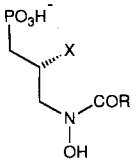
Hydroxy-ciliatin [2b]



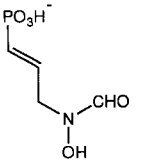
3-Phosphono-alanin [2c]



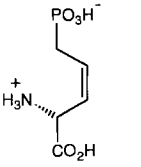
MP-101 [3a]



FR-31564 (X = H, R = H) [3b]
FR-900098 (X = H, R = CH_3) [3b]
FR-33289 (X = OH, R = CH_3) [3b]



FR-32836 [3b]



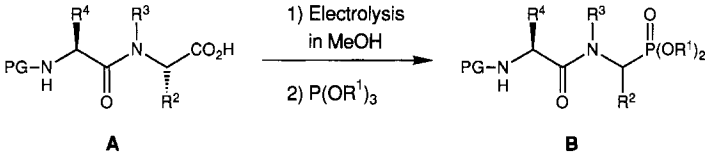
Component of Plumbemycin A (an antagonist of L-threonine) [4]

[1]) Part of the Ph. D. thesis of *C. G.* (Dissertation No. 9441, ETH Zürich, 1991).

amide bond [6]. Normally, aminophosphonic-acid containing peptides are constructed from the corresponding building blocks, and there are now numerous methods available for preparing α-aminophosphonic acids[2]).

Five years ago, we showed that oligopeptides with C-terminal modification by replacement of carboxylate with phosphonate could be readily prepared using an electrochemical key step [8]: as indicated in *Scheme 2* for a dipeptide, the Z-protected peptide **A** is decarboxylated by anodic oxidation in MeOH which gives an intermediate N,O-acetal

Scheme 2. *Preparation of Dipeptides with a Phosphonate instead of Carboxylate C-Terminus from Normal Dipeptides, and C-Alkylation of Sarcosine Moieties within a Peptide*



A **B**

R^1 = Me, Et, Ph; R^2, R^4 derived from various amino-acid side chains
R^3 = H, Me; PG = H, protecting group (BnOCO) or part of proline ring

C **D**

(RCON(R^3)–CHR^2–OMe), the MeO group of which can be replaced by a phosphono group. This quite general method provides simple access to a variety of modified peptides from normal ones (prepared in the usual way). Recently [9], we have also shown that it is possible to modify certain peptides by *C*-alkylating sarcosine units within the backbone through polylithiated species (see **C** → **D** in *Scheme 2*).

We wondered whether it would be feasible to combine these two 'protocols', and the results of our corresponding experiments are described here.

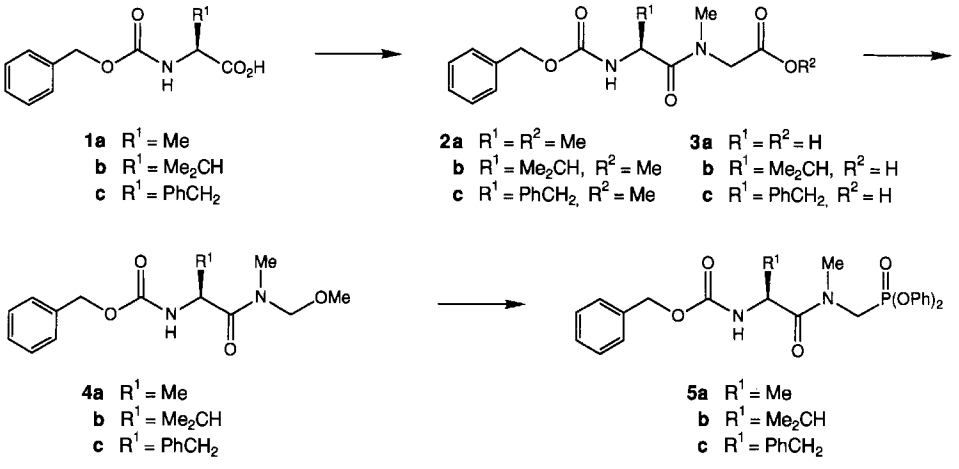
As outlined in *Scheme 3*, the commercially available benzyloxycarbonyl (Z)-protected L-alanine, L-valine, and L-phenylalanine **1a–c** were coupled with methyl sarcosinate using the mixed-anhydride ($ClCO_2Et$) or, preferably, the BOP-Cl method (bis(2-oxooxazolidin-3-yl)phosphinic chloride)[3]). The Z-dipeptide methyl esters **2a–c** thus obtained in

---

[2]) By addition of phosphites to the C=N bond of, *e.g.* (chiral) imines [7a] or nitrones [7b]; by reductive amination of α-ketophosphonates [7c]; by stereoselective [3 + 2] cycloaddition of ethylene to a nitrone [7d]; by alkylation of (chiral) imines of (1-aminomethyl)phosphonates with halogeno alkanes [7e] or α,β-unsaturated esters [7f]; through reactions of diethyl (isocyanomethyl)phosphonate with halogeno alkanes [7g], isocyanates of amino acids [7h], or aldehydes [7i], with a chiral catalyst in the latter case.

[3]) The yield and the purity of products were higher using the BOP-Cl method, see the discussion and references in [9]. Since epimerization was not a problem in our previous work on peptide coupling with the BOP-Cl method [9], on transformations of peptides involving acyliminium ions [8b], and on alkylations of polylithiated peptides [9], we had no reason to check the enantiomeric excess of the products **2–8** described here (which were found to be optically active at least at one stage between the starting materials **1** and the free amino phosphonic acids **9**, **10**).

Scheme 3. *Preparation of the Decarboxy-dipeptidyl Phosphonates for the C-Alkylations*



essentially quantitative yield were saponified in aqueous MeOH at pH 11 (40°) to give the Z-protected L-alanyl- (**3a**), L-valyl- (**3b**), and L-phenylalanylsarcosines (**3c**), again in $\geq 95\%$ yield. The electrolyses were carried out in MeOH (*ca.* 20% or 0.5M solution) with the vessel (cooling jacket, 0–6°, cryostat) and power supply described previously [8]. The electrolyte was generated by adding 2–5% Et_3N. The resulting N,O-acetals **4a–c** were chromatographed on silica gel, the yields of oily or resin-type products being *ca.* 80%.

For the *Arbuzov* reaction with which the MeO group was replaced by a phosphono group, various phosphites (methyl, ethyl, aryl) can be employed[4]). We chose triphenyl phosphite, hoping that the products would have a greater tendency to crystallize, would be more readily purifiable, and – in the case of diastereoisomers – more easily separable. A CH_2Cl_2 solution of the N,O-acetals **4a–c** and 1.1–1.5 equiv. of $P(OPh)_3$ was cooled to dry-ice temperature and combined with 1.1 equiv. of $TiCl_4$; the reaction either commenced during warming to room temperature overnight (→ **5a, b**) or was enforced by refluxing the dark brown mixture for 1 h (→ **5c**, *Scheme 3*). Workup and chromatography led to the colorless, resinous phosphonates **5a–c** in 60–70% yield. Up to this point, all reactions were carried out on a 7–30-g scale, including the purification steps.

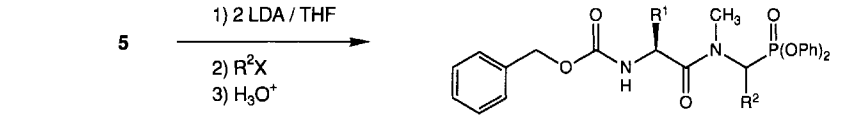
Treatment of THF solutions of phosphonates **5** first with 2.3 equiv. of lithium diisopropylamide (LDA) and then with an alkyl halide[5]) at temperatures between −78 and 0°, workup, and chromatography gave the Z-protected dipeptide ester analogues **6–8**, with a *N*-methyl-substituted diphenyl (2-decarboxyalaninyl)-, (2-decarboxy-3-vinyl-alaninyl)-, and (2-decarboxyphenylalaninyl)phosphonate end group, respectively, in yields ranging from 40 to 70% (*Scheme 4*). The reactions were essentially unselective, yielding 1.2:1–2.2:1 mixtures of diastereoisomers. In all cases (except for **7a**), the ^{31}P-

[4]) *Shono* and coworkers have also described both electrolyses of simple dipeptides and *Michaelis-Arbuzov* reactions with electrochemically generated non-peptide-derived *N*-acyl-N,O-acetals (through intermediate acyliminium ions) [10].

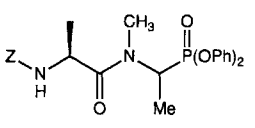
[5]) Reactions of the lithiated phosphonate with other electrophiles are conceivable, but have not been tested. Thus, an olefination of aldehydes by **5** (*Horner-Emmons-Wadsworth*) might provide enamide-type end groups which would be ready for further conversions.

NMR signal of the major product appeared at lower field than that of the minor component. In those four cases in which we separated the diastereoisomers by preparative HPLC, the major product had a lower $[\alpha]_D$ value than the minor product. Comparing the set of data ($[\alpha]_D$ values and ^{31}P-NMR shifts) obtained for the enantiomerically pure alkylation products **6a–c** and **8c** with the corresponding set of data from the previously published non-*N*-methylated compounds, we propose the absolute configuration of the former as shown in *Scheme 4* and the *Table*.

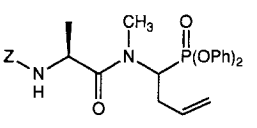
Scheme 4. *Products of Alkylation of Lithiated Phosphonates* **5** *with MeI, 1-Bromoprop-2-ene, and* $PhCH_2I$



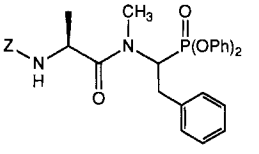
6 R^2 = Me (mixture of epimers)
7 R^2 = CH_2=$CHCH_2$ (mixture of epimers)
8 R^2 = $PhCH_2$ (mixture of epimers)



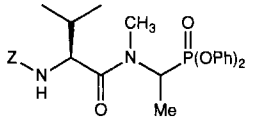
L,L- and L,D-**6a**
(40%, 2 : 1)[a])



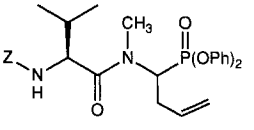
L,L- and L,D-**7a**
(69%, 1 : 1.6)



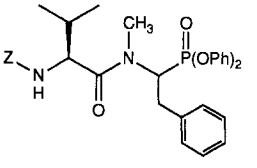
L,L- and L,D-**8a**
(43%, 1.8 : 1)



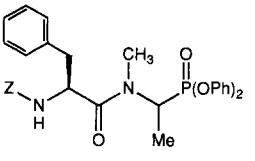
L,L- and L,D-**6b**
(63%, 1.8 : 1)[a])



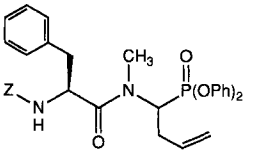
L,L- and L,D-**7b**
(49%, 1.5 : 1)



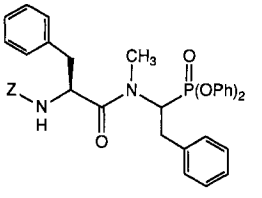
L,L- and L,D-**8b**
(62%, 1.2 : 1)[b])



L,L- and L,D-**6c**
(39%, 1.3 : 1)[a])



L,L- and L,D-**7c**
(38%, 2 : 1)[b])



L,L- and L,D-**8c**
(51%, 2.2 : 1)[a])

[a]) Successful preparative separation of the corresponding diastereoisomers.
[b]) Successful analytical separation of the corresponding diastereoisomers.

Table. *Comparison of Selected Physical Data of the Enantiomerically Pure Dipeptide Analogues of Known Absolute Configuration with the Related* N-*Methylated Compounds* **6a–c**, *and* **8c**. Their configuration is proposed as indicated.

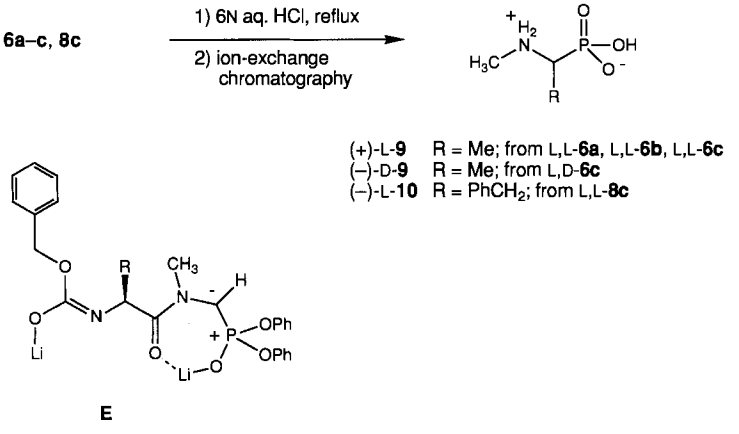
Protected dipeptide analogue[a]		$[\alpha]_D$ in EtOH		Chemical shift δ in the ^{31}P-NMR spectra [ppm]		HPLC retention times[b] [min]	
		L,L	L,D	L,L	L,D	L,L	L,D
Z-Ala-'Ala'-PO(OPh)$_2$	[8b]	− 36	+ 16	18,5	18,4	10,5	13,1
Z-Leu-'Ala'-PO(OPh)$_2$	[8b]	− 29	+ 7	18,60	18,55	16,6	14,1
Z-Val-'Leu'-PO(OMe)$_2$	[8b]	− 34	+ 23	28,11	28,05	11,6	9,8
Z-Pro-'Leu'-PO(OMe)$_2$	[8b]	− 63	− 10	28,7	28,4	13,0	10,2
Z-Ala-Me'Ala'PO(OPh)$_2$	**6a**	− 59	+ 23	17,5	16,5	*9,4*	13,0
Z-Val-Me'Ala'-PO(OPh)$_2$	**6b**	− 59	+ 18	17,9	17,2	*16,1*	13,8
Z-Phe-Me'Ala'-PO(OPh)$_2$	**6c**	− 38	+ 18	17,7	17,0	*12,6*	10,3
Z-Phe-Me'Phe'-PO(OPh)$_2$	**8c**	− 51	+ 27	16,5	15,8	*19,0*	21,4

[a]) Amino-acid symbols between inverted commas indicate that the COOH group is removed and replaced by the group on the right of this symbol; the configuration may be L or D.

[b]) For details, see *Exper. Part.* The t_R value of the major product from the alkylation is given in italics.

As can be seen from *Scheme 5*, hydrolysis of the enantiomerically pure **6a–c** and **8c** gave the amino phosphonic acids **9** and **10**, respectively, which were isolated by ion-exchange chromatography.

Scheme 5. *Hydrolysis of Some Decarboxy-dipeptidyl Phosphonates and Isolation of* N-*Methyl-aminoethanephosphonic Acids*. Possible structure of the nucleophilic reagent which is alkylated non-stereoselectively.



Although we have not conducted any structural investigations, it may be inferred from work on lithiated phosphonates [11] and carbox amides [12] that the dilithiated derivatives, which are actually alkylated in the present study, bear one of the Li-atoms on the O-atom of the phosphonate and the other one on the O-atom of the carbamate moiety in (*Z*)-form (**E** in *Scheme 5*).

Experimental Part

General. THF was freshly distilled from K under Ar. Z-L-Ala (**1a**), Z-L-Val (**1b**), Z-L-Phe (**1c**), $P(OPh)_3$, MeI, allyl chloride, and benzyl bromide were purchased from *Fluka*. The donation of Sar-OMe by *Lonza AG*, Visp, is gratefully acknowledged. LDA solns. were prepared by adding an equimolar amount of BuLi (*ca.* 1.5M in hexane) to $(i\text{-}Pr)_2NH$ in THF at 0°. Org. extracts were dried ($MgSO_4$) and evaporated using a rotary evaporator. TLC: *Merck* silica gel *60* F_{254} anal. plates; solvent as indicated for LC; solvent for the free amino and aminophosphonic acids was EtOH/25% NH_3 soln./conc. NaCl soln. 7:2:1; detection either by UV or by dipping in a 0.2% soln. of ninhydrin in BuOH/AcOH/H_2O 140:1:6, in a 3% soln. of anisaldehyde in EtOH/H_2SO_4/AcOH 55:2:1, or in a 5% soln. of $(NH_4)_2MoO_4$ in H_2O/H_2SO_4 17:3 followed by heating with a hot-air blower. LC: at 0.3–0.5 bar, *Merck* silica gel *60* (230–400 mesh). Anal. HPLC: pump system *Kontron* with two pumps; mixing chamber; programmer *200;* UV detector *Uvikon LCD-75;* integrator *Shimadzu C-R1B;* columns, 4 × 250 mm *Lichrosorb Si 60* (7 μm; *Knauer*), 4 × 250 mm *Chiraspher* (5 μm; *Merck*), 4 × 250 mm *Spherisorb S5 ODS 2* (5 μm; *Merck*); flow 1 ml/min. Prep. HPLC: pump system *Knauer* with two pumps type *64* (prep. heads); programmer *50;* compensating line writer; columns, 32 × 250 mm *Lichrosorb Si 60* (7 μm; *Knauer*) or 25 × 250 mm *Chiraspher* (5 μm; *Merck*) solvents as indicated: MeCN, hexane, and cyclohexane from *Macherey-Nagel,* i-PrOH from *Fluka*. M.p.: *Büchi-510* apparatus, uncorrected. Optical rotations: 10-cm, 1-ml cell, *Perkin-Elmer-241* polarimeter. IR spectra: in $CHCl_3$ unless otherwise stated; *Perkin-Elmer-782* spectrophotometer. ^{1}H-NMR (relations of isomers from integration), ^{13}C-NMR (relations of isomers from signal intensities), and ^{31}P-NMR spectra (relation of isomers from integration, otherwise stated): if not otherwise stated in $CDCl_3$ at r.t., *Bruker-WM-300* (300, 75, 121 MHz), *Varian-FT-80A* (80 MHz). Amino-acid numbering is retained for 2-decarboxylated amino-acid residues.

General Procedure for Peptide Couplings with $ClCO_2Et$. To a stirred, *ca.* 0.4M soln. of the Z-protected amino acid **1** in CH_2Cl_2 or $CHCl_3$/toluene 1:1 was added dropwise at −15° 1 equiv. of Et_3N followed by 1 equiv. of $ClCO_2Et$. After 75 min, the resulting suspension was combined with a precooled (*ca.* −20°), *ca.* 0.4M soln. of 1.05 equiv. of Sar-OMe·HCl and 1.06 equiv. of Et_3N in CH_2Cl_2 or $CHCl_3$. A slight rise of temp. was observed (→ −10°). The mixture was stirred for 1.5–2 h, then slowly warmed to r.t. by removing the cooling bath, and subsequently heated to 40–50° until no more CO_2 was evolved. Aq. workup (1M H_2SO_4, $NaHCO_3$, brine), drying of the org. phases, and evaporation gave crude Z-Xaa-Sar-OMe **2**.

General Procedure for Peptide Coupling with BOP-Cl. To a stirred, *ca.* 0.25M soln. of the Z-protected amino acid **1** in CH_2Cl_2 were added at −15 to −20° 2 equiv. of *Hünig* base ($(i\text{-}Pr)_2NEt$) followed by 1.1 equiv. of BOP-Cl. The heavy suspension was stirred for 2 h at ≤ −15° and then treated dropwise with a *ca.* 0.4M soln. of 0.95 equiv. of Sar-OMe·HCl and 0.95 equiv. of *Hünig* base in CH_2Cl_2. The cooling bath was removed after 2 h and the mixture stirred for 12 h. The light suspension was filtered and the solvent removed. Aq. workup (1M H_2SO_4, $NaHCO_3$, brine) of the residue dissolved in Et_2O, drying of the org. phases, and evaporation gave crude Z-Xaa-Sar-OMe **2**.

General Procedure for Methyl-Ester Hydrolysis. To a soln. of the Z-protected dipeptide methyl ester **2** in MeOH (*ca.* 0.4M) was added H_2O until an emulsion began to form; this was redissolved by addition of a small amount of MeOH. This soln. was treated continuously with 1M NaOH to constant pH (*i.e.* pH 11) at 40° until completion of the reaction. The soln. was neutralized with 1M H_2SO_4 (pH *ca.* 4), and MeOH was evaporated. The residue was treated with sat. Na_2CO_3 soln. or 1M NaOH to reach pH 9–11 and washed 2 or 3 times with AcOEt or CH_2Cl_2, followed by acidification with 1M H_2SO_4 (→ pH ≤ 1) and extraction with AcOEt, CH_2Cl_2, or Et_2O. Final workup as indicated (see *General*) gave product **3** which was used for the subsequent anodic oxidation.

General Procedure for Anodic Oxidations of Z-Protected Dipeptides. A *ca.* 0.6M soln. of dipeptide **3** in MeOH and an amount of Et_3N as specified for the individual reactions (*ca.* 5 mol-%) was electrolyzed galvanostatically at ≤ 20° with *ca.* 2.5 $F \cdot mol^{-1}$ (current density $i \approx 200$ $mA \cdot cm^{-2}$). The residue obtained from evaporation of the reaction mixture was dissolved in CH_2Cl_2 and washed with 5% $NaHCO_3$ soln. and brine. Final workup as indicated (see *General*) gave crude **4**.

General Procedure for $TiCl_4$*-Mediated* Michaelis-Arbuzov *Reactions with N,O-Acetals.* To a *ca.* 0.25M soln. of **4** and 1.1–1.5 equiv. of $P(OPh)_3$ in CH_2Cl_2 under Ar at −78° were added dropwise 1.1 equiv. of $TiCl_4$ (either neat or as a *ca.* 2M soln. in CH_2Cl_2) over 10 min. The dark brown soln. was warmed to r.t. overnight and then combined with a 1.25-fold volume of a suspension of 1.75 equiv. of $Na_2CO_3 \cdot 10\ H_2O$ in CH_2Cl_2. After being stirred for 30 min at r.t., the suspension was filtered and evaporated to give the crude phosphonate **5**.

General Procedure for the Alkylation of Diphenyl {$N^{2,1}$*-[(Benzyloxy)carbonyl]-2.2-decarboxy-dipeptid-2.2-yl}phosphonates.* To a soln. of 2.3 equiv. of *ca.* 0.4M LDA was added a *ca.* 0.5M soln. of phosphonate **5** in THF at ≤ −50°. The electrophile was added in one portion at −78° after 50 min. The soln. was stirred for the time and at the

temp. indicated and then treated with an aq. soln. of a base, a phosphate buffer (pH 5), or an acid followed by AcOEt or Et_2O. This mixture was then washed either with sat. $NaHCO_3$ soln., 1M H_2SO_4, again with $NaHCO_3$, and finally with brine (previous addition of a base), or with 1M H_2SO_4, sat. $NaHCO_3$ soln., and brine (previous addition of acid or buffer soln.). Drying and removal of solvent gave crude **6**, **7**, or **8**.

General Procedure for Total Hydrolysis of Diphenyl $N^{2.1}$*-[(Benzyloxy)carbonyl]-2.2-decarboxy-dipeptid-2.2-yl}phosphonates.* An emulsion of phosphonate **6** or **8** in at least 6M HCl was refluxed until the hydrolysis was complete (TLC). The brownish yellow mixture was washed with Et_2O or CH_2Cl_2 and evaporated. The remaining solid was dissolved in a minimum amount of H_2O and chromatographed on *Dowex 50 W* × *8* (H^+ form) with H_2O. The resulting aminophosphonic acid was crystallized from H_2O/MeOH.

Methyl $N^{2.1}$*-[(Benzyloxy)carbonyl]-*L*-alanylsarcosinate* (**2a**). To the mechanically stirred soln. of **1a** (25.1 g, 0.100 mol) and Et_3N (14 ml, 0.10 mol) in toluene and CH_2Cl_2 (150 ml each) was added dropwise $ClCO_2Et$ (9.5 ml, 0.10 mol) at −15° within 3 min. The mixture was stirred for 75 min at ≤ −13°, during which time a suspension formed. A soln. of Sar-OMe·HCl (14.7 g, 0.105 mol) and Et_3N (14.7 ml, 0.106 mol) in CH_2Cl_2 (300 ml) at −20° was added in one portion ($T \rightarrow -14°$). The mixture was raised to 3° during 90 min, kept for another 90 min at 40°, washed 3 times each with 1M H_2SO_4, sat. $NaHCO_3$ soln., and brine, dried, and evaporated to give 26.7 g of crude product. LC (SiO_2 (8 × 20 cm), hexane/AcOEt 2:3 to 3:7) yielded 19.6 g (64%) of **2a**. Colorless oil. $[\alpha]_D = -31.0$ ($c = 2.9$, EtOH). IR (film): 3280*w*, 3040*w*, 2940*m*, 1740*s*, 1710*s*, 1650*s*, 1540*m*, 1510*w*, 1210*s*, 740*m*, 695*m*. ^{1}H-NMR (80 MHz, (D_6)DMSO, 150°): 1.28 (*d*, $J = 7$, Me(3.1)); 3.06 (*s*, MeN); 3.66 (*s*, MeO); *ca.* 4.1, 4.2 (*AB*, $J \approx 16$, 2 H–C(2.2)); 4.55 (*quint.*, $J \approx 7$, H–C(2.1)); 5.05 (*s*, PhCH_2); 6.7 (br., NH); 7.34 (*s*, 5 arom. H).

$N^{2.1}$*-[(Benzyloxy)carbonyl]-*L*-alanylsarcosine* (**3a**). According to the general procedure **2a** (19.6 g, 63.6 mmol) was hydrolyzed: 17.7 g (95%) of **3a**. Colorless resin. $[\alpha]_D = -24.9$ ($c = 3.0$, EtOH). IR (film): 3280 (br.), 3040*w*, 3020*w*, 2960*w*, 2920*w*, 2580*w*, 1720 (br.), 1660 (br.), 1510 (br.), 1490*s*, 1450*m*, 1400*m*, 1370*w*, 1240*m*, 1210*s*, 1060*s*, 740*m*, 690*m*. ^{1}H-NMR (80 MHz, ≥ 60°): 1.3 (*d*, $J = 7$, Me(3.1)); 3.05 (*s*, MeN); 3.94, 4.21 (*AB*, $J \approx 18$, 2, 2 H–C(2.2)); 4.65 (*quint.*, $J = 7$, H–C(2.1)); 5.12 (*s*, PhCH_2); 5.75 (br. *d*, $J = 7$, NH); 7.25 (*s*, 5 arom. H); 8.35 (br. *s*, OH).

N^2*-[(Benzyloxy)carbonyl]-*N^1*-(methoxymethyl)-*N^1*-methyl-*L*-alaninamide* (**4a**). According to the general procedure, a soln. of **3a** (17.7 g, 60.2 mmol) and Et_3N (0.36 ml, 4.9 mmol, 8 mol-%) in MeOH (110 ml) was electrolyzed at 0–3° with 12780 C (2.2 F·mol^{-1}, $i = 150$ mA·cm^{-2}): 17 g. LC (8 × 20 cm, hexane/AcOEt 3:2 to 1:1) gave 13.09 g (78%) of **4a**. Colorless oil. IR (film): 3309*m*, 2937*m*, 1718*s*, 1655*s*, 1528*s*, 1455*s*, 1405*s*, 1247*s*, 1065*s*, 1029*s*, 954*w*, 913*m*, 741*m*, 699*m*. ^{1}H-NMR (300 MHz): 1.34, 1.36 (2*d*, $J = 6.8$, 7.0, *ca.* 1:1, Me(3)); 3.00, 3.06 (2*s*, 1.2:1, MeN); 3.25, 3.23 (2*s*, 1.2:1, MeO); 4.56, 4.88 and 4.76, 4.83 (2 *AB*, $J = 10.7$ and 9.9, MeOCH_2); 4.66–4.82 (*m*, H–C(2)); 5.06, 5.10 and 5.09 (*AB* and *s*, $J = 12.3$, PhCH_2); 5.85 (br., NH); 7.28–7.34 (*m*, 5 arom. H). ^{13}C-NMR (75 MHz): 18.7, 19.6 (C(3)); 33.2, 34.0 (MeN); 46.9, 47.2 (C(2)); 55.4, 55.8 (MeO); 66.7 (PhCH_2); 78.0, 80.8 (MeOCH_2); 128.0, 128.5, 136.4 (arom. C); 155.6 (OCON); 173.9 (C(1)).

Diphenyl {$N^{2.1}$*-[(Benzyloxy)carbonyl]-*L*-alanyl-(2.2-decarboxysarcosin-2.2-yl)}phosphonate* (**5a**). According to the general procedure **4a** (7.219 g, 25.8 mmol) was treated with $P(OPh)_3$ (7.5 ml, 28.5 mmol) and a soln. of $TiCl_4$ (3.1 ml, 28.3 mmol) in CH_2Cl_2 (15 ml). Once r.t. was reached, more $P(OPh)_3$ (0.37 ml, 1.4 mmol) and $TiCl_4$ (155 µl, 1.4 mmol) were added. After stirring for 2 h and usual workup (→ yellow oil, 17.7 g), LC (SiO_2 (8 × 20 cm), hexane/AcOEt 1:2 to 0:1) gave **5a** (7.7 g, 62%). Colorless resin. IR (film): 3292*m*, 2956*m*, 2854*w*, 1715*s*, 1651*s*, 1535*s*, 1497*s*, 1456*s*, 1417*s*, 1376*m*, 1248*s*, 1028*s*, 912*w*, 873*s*, 832*m*, 800*m*, 743*m*, 700*m*. ^{1}H-NMR (300 MHz): 1.29, 1.36 (2*d*, $J = 6.8$, 6.6, 7:1, Me(3)); 3.17, 3.28 (2*s*, 1:7, MeN); 4.00, 4.47 (2*dd*, $J(B,P) = 9.9$, $J(A,B) = 15.6$, $J(A,P) = 11.4$, 2 H–C(2.2)); 4.70 (*quint.*, $J = 7$, H–C(2.1)); 5.09 (*s*, PhCH_2); 5.73 (*d*, $J = 7.9$, NH); 7.1–7.3 (*m*, 15 arom. H).

Diphenyl {$N^{2.1}$*-[(Benzyloxy)carbonyl]-*L*-alanyl-(2.2-decarboxy-*$N^{2.2}$*-methyl-*DL*-alanin-2.2-yl)}phosphonate* (**6a**). According to the general procedure, **5a** (2.496 g, 5.173 mmol) in THF (10 ml), the LDA soln. from $(i\text{-Pr})_2NH$ (1.70 ml, 11.99 mmol) in THF (30 ml), and MeI (350 µl, 5.622 mmol) were combined. The mixture was kept for 15 h at −78°, raised to +6° by removing the cooling bath, and treated with sat. $NaHCO_3$ soln. (10 ml) followed by AcOEt (130 ml): 1.71 g of a greenish oil. LC (SiO_2 (5 × 26 cm), hexane/AcOEt 1:1) gave L,L-**6a**/L,D-**6a** (49 mg) and 2 highly enriched fractions of first mainly L,L-**6a** (677 mg) and then mainly L,D-**6a** (338 mg), in a total yield of 40% (1.015 g). Colorless resins. The fractions containing mainly one diastereoisomer were purified by prep. HPLC.

L,L-**6a**: Prep. HPLC, *Chiraspher*, 7.5 ml·min^{-1} of 3% i-PrOH in cyclohexane. Anal. HPLC, *Lichrosorb Si 60*, 10% i-PrOH in hexane, t_R 9.4 min; *Chiraspher*, 5% i-PrOH in hexane, t_R 6.4 min. $[\alpha]_D = -59.3$ ($c = 1.2$, EtOH). ^{1}H-NMR (400 MHz): 1.23, 1.36 (2*d*, $J = 6.8$, *ca.* 10:1, Me(3.1)); 1.58, 1.70 (2*dd*, J(H,H) = 7.4, 7.2, J(H,P) = 18.1, 17.8, *ca.* 7:1, Me(3.2)); 3.07, 3.21 (2*s*, *ca.* 1:7, MeN); 4.69 (*quint.*, $J = 7$, H–C(2.1)); 5.09, 5.10 and 5.07 (*AB*, *s*, $J = 12.6$, PhCH_2); 5.61 (*qd*, J(H,H) = 7.4, J(H,P) = 19.2, H–C(2.2)); 5.71, 5.89 (2*d*, $J = 7.9$, 7.4, *ca.* 10:1, NH);

7.03–7.45 (*m*, 15 arom. H). ^{13}C-NMR (100 MHz): 12.45 (*d*, *J*(C,P) = 1.8, C(3.2)); 18.58 (C(3.1)); 31.01 (MeN); 46.11 (*d*, *J*(C,P) = 157.9, C(2.2)); 47.12 (C(2.1)); 66.81 (Ph*C*H$_2$); 120.17, 120.38 (2*d*, *J*(C,P) = 4.5, 4.2 C(2) of PhO); 125.30, 125.36 (2*d*, *J*(C,P) = 0.9, 1.1, C(4) of PhO); 128.02, 128.13, 128.53 (C(2), C(3), C(4) of *Ph*CH$_2$); 129.82, 129.84 (2*d*, *J*(C,P) = 0.8, 0.9, C(3) of PhO); 136.40 (C(1) of *Ph*CH$_2$); 150.10, 150.38 (2*d*, *J*(C,P) = 9.8, 9.9, C(1) of PhO); 155.56 (OCON); 173.16 (*d*, *J*(C,P) = 4.8, C(1.1)). ^{31}P-NMR (121 MHz): 15.5, 17.5 (*ca.* 1:20, from signal intensities).

L,D-**6a**: Prep. HPLC: *Lichrosorb Si 60*, 30 ml·min^{-1} of 7.5% i-PrOH in cyclohexane, repeated. Anal. HPLC: *Lichrosorb Si 60*, 10% i-PrOH in hexane, t_R 13.0 min; *Chiraspher*, 5% i-PrOH in hexane, t_R 7.8 min. $[\alpha]_D$ = +23.2 (*c* = 0.9, EtOH). ^{1}H-NMR (300 MHz): 1.32 (*d*, *J* = 6.8, Me(3.1)); 1.57 (*dd*, *J*(H,H) = 7.4, *J*(H,P) = 17.9, Me(3.2)); 3.12 (*s*, MeN); 4.56 (*quint.*, *J* = 7, H–C(2.1)); 5.07, 5.10 (*AB*, *J* = 12.3, PhC*H*$_2$); 5.55 (*qd*, *J*(H,H) = 7.4, *J*(H,P) = 19.4, H–C(2.2)); 5.70 (*d*, *J* = 7.7, NH); 7.04–7.37 (*m*, 15 arom. H)[6]). ^{13}C-NMR (75 MHz): 12.86 (C(2.2)); 18.80 (C(3.1)); 30.01 (MeN); 46.15 (*d*, *J* = 154.7, C(1.2)); 47.18 (C(2.1)); 66.78 (Ph*C*H$_2$); 120.13, 120.46 (C(2) of PhO); 125.31, 125.38 (C(4) of PhO); 128.09, 128.16, 128.55 (C(2), C(3), C(4) of *Ph*CH$_2$); 129.71, 129.82 (C(3) of PhO); 136.44 (C(1) of *Ph*CH$_2$); 150.04, 150.33 (2*d*, *J*(C,P) = 9.8, 10.2, C(1) of PhO); 155.30 (OCON); 172.89 (*d*, *J*(C,P) = 4.8, C(1.1)). ^{31}P-NMR (121 MHz): 16.5.

L-*[1-(Methylamino)ethyl]phosphonic Acid* (L-**9**) *from* L,L-**6a**. According to the general procedure, L,L-**6a** (211 mg, 0.425 mmol) was hydrolyzed in sat. HCl soln. (10 ml) for 2 d and in 48% HBr soln./AcOH 1:1 (10 ml) for another d: 26.1 mg (44%) of colorless L-**9**. $[\alpha]_D$ = +0.6 (*c* = 2.6, H$_2$O). ^{1}H-NMR (80 MHz, D$_2$O): 1.35 (*dd*, *J*(H,H) = 7, *J*(H,P) = 14, Me(2)); 2.70 (*s*, MeN); 3.20 (*qd*, *J*(H,H) = 7, *J*(H,P) = 14, H–C(1)). For ^{13}C-NMR and ^{31}P-NMR: see L-**9** from L,L-**6b**.

Diphenyl N$^{2.1}$-*[(Benzyloxy)carbonyl]*-L-*alanyl-(2.2-decarboxy-*N$^{2.2}$-*methyl-3.2-vinyl*-DL-*alanin-2.2-yl)phosphonate* (**7a**). According to the general procedure, **5a** (2.272 g, 4.71 mmol) in THF (10 ml), the LDA soln. from (i-Pr)$_2$NH (1.47 ml, 10.4 mmol) in THF (30 ml), and allyl bromide (0.629 g, 5.20 mmol) were combined. The soln. was kept over night at –78° and then treated with 10 ml of 1N H_2SO_4 followed by workup. LC (5 × 20 cm SiO_2, hexane/AcOEt 11:9) gave 1.372 g (69%) of two diastereoisomers **7a**. Colorless resin. ^{1}H-NMR (300 MHz): 1.23, 1.26 (2*d*, *J* = 6.8, *ca.* 1:1.6, Me(3.1)); 2.70–2.85 (*m*, 2 H–C(3.2)); 3.06, 3.17 (2*s*, 2:1, MeN); 4.53, 4.67 (2 *quint.*, *J* ≈ 7, 2:1, H–C(2.1)); 5.05–5.19 (*m*, C*H*$_2$=CH, PhC*H*$_2$); 5.53–5.74 (*m*, H–C(2.2), CH$_2$=C*H*, NH); 7.05–7.38 (*m*, 15 arom. H). ^{13}C-NMR (75 MHz): 18.6, 19.1 (1:1.8, C(3.1)); 30.63, 31.01 (1:2, C(3.2)); 31.08 (MeN); 47.10, 47.25 (1:1.4, C(2.1)); 49.81, 50.23 (2*d*, *J* = 157.1, 156.5, 1:1, C(2.2)); 66.75, 66.87 (9:1, Ph*C*H$_2$); 118.72, 118.92 (2:1, *C*H$_2$=CH); 120.16, 120.47 (2*d*, *J* = 4.6, 6.2, C(2) of PhO); 125.37 (C(4) of PhO); 127.98, 128.09, 128.53 (C(2), C(3), C(4) of *Ph*CH$_2$); 129.71, 129.84, 129.99 (6.7:18.4:1, C(3) of PhO); 132.28, 132.49, 132.72 (1:2.9:2,5, CH$_2$=*C*H); 136.47 (C(1) of *Ph*CH$_2$); 149.94, 150.28 (2*d*, *J* = 9.8, 9.2, C(1) of PhO); 155.28, 155.41 (1.4:1, OCON); 173.70 (C(1.1)). ^{31}P-NMR (121 MHz): 15.6, 16.2 (1.6:1; after LC, *ca.* 1.5:1).

Diphenyl N$^{2.1}$*[(Benzyloxy)carbonyl]*-L-*alanyl-(2.2-decarboxy-*N$^{2.2}$-*methyl*-DL-*phenylalanin-2.2-yl)phosphonate* (**8a**). According to the general procedure, **5a** (2.415 g, 5.005 mmol) in THF (10 ml), the LDA soln. from (i-Pr)$_2$NH (1.56 ml, 11.0 mmol) in THF (40 ml), and benzyl bromide (0.60 ml, 5.05 mmol) were combined. The yellow soln. was kept at –78° for 9.5 h and treated with 1M H_2SO_4 (10 ml), followed by workup: 2.11 g of a resin. LC (5 × 20 cm SiO_2, hexane/AcOEt 1:2) gave 1.241 g (43%) of **8a** (1:1.8 mixture of diastereoisomers from ^{1}H-NMR (300 MHz), signals from H–C(2.1)) and 222 mg (9%) of **5a**. **8a**: ^{1}H-NMR (300 MHz): 0.64, 0.66, 1.16 (3*d*, *J* = 6.6, 6.7, 6.8, *ca.* 1:1:4, Me(3.1)); 2.98, 3.12, 3.18 (3*s*, MeN); 2.85–3.35 (*m*, 1 H, CH$_2$(3.2)); 3.45 (*A* of *APQX*, *J*(*A*,P) ≈ *J*(*A*,*X*) ≈ 4.6, *J*(*A*,*Q*) ≈ 14.9, 1 H, CH$_2$(3.2)); 4.32, 4.47 (*quint.*-like, *J* ≈ 7.3, 1:2, H–C(2.1)); 5.04, 5.09 and 5.05 (*AB* and *s*, PhC*H*$_2$O); 5.30–5.45, 5.59 (br. *d*, *J* = 7.9, NH); 5.80–6.05 (br. *m*, H–C(2.2)); 7.01–7.39 (*m*, 20 arom. H). ^{13}C-NMR (75 MHz): 18.07, 18.46 (1:2.5, C(3.1)); 30.59, 31.08 (MeN); 32.44, 32.50, 32.66, 32.73 (2:2:1:1, C(3.2)); 46.81, 46.91 (2:1, C(2.1)); 57.09 (*d*, *J* = 155, C(2.2)); 66.65, 66.73 (7:1, Ph*C*H$_2$O); 120.13, 120.19, 120.36, 120.42, 120.52, 120.58 (3:3:2:3:2:1, C(2) of PhO); 125.36 (C(4) of PhO); 127.12, 127.92, 128.09, 128.48, 128.65, 129.68, 129.81 (C(3) of PhO), C(2), C(3), C(4) of *Ph*CH$_2$O and of *Ph*–C(3.2)); 135.30, 135.41, 135.51, 136.45 (C(1) of *Ph*CH$_2$O and of *Ph*–C(3.2)); 150.04, 150.30 (2*d*, *J* = 9.5, 9.4, C(1) of PhO); 155.23 (OCON); 173.22, 173.53 (1.6:1, C(1.1)). ^{31}P-NMR (121 MHz): 14.38, 15.69, 16.25 (1:3.2:6.5 from signal intensities, *ca.* 1:1.6 mixture).

Methyl N$^{2.1}$*-[(Benzyloxy)carbonyl]*-L-*valylsarcosinate* (**2b**). According to the general BOP-Cl procedure, **1b** (20.0 g, 79.6 mmol) in CH_2Cl_2 (300 ml) was coupled with Sar-OMe·HCl. Without LC, 25.4 g (99%) of **2b**. Colorless foam (found to be pure enough for further use (^{1}H-NMR (80MHz)). Data of **2b** from another reaction, after LC (SiO_2, hexane/AcOEt 1:2): $[\alpha]_D$ = –34.7 (*c* = 2.8, EtOH). IR: 3420*m*, 3000*m*, 2960*m*, 2880*m*, 1750*s*,

---

[6]) In addition to these resonances, signals are observed corresponding to *ca.* 10% of a second rotamer around the C(1.1)–N^2 bond.

1715*s*, 1650*s*, 1510*s*, 1465*w*, 1455*w*, 1415*s*, 1405*s*, 1370*m*, 1315*w*, 1180*w*, 1120*w*, 1090*s*, 1025*s*, 980*w*, 690*s*. ^{1}H-NMR ((D$_6$)DMSO, 300 MHz, 100°): 0.88 (*d*, *J* = 6.6, 2 Me–C(3.1)); 1.99 (*oct.*, *J* ≈ 6.9, H–C(3.1)); 2.75–3.20 (br. MeN); 3.63 (*s*, MeO); 3.80–4.00, 4.20–4.40, 4.23 (br., br. *d*, *J* = 17.2, H–C(2.1), 2 H–C(2.2)); 5.02, 5.05 (*AB*, *J* = 12.7, PhC*H*$_2$); 6.74 (br. NH); 7.25–7.37 (*m*, 5 arom. H). ^{13}C-NMR ((D$_6$)DMSO, 75 MHz): 18.1, 18.8 (2 C(4.1)); 29.8 (C(3.1)); 36.3 (MeN); 49.2 (C(2.2)); 51.6 (MeO); 55.5 (C(2.1)); 65.3 (Ph*C*H$_2$); 127.5, 127.7, 128.2 (C(2), C(3), C(4) of *Ph*CH$_2$); 137.0 (C(1) of *Ph*CH$_2$); 156.1 (OCON); 169.5, 171.7, 172.2 (*ca.* 2:1:2, C(1.1), C(1.2))[7]).

N$^{2.1}$-*[(Benzyloxy)carbonyl]*-L-*valylsarcosine* (**3b**). According to the general procedure, **2b** (25.4 g, 75.5 mmol) was hydrolyzed: 23.45 g (96% rel. to SarOMe·HCl used in the coupling step) of **3b**. Colorless foam. $[\alpha]_D = -27.5$ (*c* = 1.8, EtOH). IR: 3560–2400*w* (br.), 3420*m*, 3000*m*, 2970*m*, 1710*s*, 1650*s*, 1510*s*, 1465*w*, 1455*w*, 1410*m*, 1370*w*, 1315*w*, 1120*w*, 1085*m*, 1035*m*, 1025*m*, 659*m*. ^{1}H-NMR ((D$_6$)DMSO, 300 MHz): 0.79, 0.82 and 0.87, 0.95 (2*d*, *J* = 7.2, 7.0, *ca.* 1:3, Me–C(3.1)); 1.91–2.00 (*m*, H–C(3.1)); 2.83, 3.12 (2*s*, 1:3, MeN); 3.79, 4.22 and 4.10, 4.46 (2 *AB*, *J* = 17.2, and 18.6, 3:1, PhC*H*$_2$); 4.06, 4.31 (2*t*, *J* = 8.7, 8.4, *ca.* 1:3, H–C(2.1)); 5.00, 5.04 and *ca.* 4.98 (*AB* and part of *AB*, *J* = 12.6, 12.7, *ca.* 5:1, PhC*H*$_2$); 7.27–7.49 (*m*, 5 arom. H, NH); 12.7 (br. *s*, OH). ^{1}H-NMR ((D$_6$)DMSO, 300 Hz, 100°): 0.87, 0.89 (2*d*, *J* = 6.7, Me–C(3.1)); 2.00 (*oct.*, *J* = 6.9, H–C(3.1)); 2.75–3.20 (br., MeN); 3.70–4.40 (br., H–C(2.1), 2 H–C(2.2)); 5.02, 5.05 (*AB*, *J* = 12.7, PhC*H*$_2$); 6.70 (br., NH); 7.20–7.40 (*m*, 5 arom. H); OH not observed. ^{13}C-NMR ((D$_6$)DMSO, 75 MHz, 100°): 17.2, 18.5 (C(4.1)); 29.6 (C(3.1)); *ca.* 36 (MeN); *ca.* 49 (C(2.2)); 55.3 (C(2.1)); 65.1 (Ph*C*H$_2$); 126.9, 127.1, 127.7 (C(2), C(3), C(4) of *Ph*CH$_2$); 136.6 (C(1) of *Ph*CH$_2$); 155.4 (OCON); 169.5, 171.3 (C(1.1), C(1.2)).

N^2-*[(Benzyloxy)carbonyl]*-N^1-*(methoxymethyl)*-N^1-*methyl*-L-*valinamide* (**4b**). According to the general procedure, **3b** (21.606 g, 67.0 mmol) in Et$_3$N (0.3 ml, 2.2 mmol) and MeOH (130 ml) was electrolyzed (12931 C (2.0 F·mol^{-1}), *i* = 100 mA·cm^{-2}) at 5° and the solvent removed (no aq. workup): 21.5 g of a yellow oil. LC (8 × 26 cm SiO$_2$, hexane/AcOEt 2:3) gave 16.6 g (80%) of **4b**. Colorless oil. $[\alpha]_D = +5.0$ (*c* = 3.7, EtOH). IR (film): 3300*s*, 2970*s*, 2930*s*, 2875*m*, 1720*s*, 1650*s*, 1530*s*, 1500*s*, 1455*s*, 1405*s*, 1320*m*, 1300*m*, 1270*s*, 1240*s*, 1200*m*, 1100*s*, 1030*s*, 980*w*, 960*w*, 910*m*, 850*w*, 780*w*, 740*m*, 700*m*. ^{1}H-NMR (300 MHz): 0.91, 0.92 and 0.94, 1.01 (2*d*, *J* = 6.8, 7.0 and 7.5, 6.8, 1:1, Me–C(3)); 1.95–2.10 (*m*, H–C(3)); 2.99, 3.10 (2*s*, 1:1, MeN); 3.25, 3.31 (2*s*, 1:1, MeO); 4.51–4.66 (*m*, H–C(2)); 4.60, 4.96 and 4.72, 4.88 (2 *AB*, *J* = 10.8 and 9.8, 1:1, MeOC*H*$_2$); 5.05, 5.10 and 5.09 (*AB* and *s*, *J* = 12.5, PhC*H*$_2$); 5.61–5.65 (*m*, NH); 7.27–7.37 (*m*, 5 arom. H). ^{13}C-NMR (75 MHz): 17.09, 17.48, 17.55 (2 C(4)); 31.08, 31.85 (1:1, C(3)); 33.54, 33.66 (1:1, MeN); 55.35, 55.93 (MeO); 55.93, 56.03 (2:1, (1:1 in the DEPT spectrum, 55.93 also of MeO), C(2)); 66.88 (Ph*C*H$_2$); 78.01, 80.96 (MeO*C*H$_2$); 127.99, 128.89, 128.48 (C(2), C(3), C(4) of *Ph*CH$_2$); 136.39 (C(1) of *Ph*CH$_2$); 156.35, 156.51 (OCON); 173.19, 173.35 (C(1)).

Diphenyl N$^{2.1}$-*[(Benzyloxy)carbonyl]*-L-*valyl-(2.2-decarboxysarcosin-2.2-yl)phosphonate* (**5b**). According to the general procedure, **4b** (16.6 g, 53.8 mmol) and P(OPh)$_3$ (15.6 ml, 59.3 mmol) in CH$_2$Cl$_2$ (220 ml) was treated with a soln. of TiCl$_4$ (7.1 ml, 64.7 mmol) in CH$_2$Cl$_2$ (25 ml). The oil obtained was taken in Et$_2$O and washed with 1N NaOH, 1N H$_2$SO$_4$, and brine: 21.4 g of crude **5b** which was not easily separated from remaining **4b** (⩽ 10% from ^{1}H-NMR (80 MHz)). Repeated LC (SiO$_2$, hexane/AcOEt 10:11) gave *ca.* 16 g (58%) of **5b**. Colorless oil. IR (film): 3300*m*, 3075*m*, 3025*w*, 2975*m*, 2925*m*, 2875*w*, 1670*s*, 1650*s*, 1590*s*, 1540*s*, 1490*s*, 1460*s*, 1410*m*, 1390*m*, 1320*m*, 1280*s*, 1260*s*, 1240*s*, 1210*s*, 1190*s*, 1165*s*, 1110*w*, 1090*m*, 1075*w*, 1030*s*, 1010*m*, 940*s*, 850*m*, 765*s*, 690*s*. ^{1}H-NMR (300 MHz): 0.89, 1.00 (2*d*, *J* = 6.8, Me–C(3.1)); 2.02 (*ca. oct.*, *J* ≈ 6.5, H–C(3.1)); 3.35 (*s*, MeN); 3.85, 4.64 (*AB* of *ABX*, *J*(H,H) = 15.7, *J*(H,P) = 9.4, 11.4, 2 H–C(2.2)); 4.60 (*dd*, *J* ≈ 6, 9, H–C(2.1)); 5.06, 5.10 (*AB*, *J* = 12.2, PhC*H*$_2$); 5.56 (*d*, *J* = 9.2, NH); 7.10–7.35 (*m*, 15 arom. H)[6]). ^{13}C-NMR (75 MHz): 17.19, 19.44 (2 C(4.1)); 31.43 (C(3.1)); 37.01 (MeN); 43.95 (*d*, *J* = 159.6, C(2.2)); 55.55 (C(2.1)); 66.94 (Ph*C*H$_2$); 120.52 (C(2) of PhO); 125.42 (C(4) of PhO); 128.00, 128.12, 128.51 (C(2), C(3), C(4) of *Ph*CH$_2$); 129.80 (C(3) of PhO); 136.36 (C(1) of *Ph*CH$_2$); 149.97, 150.07 (2*d*, *J* = 9.0, 8.2, C(1) of PhO); 156.42 (OCON); 172.36 (C(1.1)). ^{31}P-NMR (121 MHz): 15.0[6]).

Diphenyl N$^{2.1}$-*[(Benzyloxy)carbonyl]*-L-*valyl-(2.2-decaroxy*-N$^{2.2}$-*methyl*-DL-*alanin-2.2-yl)phosphonate* (**6b**). According to the general procedure, **5b** (540 mg, 1.056 mmol) in THF (5 ml), the LDA soln. from (i-Pr)$_2$NH (375 µl, 2.65 mmol), and MeI (80 µl, 1.29 mmol) were combined. The cooling bath was removed, and when the mixture reached 0°, it was treated with 10 ml of buffer followed by Et$_2$O: 520 mg. LC (3 × 20 cm SiO$_2$, hexane/AcOEt 1:1) gave 347 mg (63%) of **6b**. Colorless crystal/oil mixture (L,L-**6b**/L,D-**6b** 1.4:1, ^{31}P-NMR after LC; from another experiment, 1.8:1). L,L-**6b** was purified by repeated crystallization from Et$_2$O/hexane, and pure L,D-**6b** was obtained from the mother liquor using prep. HPLC.

L,D-**6b**: Prep. HPLC: *Chiraspher*, 2.5% i-PrOH in hexane. Anal. HPLC: *Chiraspher*, 2.5% i-PrOH in hexane, t_R 13.79; *Chiraspher*, 1% i-PrOH in hexane, t_R 20.3. $[\alpha]_D = +17.6$ (*c* = 1.0, EtOH). ^{1}H-NMR (300 MHz): 0.90, 0.98 (2*d*, *J* = 6.8, 2 Me–C(3.1)); 1.57 (*dd*, *J*(H,H) = 7.4, *J*(H,P) = 17.8, Me(3.2)); 1.97 (*m*, H–C(3.1)); 3.21 (*s*,

---

[7]) In addition to these resonances, signals are observed corresponding to *ca.* 25% of a second rotamer around the C(1.1)–N^2 bond.

MeN); 4.51 (*dd, J* = 7.0, 9.2, H–C(2.1)); 5.03, 5.09 (*AB, J* = 12.2, PhC*H*$_2$); 5.50 (*d, J* = 9.1, NH); 5.58 (*qd, J*(H,H) = 7.3, *J*(H,P) = 19.5, H–C(2.2)); 7.05–7.36 (*m*, 15 arom. H)[6]. ^{13}C-NMR (75 MHz): 13.0 (C(3.2)); 17.3, 19.4 (C(4.1)); 31.5 (C(3.1), MeN); 46.1 (*d, J* = 158, C(2.2)); 55.5 (C(2.1)); 66.9 (Ph*C*H$_2$); 120.3, 120.4 (C(2) of PhO); 125.3 (C(4) of PhO); 128.0, 128.1, 128.5 (C(2), C(3), C(4) of *Ph*CH$_2$); 129.7, 129.8 (C(3) of PhO); 136.4 (C(1) of *Ph*CH$_2$); 150.1 (*d, J* = 10, C(1) of PhO); 156.2 (OCON); 172.4 (*d, J* = 5, C(1.1)). ^{31}P-NMR (121 MHz): 17.2[6]).

L,L-**6b**: Anal. HPLC: *Chiraspher*, 2.5% i-PrOH in hexane, t_R 16.1; *Chiraspher*, 1% i-PrOH in hexane, t_R 24.3. M.p. 126–127°. $[\alpha]_D = -58.7$ (*c* = 1.2, EtOH). ^{1}H-NMR (300 MHz): 0.85, 0.95 (2*d, J* = 6.8, 2 Me–C(3.1)); 1.58 (*dd, J*(H,H) = 7.4, *J*(H,P) = 18.0, Me(3.2)); 2.00 (*m*, H–C(3.1)); 3.08, 3.29 (2*s*, *ca.* 1:10, MeN); 4.60 (*dd, J* = 5.3, 9.1, H–C(2.1)); 5.09, 5.12 (*AB, J* = 12.3, PhC*H*$_2$); 5.53 (*d, J* = 8.8, NH); 5.66 (*qd, J*(H,H) = 7.4, *J*(H,P) = 19.2, H–C(2.2)); 7.00–7.37 (*m*, 15 arom. H). ^{13}C-NMR (75 MHz): 12.43 (C(3.2)); 16.93, 19.55 (C(4.1)); 31.28 (C(3.1), MeN); 45.96 (*d, J* = 158.7, C(2.2)); 55.81 (C(2.1)); 66.96 (Ph*C*H$_2$); 120.36 (C(2) of PhO); 125.31 (C(4) of PhO); 128.03, 128.14, 128.52 (C(2), C(3), C(4) of *Ph*CH$_2$); 129.80 (C(3) of PhO); 136.35 (C(1) of *Ph*CH$_2$); 150.17 (C(1) of PhO); 156.49 (OCON); 172.60 (C(1.1)). ^{31}P-NMR (121 MHz): 17.9[6]).

L-*[1-(Methylamino)ethyl]phosphonic Acid* (L-**9**) *from* L,L-**6b**. According to the general procedure, L,L-**6b** (206 mg, 0.390 mmol) was hydrolyzed in sat. HCl soln. (10 ml) for 2 d: 46.8 mg (86%) of L-**9** as colorless crystals. $[\alpha]_D = +0.6$ (*c* = 4.7, H$_2$O). ^{1}H-NMR (300 MHz, D$_2$O; contains a small amount of EtOH): 1.34 (*dd, J*(H,H) = 7.3, *J*(H,P) = 14.7, Me(2)); 2.68 (*s*, MeN); 3.17 (*dq, J*(H,H) = 7.2, *J*(H,P) = 14.5, H–C(1)). ^{13}C-NMR (75 MHz, D$_2$O; contains a small amount of EtOH): 14.03 (C(2)); 33.99 (*d, J* = 5.4, MeN); 55.05 (*d, J* = 142.7, C(1)). ^{31}P-NMR (121 MHz, D$_2$O): 13.41.

Diphenyl N$^{2.1}$-*[(Benzyloxy)carbonyl]*-L-*valyl-(2.2-decarboxy-*N$^{2.2}$-*methyl-3.2-vinyl-*DL-*alanin-2.2-yl)phosphonate* (**7b**). According to the general procedure, **5b** (2.238 g, 4.39 mmol) in THF (10 ml), the LDA soln. from (i-Pr)$_2$NH (1.37 ml, 9.68 mmol) in THF (30 ml), and allyl bromide (0.55 ml, 6.5 mmol) were combined. The mixture reached –24° after 2.5 h and was treated with 10 ml of buffer followed by Et$_2$O: 2.14 g. LC (SiO$_2$, hexane/AcOEt 3:2 to 1:1) gave 1.177 g (49%) of **7b** (*ca.* 1:1.6 mixture). Slightly yellow resin. ^{1}H-NMR (300 MHz; data of minor diastereoisomer in parentheses): 0.847, 0.853, 0.97 (3*d*, 1:2:2.5, *J* = 6.7, 2 Me–C(3.1)); 1.86–2.05 (*m*, H–C(3.1)); 2.65–2.84 (*m*, 2 H–C(3.2)); (3.26), 3.14 (2*s*, MeN); 4.50, 4.57 (2*dd, J*(H,H–C(3.1)) = 5.1, 5.8, *J*(H,NH) = 9.2, H–C(2.1)); 5.01–5.21 (*m*, C*H*$_2$=CH, PhC*H*$_2$); 5.47–5.73 (*m*, H–C(2.2), CH$_2$=C*H*, NH); 7.07–7.35 (*m*, 15 arom. H). ^{13}C-NMR (75 MHz; data of minor diastereoisomer in parentheses): (16.70, 19.78), 17.06, 19.55 (2 C(4.1)); 30.75, 30.99 (1:1, C(3.2)); 31.25, (31.48) (MeN); 50.05 (*d, J* = 157, C(2.2)); 55.85 (C(2.1)); 66.88 (Ph*C*H$_2$); 118.81 (*C*H$_2$=CH); 120.23, 120.38, 120.46 (C(2) of PhO); 125.35 (C(4) of PhO); 127.93, 128.12, 128.43, 128.51, 129.71, 129.80 (C(2), C(3), C(4) of *Ph*CH$_2$, C(3) of PhO); 132.41, 132.92 (2*d, J* = 17.1, 18.4, 1.7:1, CH$_2$=*C*H); 136.43 (C(1) of *Ph*CH$_2$); 150.17 (*d, J* = 9.2, C(1) of PhO); 156.23, 156.36 (OCON); (172.86), 173.38 (2*d, J* = 4.8, 5.1, C(1.1)). ^{31}P-NMR (121 MHz): 15.87, 16.76 (1:1.6).

Diphenyl N$^{2.1}$-*[(Benzyloxy)carbonyl]*-L-*valyl-(2.2-decarboxy-*N$^{2.2}$-*methyl-*DL-*phenylalanin-2.2-yl)phosphonate* (**8b**). According to the general procedure, **5b** (2.351 g, 4.60 mmol) in THF (10 ml), the LDA soln. from (i-Pr)$_2$NH (1.45 ml, 10.2 mmol) in THF (20 ml) and benzyl bromide (0.60 ml, 5.05 mmol) were combined. The cooling bath was removed, and when the mixture reached –20° (3.5 h), it was treated with buffer followed by Et$_2$O: 2.41 g. LC (SiO$_2$ (5 × 20 cm), hexane/AcOEt 2:1) gave 1.55 g (56%) of **8b**. Colorless resin (1.2:1 mixture of diastereoisomers, from ^{31}P-NMR). HPLC separation (*Spherisorb S5 ODS2*, 46% MeCN in H$_2$O): t_R 23.1 and 25.0 min. ^{1}H-NMR (300 MHz): 0.38, 0.59 and 0.82, 0.90 (4*d, J* = 6.7, 6.6 and 6.6, 6.7, Me–C(3.1)); 1.30, 1.90 (2*m*, H–C(3.1)); 3.09–3.39 (*m*, MeN, 1 H–C(3.2)); 3.41–3.49 (*m*, 1 H–C(3.2)); 4.32, 4.36 (2*dd, J* = 4.6, 9.1 and 6.4, 9.3, H–C(2.1)); 4.85–5.10 (*m*, PhC*H*$_2$); 5.14, 5.38 (2*d, J* = 9.3, 9.0, NH); 5.85–5.06 (br. *m*, *t*-like, H–C(2.2)); 7.04–7.41 (*m*, 20 arom. H). ^{13}C-NMR (75 MHz): 16.35, 17.33, 19.45 (1:1:1.5, 2 C(4.1)); 30.95, 31.29 (C(3.1)); 32.0 (br., MeN); 32.66 (C(3.2)); 51.0 (*d, J* ≈ 150, C(2.2)); 55.71 (C(2.1)); 66.88 (Ph*C*H$_2$O); 120.29, 120.38, 120.45 (*ca.* 1:2:3, C(2) of PhO); 125.44 (C(4) of PhO); 127.06, 127.23, 127.96, 128.05, 128.17, 128.58, 128.80, 129.10, 129.80, 129.89, 130.08 (C(2), C(3), C(4) of *Ph*CH$_2$O and of *Ph*–C(3.2), C(3) of PhO); 135.42, 135.63 (C(1) of *Ph*–C(3.2)); 136.49 (C(1) of *Ph*CH$_2$O); 150.04, 150.13, 150.26, 150.33 (1:2.5:2.8:1.5, C(1) of PhO); 156.10, 156.22 (OCON); 172.79, 173.01 (C(1.1)). ^{31}P-NMR (121 MHz): 16.0, 16.8 (1:1.2).

Methyl N$^{2.1}$-*[(Benzyloxy)carbonyl]*-L-*phenylalanylsarcosinate* (**2c**). According to the general BOP-Cl procedure, **1c** (24.0 g, 80.2 mmol) in CH$_2$Cl$_2$ (300 ml) was coupled with Sar-OMe·HCl (10.64 g, 76.22 mmol) in CH$_2$Cl$_2$ (200 ml; extraction into AcOEt/Et$_2$O 5:2): 29.5 g. LC (8 × 23 cm SiO$_2$, hexane/AcOEt 11:10) in 2 portions gave 25.5 g (87%) of **2c**. Slightly yellow oil (68% from the same batch size, but with ClCO$_2$Et). $[\alpha]_D = -13.5$ (*c* = 3.6, EtOH). IR: 3600–3200 (br.), 3420*m*, 3060*w*, 3000*m*, 2950*m*, 1750*s*, 1710*s*, 1650*s*, 1500*s*, 1450*m*, 1440*m*, 1415*m*, 1405*m*, 1365*w*, 1345*w*, 1285*m*, 1180*m*, 1080*w*, 1050*s*, 975*w*, 695*s*. ^{1}H-NMR (80 MHz): 2.85, 2.90 (2*s*, *ca.* 2.5:1, MeN); 2.70–3.20 (*m*, *AB* of *ABX*, 2 H–C(3.1)); 3.65, 3.70 (2*s*, *ca.* 1:2.5, MeO); 3.95, 4.11 (*AB, J* = 19, 2 H–C(2.2)); 4.65–5.10 (*m*, H–C(2.1)); 5.05 (*s*, PhC*H*$_2$); 5.55 (br. *d, J* ≈ 8, NH); 7.20, 7.30 (2*s*, 5 arom. H each).

$N^{2.1}$-*[(Benzyloxy)carbonyl]*-L-*phenylalanylsarcosine* (**3c**). According to the general procedure, **2c** (25.0 g, 65.0 mmol) was hydrolyzed: 23.5 g (98%) of **3c**. Colorless voluminous and hard foam. M.p. 46–50°. $[\alpha]_D = -9.5$ ($c = 4.0$, EtOH). IR: 3600–2400*w* (br.), 3420*m*, 3060*m*, 3010*m*, 2980*m*, 2940*m*, 1720*s*, 1650*s*, 1510*s*, 1500*s*, 1455*m*, 1415*s*, 1375*m*, 1285*m*, 1080*m*, 1045*s*, 1025*m*, 975*w*, 910*w*, 695*s*. ^{1}H-NMR (80 MHz, *ca.* 70°): 2.85 (*s*, MeN); 2.25–3.05 (*m*, *AB* of *ABX*, 2 H–C(3.1)); 3.91, 4.02 (*AB*, $J = 18$, 2 H–C(2.2)); 4.65–5.10 (*m*, H–C(2.1)); 5.00 (*s*, PhCH_2); 5.55 (br. *d*, $J \approx 8$, NH); 7.15, 7.25 (2*s*, 5 arom. H each); 8.10–8.60 (br. OH).

N^2-*[(Benzyloxy)carbonyl]*-N^1-*(methoxymethyl)*-N^1-*methyl*-L-*phenylalaninamide* (**4c**). According to the general procedure, **3c** (23.0 g, 62.1 mmol) in Et_3N (0.15 ml, 1.1 mmol, 2 mol-%) and MeOH (130 ml) were electrolyzed at 1–6° with 16783 C (2.8 F·mol^{-1}, $i = 100$ mA·cm^{-2}): 19.25 g. LC (8 × 20 cm SiO_2, hexane/AcOEt 1:1) gave 16.95 g (77%) of **4c**. Colorless resin. IR (film): 3298*m*, 3030*w*, 3060*w*, 2935*w*, 1717*s*, 1653*s*, 1528*s*, 1497*s*, 1455*s*, 1404*m*, 1280*m*, 1245*s*, 1100*m*, 1078*m*, 1029*s*, 913*m*, 748*m*, 699*s*. ^{1}H-NMR (300 MHz): 2.78, 2.93 (2*s*, 1:1, MeN); 2.95–3.07 (*m*, 2H–C(3)); 3.15, 3.17 (2*s*, 1:1, MeO); 4.34, 4.50 and 4.67, 4.74 (2 *AB*, $J = 11.0$ and 9.8, 1:1, MeOCH_2); 4.92 (*m*, H–C(2)); 5.00–5.12 (*m*, PhCH_2O); 5.67 (br., *d*, $J = 8.6$, NH); 7.16–7.37 (*m*, 10 arom. H). ^{13}C-NMR (75 MHz): 33.12, 33.66 (1:1, MeN); 39.59, 40.11 (1:1.5, C(3)); 52.28 (C(2)); 55.19, 55.97 (1.5:1, MeO); 66.86 (PhCH_2O); 77.99, 80.63 (1:1.3, MeOCH_2); 127.02, 127.12, 128.11, 128.51, 129.42 (C(2), C(3), C(4) of 2 Ph); 135.96, 136.94 (C(4) of 2 Ph); 155.67 (OCON); 172.57 (C(1)).

Diphenyl $N^{2.1}$-*[(Benzyloxy)carbonyl]*-L-*phenylalanyl-(2.2-decarboxysarcosin-2.2-yl)phosphonate* (**5c**). To the soln. of **4c** (9.0 g, 25.3 mmol) and $P(OPh)_3$ (8.0 ml, 30.4 mmol) in CH_2Cl_2 (30 ml) under Ar at 10° was added $TiCl_4$ (3.3 ml, 30.1 mmol) over 10 min ($T \leq -12°$). The temp. was raised to r.t. during 10 min, refluxed for 50 min (→ red to brown soln.), cooled to 0°, and combined with a soln. (0°) of NaOH (4.9 g, 122 mmol) in H_2O (100 ml). The resulting suspension was diluted with some H_2O and Et_2O, centrifuged (10 min at 10^4 r.p.m.), decanted, and extracted with Et_2O and AcOEt (pH of the aq. phase, 4). The combined org. extracts were treated as usual: 18 g. LC (3 times 8 × 20 cm, once 5 × 20 cm SiO_2, hexane/AcOEt 3:2 to 1:3) gave 9.73 g (69%) **5c**. Colorless resin. IR: 3690*w*, 3426*m*, 3076*w*, 3008*s*, 1716*s*, 1653*s*, 1592*m*, 1510*s*, 1490*s*, 1456*s*, 1414*m*, 1162*s*, 1110*w*, 1042*m*, 1026*m*, 1015*m*, 947*s*, 850*w*. ^{1}H-NMR (300 MHz): 2.85–3.05 (*m*, 2 H–C(3.1)); 2.99 (*s*, MeN); 4.09, 4.22 (*AB* of *ABX*, J(H,H) = 15.6, J(H,P) = 10.8, 11.0, 2 H–C(2.2)); 4.90–5.02 (*m*, H–C(2.1)); 4.09, 4.22 (*AB*, $J = 12$,6, PhCH_2O); 5.70 (br. *d*, $J = 8.8$, NH); 7.08–7.35 (*m*, 20 arom. H)[8]). ^{13}C-NMR (75 MHz): 36.42 (MeN); 39.47 (C(3.1)); 43.91 (*d*, $J = 159.0$, C(2.2)); 51.95 (C(2.1)); 66.80 (PhCH$_2$O); 120.49 (C(2) of PhO); 125.40 (C(4) of PhO); 127.02, 127.94, 128.07, 128.50, 129.42, 129.77 (C(2), C(3), C(4) of *Ph*CH$_2$O and of *Ph*–C(3.1), C(3) of PhO); 135.85, 136.31 (C(1) of *Ph*CH$_2$O and *Ph*–C(3.1)); 149.94, 150.01 (2*d*, $J = 10.0$, 9.7, C(1) of PhO); 155.61 (OCON); 171.88 (C(1.1)). ^{31}P-NMR (121 MHz): 14.6[8]).

Diphenyl {$N^{2.1}$-*[(Benzyloxy)carbonyl]*-L-*phenylalanyl-(2.2-decarboxy*-$N^{2.2}$-*methyl*-DL-*alanin-2.2-yl)*}*phosphonate* (**6c**). According to the general procedure, **5c** (2.966 g, 5.310 mmol) in THF (20 ml), the LDA soln. from (i-Pr)$_2$NH (1.51 ml, 10.7 mmol) in THF (30 ml), and MeI (0.36 ml, 5.8 mmol) were combined. The mixture was kept for 12 h at −78° and treated with 1N H_2SO_4 (11 ml) followed by Et_2O: 2.8 g of crude **6c** as a mixture of (^{1}H-NMR (300 MHz) and ^{31}P-NMR (121 MHz)) **5c**/**6c** (3:7) and L,D-**6c**/L,L-**6c** ($\leq$ 1:1.5). Repeated LC (5 × 20 cm SiO_2, hexane/AcOEt 3:2) and subsequent prep. HPLC (*Lichrosorb Si 60*, 1% i-PrOH in cyclohexane) gave pure L,L- and L,D-**6c**.

L,D-**6c**: Anal. HPLC: *Lichrosorb Si 60* (7 μm), 3% i-PrOH in cyclohexane, t_R 10.3; 1.5% i-PrOH in cyclohexane, t_R 15.0. $[\alpha]_D = +37.8$ ($c = 2.5$, EtOH). ^{1}H-NMR (300 MHz): 1.35 (*dd*, J(H,H) = 7.5, J(H,P) = 17.9, Me(3.2)); 2.70 (*s*, MeN); 2.96, 3.04 (*AB* of *ABXY*, $J(A,B) = 12.9$, $J(A,X) = 8.9$, $J(B,X) = 5.6$, 2 H–C(3.1)); 4.85 (*X* of *ABXY*, $J(X,A) = J(X,Y) = 8.8$, $J(X,B) = 5.6$, H–C(2.2)); 5.05, 5.09 (*AB*, $J = 12.3$, PhCH$_2$O); 5.50 (*qd*, J(H,H) = 7.4, J(H,P) = 19.4, H–C(2.2)); 5.58 (*Y* of *ABXY*, $J(Y,X) = 8.5$, NH); 7.03–7.37 (*m*, 20 arom. H)[6]). ^{13}C-NMR (75 MHz): 12.48 (C(3.2)); 30.95 (MeN); 40.24 (C(3.1)); 46.00 (*d*, $J = 156.8$, C(2.2)); 52.08 (C(2.1)); 66.88 (PhCH_2O); 120.16, 120.45 (*s*, *d*, $J \approx 5$, C(2) of PhO); 125.24, 125.33 (C(4) of PhO); 127.25, 128.07, 128.19, 128.57, 129.55, 129.67, 129.80 (C(2), C(3), C(4) of *Ph*CH$_2$O and *Ph*–C(3.1) and C(3) of PhO); 135.86, 136.34 (C(1) of *Ph*CH$_2$O and *Ph*–C(3.1)); 150.06, 150.27 (2*d*, $J = 9.5$, C(1) of PhO); 155.39 (OCON); 171.99 (*d*, $J = 4.9$, C(1.1)). ^{31}P-NMR (121 MHz): 17.0[6]).

D-*[1-(Methylamino)ethyl]phosphonic Acid* (D-**9**) *from* L,D-**6c**. According to the general procedure, L,D-**6c** (111 mg, 0.194 mmol) was hydrolyzed in sat. HCl soln. (10 ml) for 2 d and 48% HBr soln./AcOH 1:1 (10 ml) for another d: 32.5 mg of resinous **9**, pure by ^{1}H-NMR (80 MHz). $[\alpha]_D = -0.3$ ($c = 3.3$, H_2O). ^{1}H-NMR (80 MHz, D_2O): like L-**9** from L,L-**6b**.

---

[8]) In addition to these resonances, signals are observed corresponding to *ca.* 15% of a second rotamer around the C(1.1)–N^2 bond.

L,L-**6c** (containing *ca.* 6% of L,D-**6c** (Me(3.2), ^{1}H-NMR (300 MHz)); *ca.* 3% (^{31}P-NMR (121 MHz)): Anal. HPLC: *Lichrosorb Si 60* (7 μm), 3% i-PrOH in cyclohexane, t_R 12.59; 1.59% i-PrOH in cyclohexane, t_R 19.2. $[\alpha]_D = -38.4$ (*c* = 1.1, EtOH). ^{1}H-NMR (300 MHz): 1.57 (*dd*, *J*(H,H) = 7.3, *J*(H,P) = 18.0, Me(3.2)); 2.81, 2.98 (*AB* of *ABXY*, *J*(*A*,*B*) = 13.7, *J*(*A*,*X*) = 7.1, *J*(*B*,*X*) = 5.9, 2 H–C(3.1)); 3.14 (MeN); 4.88–5.08 (*m*, H–C(2.1)); 5.02, 5.07 (*AB*, *J* = 12.4, *Ph*CH_2O); 5.55 (*d*, *J* = 8.9, NH); 5.61 (*qd*, *J*(H,H) = 7.4, *J*(H,P) = 19.2, H–C(2.2)); 6.99–7.37 (*m*, 20 arom. H)[7]). ^{13}C-NMR (75 MHz): 12.61 (C(3.2)); 31.20 (MeN); 38.94 (C(3.1)); 46.37 (*d*, *J* = 158.7, C(2.2)); 52.22 (C(2.1)); 66.85 (Ph*C*H_2O); 120.45 (C(2) of PhO); 125.39 (C(4) of PhO); 126.96, 127.90, 127.96, 128.11, 128.52, 128.80, 129.45, 129.83, 129.97 (C(2), C(3), C(4) of *Ph*CH_2O and of *Ph*–C(3.1), C(3) of PhO); 135.83, 136.34 (C(1) of *Ph*CH_2O and of *Ph*–C(3.1)); 150.20 (*d*, *J* = 9.8, C(1) of PhO); 155.73 (OCON); 172.22 (C(1.1))[7]). ^{31}P-NMR (121 MHz): 17.7[7]).

L-*[1-(Methylamino)ethyl]phosphonic Acid* (L-**9**) *from* L,L-**6c**. According to the general procedure, L,L-**6c** (200 mg, 0.349 mmol) was hydrolyzed in sat. HCl soln. (10 ml) for 5 d: 36.4 mg (75%) of **9**. Colorless solid. $[\alpha]_D = +1.0$ (*c* = 3.6, H_2O). ^{1}H-NMR (80 MHz, D_2O): like the spectrum of L-**9** from L,L-**6b**.

Diphenyl {$N^{2.1}$-*[(Benzyloxy)carbonyl]*-L-*phenylalanyl-(2.2-decarboxy-*$N^{2.2}$*-methyl-3.2-vinyl-*DL-*alanin-2.2-yl)*}*phosphonate* (**7c**). According to the general procedure, **5c** (1.276 g, 2.284 mmol) in THF (10 ml), the LDA soln. from (i-Pr)$_2$NH (0.81 ml, 5.71 mmol) in THF (15 ml), and allyl bromide (232 μl, 2.74 mmol) were combined. The mixture was kept for 1 h at –78°, raised to r.t. within 20 min and poured to 150 ml of buffer followed by extraction with Et_2O: 1.014 g. LC (5 × 20 cm SiO_2, hexane/AcOEt 3:2) gave 519 mg (38%) **7c**. Colorless resin. Anal. HPLC: *Lichrosorb RP-18*, 52% MeCN in H_2O, t_R 48.5, 50.7. ^{1}H-NMR (300 MHz): 0.85–1.00 (*m*, impurity); 2.63–3.07 (*m*, 2 H–C(3.1), 2 H–C(3.2)); 3.00, 3.10 (2*s*, *ca.* 1:2 (signal intensities), MeN); 4.82–4.95 (*m*, H–C(2.1)); 4.98–5.15 (*m*, CH_2=CH, PhCH_2O); 4.46–5.70 (*m*, H–C(2.2), CH_2=C*H*, NH); 7.07–7.37 (*m*, 20 arom. H). ^{13}C-NMR (75 MHz): 28.26 (impurity, Me); 30.82, 30.97 (2:1, C(3.2)); 31.26 (MeN); 38.90, 39.40 (1.9:1, C(3.1)); 50.19, 50.35 (2*d*, *J* = 155.4, 157.9, 1:2.4, C(2.2)); 52.18 (C(2.1)); 66.76 (PhCH_2O); 118.77, 118.85 (1:2, *C*H_2=CH); 120.48 (C(2) of PhO); 125.42 (C(4) of PhO); 126.87, 127.00, 127.87, 127.97, 128.07, 128.48, 129.42, 129.71, 129.83 (C(2), C(3), C(4) of *Ph*–C(3.1) and of *Ph*CH_2O, C(3) of PhO); 132.36, 132.67 (2*d*, small tall, *J* = 17.4, 17.1, CH_2=*C*H); 135.95 (C(1) of Ph–C(3.1)); 136.41 (C(1) of *Ph*CH_2O); 150.09 (*d*, *J* = 9.2, C(1) of PhO); 155.45, 155.62 (1:1.6, OCON); 172.13, 172.64, 173.02 (*s*, *s*, *d*, *J* = 5.5, C(1.1)). ^{31}P-NMR (162 MHz): 14.7 (from **5c**, 5%); 15.8, 16.5 (1:2.2).

Diphenyl {$N^{2.1}$*[(Benzyloxy)carbonyl]*-L-*phenylalanyl-(2.2-decarboxy-*$N^{2.2}$*-methyl-*L-*phenylalanin-2.2-yl)*}-*phosphonate* (**8c**). According to the general procedure, **5c** (1.301 g, 2.329 mmol) in THF (10 ml), the LDA soln. from (i-Pr)$_2$NH (0.83 ml, 5.86 mmol) in THF (15 ml), and benzyl bromide (0.33 ml, 2.8 mmol) were combined. The mixture was kept for 30 min at –78°, raised to *ca.* +10° by removing the cooling bath, added to buffer (150 ml) and extracted with Et_2O: 1.25 g. LC (5 × 20 cm SiO_2, hexane/AcOEt 7:3 to 2:3) gave 763 mg (51%) of **8c** (L,D/L,L 1:2.1 according to ^{31}P-NMR (121 MHz)). Separation was achieved by repeated prep. HPLC (*Chiraspher* and *RP 18*).

L,L-**8c**: Anal. HPLC: *Chiraspher*, 3% i-PrOH in hexane, t_R 19.0; *RP 18*, 58% MeCN in H_2O, t_R 32.1. $[\alpha]_D = -51.1$ (*c* = 1.6, EtOH). ^{1}H-NMR (300 MHz): 2.75, 2.93 (*AB* of *ABXY*, *J*(*A*,*B*) = 13.6, *J*(*A*,*X*) = 6.3, *J*(*B*,*X*) = 7.3, 2 H–C(3.1)); 3.02 (*s*, MeN); 3.18, 3.42 (*CD* of *CDPQ*, *J*(*C*,*D*) = 14.5, *J*(*C*,P) ≈ *J*(*C*,*Q*) ≈ 11.4, *J*(*D*,P) ≈ *J*(*D*,*Q*) ≈ 4.3, 2 H–C(3.2)); 4.72 (*X* of *ABXY*, *J*(*X*,*A*) ≈ *J*(*X*,*B*) ≈ 6.9, *J*(*X*,*Y*) ≈ 8.9, H–C(2.1)); 4.79, 4.94 and 5.00 (*AB* and *s*, *J* = 12.4, PhCH_2O); 5.04 (*d*, *J* = 9.1, NH); 5.8–6.1 (br., H–C(2.2)); 6.79–7.40 (*m*, 25 arom. H)[8]). ^{13}C-NMR (75 MHz): 30.68, 31.42 (*ca.* 1:1, MeN); 32.69 (*d*, *J* = 4.9, C(3.2)); 39.01 (C(3.1)); 51.95 (C(2.1)); 56.99 (*d*, *J* = 153.5, C(2.2)); 66.72 (PhCH_2O); 120.43 (*d*, *J* = 5.2, C(1) of PhO); 125.43 (C(4) of PhO); 126.80, 127.09, 127.90, 128.12, 128.44, 128.53, 128.77, 129.45, 129.84 (C(2), C(3), C(4) of *Ph*CH_2O, *Ph*–C(3.1), and *Ph*–C(3.2), C(3) of PhO); 135.44, 136.09, 136.41 (*d*, *s*, *s*, *J* = 14.6, C(1) of *Ph*–C(3.2), *Ph*CH_2O, and *Ph*–C(3.1)); 150.10 (*d*, *J* = 9.8, C(1) of PhO); 155.28 (OCON); 172.47 (*d*, *J* = 4.8, C(1) of PhO)[8]). ^{31}P-NMR (121 MHz): 16.5[8]).

L-*[1-(Methylamino)-2-phenylethyl]phosphonic Acid* (L-**10**) *from* L,L-**8c**. According to the general procedure, L,L-**8c** (210 mg, 0.324 mmol) was hydrolyzed in sat. HCl soln. (10 ml): 55.6 mg (80%) of **10**. Colorless crystals. $[\alpha]_D = -44.7$ (*c* = 5.6, H_2O). ^{1}H-NMR (300 MHz, D_2O): 2.70 (*s*, MeN); 3.00 (*A* of *APQX*, *J*(*A*,P) = 8.9, *J*(*A*,*Q*) = 15.2, *J*(*A*,*X*) = 10.9, H–C(2) or H′–C(2) or H–C(1)); 3.39 (*Q* of *APQX*, *J*(*Q*,*A*) = 15.2, *J*(*Q*,P) = 6.3, *J*(*Q*,*X*) = 4.5, H–C(2) or H′–C(2) or H–C(1)); 6.20 (*X* of *APQX*, *J*(*X*,*A*) = 11.0, *J*(*X*,*Q*) = 4.4, *J*(*X*,P) = 14.3, H–C(2) or H′–C(2) or H–C(1)); 7.32–7.41 (*m*, 5 arom. H). ^{13}C-NMR (75 MHz, D_2O): 34.20 (MeN); 35.57 (C(2)); 60.42 (*d*, *J* = 138.9, C(1)); 130.3 (C(1) of Ph); 131.78, 131.86 (C(2) and C(3) of Ph); 138.50 (*d*, *J* = 11.6, C(1) of Ph). ^{31}P-NMR (162 MHz, D_2O): 11.34.

L,D-**8c**: Anal. HPLC: *Chiraspher*, 3% i-PrOH in hexane, t_R 21.4; *RP 18*, 58% MeCN in H_2O, t_R 33.7. $[\alpha]_D = +26.8$ (*c* = 1.7, EtOH). ^{1}H-NMR (400 MHz): 0.80–0.95, 1.14, 1.26 (impurities); 2.35 (br., integral for 1.5 H, H–C(3.2)?); 2.92, 3.02 (2 br. *s*, *ca.* 1:7, integrals for 2.7 H, MeN); 3.10–3.25 (br. *m*, H–C(3.1)?); 3.46 (br. *dt*,

$J(d) \approx 4.3$, $J(t) \approx 14.8$, 1.25 H, H–C(3.1)?); 3.60–3.70 (br., *m*, 0.75 H, H–C(2.1)?); 4.67 (*m*, *q*-like, $J \approx 7$, H–C(2.1)); 4.95, 5.00 (*AB*, $J = 12.4$, PhCH_2O); 5.37 (br. *d*, $J = 9$, NH); 5.85–6.05 (br., 0.75 H, H–C(2.2)); 6.75–6.85 and 7.05–7.35 (2*m*, 1:12.6, 25 arom. H, used as standard for integrals). ^{13}C-NMR (75 MHz): 31.34 (br., MeN); 32.89 (*d*, $J = 4.9$, C(3.2)); 38.62 (C(3.1)); 51.0 (br. *d*, $J \approx 150$, C(2.2)); 51.97 (C(2.1)); 66.68 (PhCH_2O); 120.19, 120.55 (C(2) of PhO); 125.38 (C(4) of PhO); 126.79, 127.33, 127.93, 128.06, 128.35, 128.47, 128.78, 128.90, 129.23, 129.74 (C(2), C(3), C(4) of *Ph*–C(3.1), *Ph*–C(3.2) and *Ph*CH_2O, C(3) of PhO); 135.67 (*d*, $J = 16.0$, C(1) of *Ph*–C(3.2)); 135.90, 136.43 (C(1) of *Ph*–C(3.1) and *Ph*CH_2O); 149.98, 150.23 (2*d*, $J = 10.0$, 9.7, C(1) of PhO); 155.41 (OCON); 172.67 (*d*, $J = 4.9$, C(1.1)). ^{31}P-NMR (121 MHz): 15.3, 15.6, 15.8 (2:1:14.5).

REFERENCES

[1] T. Koguchi, H. Kase, I. Kawamoto, M. Kasai, K. Shirahata, S. Okachi, K. Nakayama, *Japan Kokai* 83-31, 992, 24. Feb. 1983; Y. Kido, T. Hamakado, M. Anno, E. Miygawa, Y. Motoki, T. Wakamiya, T. Shiba, *J. Antibiot.* **1984,** *37,* 965; T. Koguchi, K. Yamada, M. Yamato, R. Okachi, K. Nakayama, H. Kase, *ibid.* **1986,** *39,* 364 (*CA:* **1986,** *104,* 102205d).

[2] a) M. Horiguchi, M. Kandatsu, *Nature (London)* **1959,** *184,* 901; J. S. Knitteredge, A. F. Isbel, R. R. Hughes, *Biochemistry* **1967,** *6,* 289; b) E. D. Korn, D. G. Dearborn, H. M. Fales, E. A. Sokoloski, *J. Biol. Chem.* **1973,** *248,* 2257; E. D. Korn, D. G. Dearborn, P. L. Wright, *ibid.* **1974,** *249,* 3335; determination of the configuration of (1-hydroxy-2-aminoethyl)phosphonic acid: F. Hammerschmitt, *Liebigs Ann. Chem.* **1988,** *10,* 955, 961; c) J. S. Knitteredge, R. R. Hughes, *Biochemistry* **1964,** *3,* 991.

[3] a) H. Seto, T. Sasaki, S. Imai, T. Tsuruoka, H. Ogawa, A. Satoh, S. Inouye, T. Niida, N. Otake, *J. Antibiot.* **1983,** *36,* 96; b) M. Okuhara, Y. Kuroda, T. Goto, M. Okamoto, H. Terano, M. Kohaska, H. Aoki, H. Imanaka, *ibid.* **1980,** *33,* 13; E. Iguchi, M. Okuhara, M. Kohaska, H. Aoki, H. Imanaka, *ibid.* **1980,** *33,* 18; T. Kamiya, K. Hemmi, H. Takeno, M. Hashimoto, *Tetrahedron Lett.* **1980,** *21,* 95; M. Hashimoto, K. Hemmi, H. Takeno, T. Kamiya, *ibid.* **1980,** *21,* 99.

[4] B. K. Park, A. Hirota, H. Sakai, *Agric. Biol. Chem.* **1977,** *41,* 161, 573; *ibid.* **1976,** *40,* 1905.

[5] A. Bader, *Aldrichim. Acta* **1988,** *21,* 15 and U.S.P. 4,405,531 1983 of *Monsanto Company* (*CA:* **1972,** *77,* 165079k).

[6] N. E. Jacobson, P. A. Bartlett, *J. Am. Chem. Soc.* **1981,** *103,* 654; P. A. Bartlett, J. E. Hanson, P. P. Giannousis, *J. Org. Chem.* **1990,** *55,* 6268; J. G. Allen, F. R. Atherton, M. J. Hall, C. H. Hassall, S. W. Holmes, R. W. Lambert, L. J. Nisbet, P. S. Ringrose, *Nature* **1978,** *272,* 56; F. R. Atherton, C. H. Hassall, R. W. Lambert, *J. Med. Chem* **1986,** *29,* 29; D. W. Christianson, W. N. Lipscomb, *J. Am. Chem. Soc.* **1988,** *110,* 5560; P. A. Bartlett, C. K. Marlowe, *Science* **1987,** *235,* 569; D. E. Tronrud, H. M. Holden, B. W. Matthews, *Science* **1987,** *235,* 571; P. A. Bash, U. C. Singh, F. K. Brown, R. Langridge, P. A. Kollman, *Science* **1987,** *235,* 574; A. Paldi, M. Mora, S. Bajusz, L. Graf, *Int. J. Peptide Protein Res.* **1987,** *29,* 746.

[7] a) T. Glowiak, W. Sawka-Dobrowolska, J. Kowalik, P. Mastalerz, M. Soroka, J. Zon, *Tetrahedron Lett.* **1977,** *45,* 3965; W. Sanka-Dabrowolska, T. Glowiak, J. Kowalik, P. Mastalerz, *Acta Crystallogr., Sect. C* **1985,** *41,* 1773; b) R. Huber, A. Knierzinger, J.-P. Obrecht, A. Vasella, *Helv. Chim. Acta* **1985,** *68,* 1730; c) J. Kowalik, L. Kupczyk-Subotkowska, P. Mastalerz, *Synthesis* **1981,** 57; d) A. Vasella, R. Voeffray, *Helv. Chim. Acta* **1982,** *65,* 1953; e) U. Schöllkopf, R. Schütze, *Liebigs Ann. Chem.* **1987,** 45; f) A. Dehnel, J. M. Kanabus-Kaminska, G. Lavielle, *Can. J. Chem.* **1988,** *66,* 310; g) J. Rachon, U. Schöllkopf, T. Wintel, *Liebigs Ann. Chem.* **1981,** 709; h) B. Köhler, U. Schöllkopf, *ibid.* **1987,** 267; i) A. Togni, S. D. Pastor, *Tetrahedron Lett.* **1989,** *30,* 1071; M. Sawamura, Y. Ito, T. Hayashi, *ibid.* **1989,** *30,* 2247.

[8] a) P. Renaud, D. Seebach, *Angew. Chem.* **1986,** *98,* 836; *ibid. Int. Ed.* **1986,** *25,* 843; b) D. Seebach, R. Charczuk, C. Gerber, P. Renaud, *Helv. Chim. Acta* **1989,** *72,* 401.

[9] D. Seebach, H. Bossler, H. Gründler, S. Shoda, R. Wenger, *Helv. Chim. Acta* **1991,** *74,* 197; D. Seebach, *Angew. Chem.* **1988,** *100,* 1685; *ibid. Int. Ed.* **1988,** *27,* 1624.

[10] T. Shono, Y. Matsumura, K. Tsubata, K. Uchida, *J. Org. Chem.* **1986,** *51,* 2590; T. Shono, 'Electroorganic Chemistry as a New Tool in Organic Synthesis', Springer Verlag, Berlin–Heidelberg–New York, 1984; T. Shono, *Tetrahedron* **1984,** *40,* 811; S. Torii, in 'Electroorganic Synthesis', 'Oxidations', Verlag Chemie, Kodansha, 1985, Part 1.

[11] S. E. Denmark, R. L. Dorow, *J. Am. Chem. Soc.* **1990,** *112,* 864; G. Boche, *Angew. Chem.* **1989,** *101,* 286; H.-J. Gais, J. Vollhardt, G. Hellmann, H. Paulus, H. J. Lindner, *Tetrahedron Lett.* **1988,** *29,* 1259.

[12] T. Maetzke, D. Seebach, *Organometallics* **1990,** *9,* 3032; T. Maetzke, C. P. Hidber, D. Seebach, *J. Am. Chem. Soc.* **1990,** *112,* 8248.