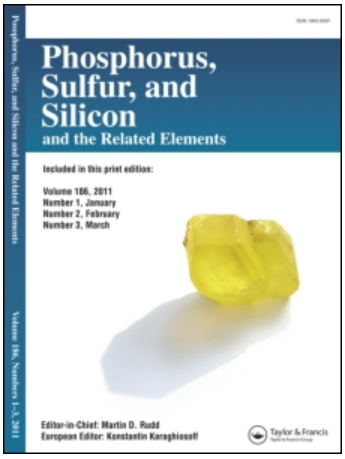

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New Tertiary Phosphines and Bisphosphines-Functionalized Tetrathiafulvalenes

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NEW TERTIARY PHOSPHINES AND BISPHOSPHINES-FUNCTIONALIZED TETRATHIAFULVALENES

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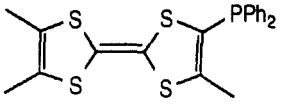
Abstract The synthesis , ^{31}P NMR and electrochemical properties of a set of four tetrathiafulvalenes substituted with -PPh_2 groups are described. The coordinating ability as well as the redox properties of these molecules are illustrated by several examples of complexes and cation-radical salts.

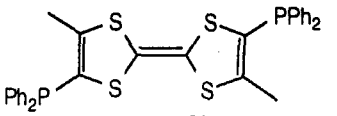
INTRODUCTION

Tetrathiafulvalene derivatives are classical building blocks of low-dimensional conducting and superconducting materials. In this area, the search for novel molecular assemblies of two-dimensional character is currently the focus of considerable interest[2] and we devised that appropriate non-planar π-donor molecules i.e., of well defined shape and geometry, could be candidates for elaborating conducting salts of higher dimensionality. We recently developped an easy synthesis of such non-planar donor molecules by binding together two or more TTF units with main-group elements.[3,4]

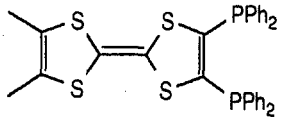
Such phosphorus-linked molecules are particularly interesting because their also provide, beside the redox properties of the attached TTF groups, a second functionnality, i.e. the coordination ability of the ternary phosphines. We reported the synthesis and properties of such molecules bearing several (up to three) TTF groups like $P(TTF)_3$, [3] $PPh(TTF)_2$ and $PPh_2(TTF)$.[4] Also, the chelating bisphosphine **o-P2** (see below) derived from the 3,4-dimethyltetrathiafulvalene was prepared and its coordinating ability illustrated by the synthesis and structural characterization of its $NiCl_2$ and $NiBr_2$ complexes.



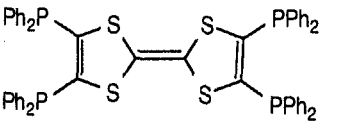
P1 δ (^{31}P): -22.7ppm



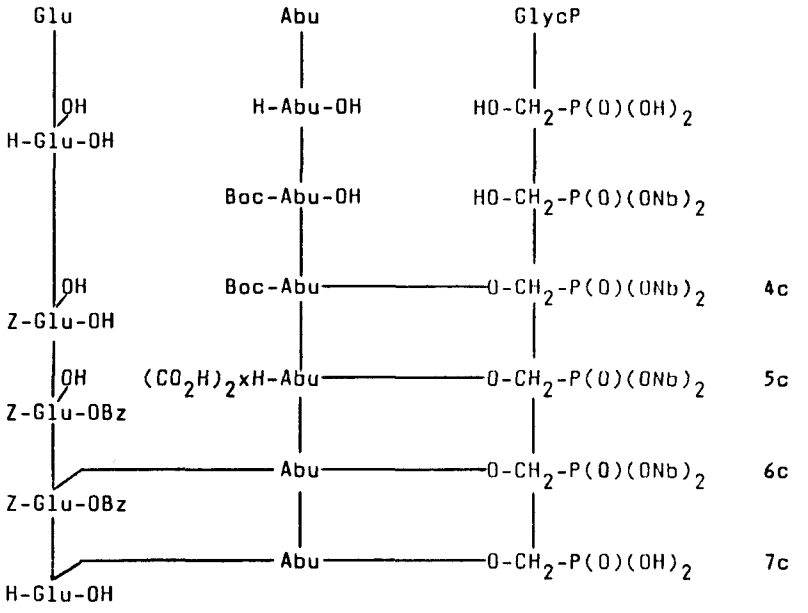
t-P2 δ (^{31}P): -22.7ppm



o-P2 δ(^{31}P): -18.8ppm



P4 δ (^{31}P): -18.2ppm



Synthesis of Glu—Abu-GlycP 7c

GlycP: $HO\text{-}CH_2P(O)(OH)_2$

SCHEME 3

The simultaneous and nondestructive removal of all protective groups in compounds **6a–d** was achieved by catalytic hydrogenation to give compounds **7a–d**.

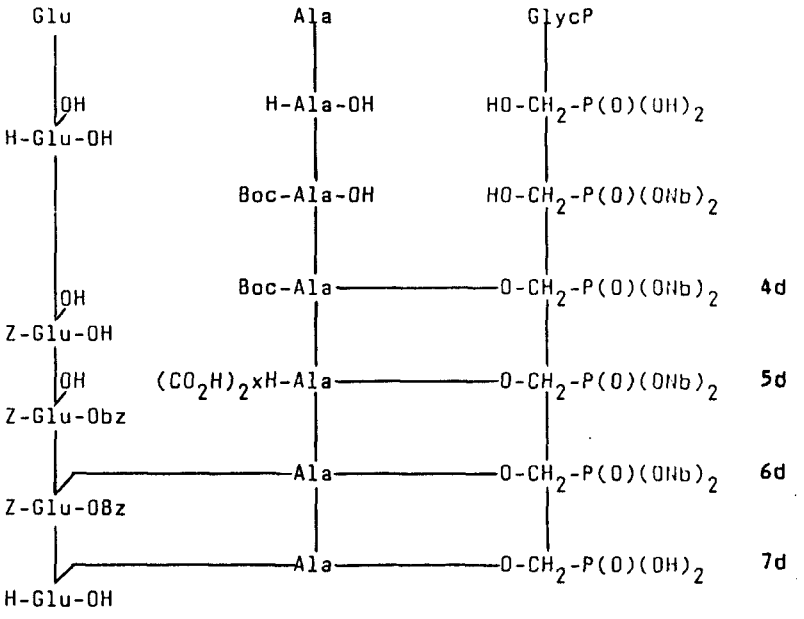
p-Toluidine formed in the hydrogenolysis was removed by ion exchange chromatography.

The newly synthesized compounds **6a–d** and **7a–d** are characterized in Tables I, II and III, respectively.

EXPERIMENTAL

Melting points are not corrected. ^{1}H-NMR spectra were recorded with a Varian EM-360A spectrometer at 60 MHz or a Bruker MSL at 300 MHz. Liquid matrix secondary ions mass spectrometry (LSIMS) was performed on a AMD 604 mass spectrometer. Optical rotations were measured using a Polamat A (Carl-Zeiss, Jena) polarimeter.

N-t-butoxycarbonylaminomethylphosphonic acid, **1**. To a solution of aminomethylphosphonic acid (1.1 g, 10 mmol) and triethylamine (7 ml, 50 mmol) in a mixture of water (10 ml) and tetrahydrofurane (10 ml), di-*tert*-butyldicarbonate (2.4 g, 11 mmol) is added. The mixture is stirred at room temperature for 3 days. The tetrahydrofurane and excess of triethylamine are removed under reduced pressure and the solution is extracted two times with ethyl ether.



SCHEME 4

The water phase is acidified with saturated potassium hydrogen sulfate, extracted 5 times with ethyl acetate and the combined extracts are dried with magnesium sulfate. The solvent is partly removed to give a crystalline product. Yield 1.22 g (61%).

^{1}H-NMR (DMSO) δ: 1.33 (*s*, 9H, $(CH_3)_3C$); 3.17 (dd, 2H, J_{PH} = 10 Hz, J_{HH} = 4 Hz, CH_2P); 6.33–6.82 (*m*, 1H, NH); 9.90 (*s*, 2H, $P(O)(OH)_2$).

$C_6H_{14}NO_5P$ (211.15) calc.: C 34.14 H 6.68 N 6.63%
found: C 34.03 H 7.00 N 6.70%

Di-p-nitrobenzyl ester of N-t-butoxycarbonylaminomethylphosphonic acid, **2**. To a solution of O-(*p*-nitrobenzyl)-*N,N'*-dicyclohexylisourea (7.19 g, 20 mmol) in a mixture of benzene (40 ml) and dimethylformamide (5 ml) *N-t*-butoxycarbonylaminomethylphosphonic acid (2.1 g, 10 mmol) is added. The reaction mixture is refluxed for 8 h. The precipitated urea is filtered off. The filtrate is evaporated under reduced pressure and ethyl acetate (40 ml) is added to the residue. The solution is washed successively with 3% sodium hydrogen carbonate solution (20 ml) and water (20 ml), dried with magnesium sulfate and evaporated. The crude ester is purified by recrystallization from ethyl acetate/*n*-hexane. Yield 3.94 g (82%); m.p. 118–119°C.

^{1}H-NMR ($CDCl_3$) δ: 1.33 (*s*, 9H, $(CH_3)_3C$); 3.70 (dd, 2H, J_{PH} = 10 Hz, J_{HH} = 4 Hz, CH_2P); 4.66–5.00 (*m*, 1H, NH); 5.20 (*d*, 4H, J_{PH} = 8 Hz, 2 $POCH_2$); 7.60, 8.23 (two *d*, 8H arom.).

$C_{20}H_{24}N_3O_9P$ (481.38) calc.: C 49.90 H 5.02 N 8.72%
found: C 50.20 H 5.07 N 8.74%

TABLE I

Synthetic and physical data of protected γ-glutamylphosphonotripeptides **6a**, **6b** and tridepsipeptides **6c**, **6d**

No	Formula	Yield /%/	M.p. /°C/ solvent	$[\alpha]_{546}^{20}$ c, solvent	Molecular formula	Analysis C H N /%/ Calc.	Found
6a	Z-GluOBz-AbuNHCH$_2$P(O)(ONb)$_2$	84	92-5 Et_2O	-22.2 (1.8, $CHCl_3$)	$C_{38}H_{42}N_5O_{13}P$ 807.73	56.52 5.24 8.67	56.78 5.00 8.80
6b	Z-GluOBz-AlaNHCH$_2$P(O)(ONb)$_2$	77	130-132 AcOEt	-26.4 (1.5, $CHCl_3$)	$C_{37}H_{40}N_5O_{13}P$ 793.70	55.98 5.08 8.82	56.30 4.96 8.82
6c	Z-GluOBz-AbuOCH$_2$P(O)(ONb)$_2$	74	102-104 Et_2O	-6.0 (1.5, $CHCl_3$)	$C_{38}H_{41}N_4O_{14}P$ 808.71	56.43 5.11 6.92	56.10 4.90 6.86
6d	Z-GluOBz-AlaOCH$_2$P(O)(ONb)$_2$	60	86-88 Et_2O	-6.7 (1, $CHCl_3$)	$C_{37}H_{39}N_4O_{14}P$ 794.68	55.92 4.94 7.05	56.01 4.72 6.89

Abbreviations used: Z = $C_6H_5CH_2OCO$, Nb = $CH_2C_6H_4$-p-NO_2, Bz = $-CH_2C_6H_5$

TABLE II

^{1}H-NMR Spectra of compounds **6a–d** δ (ppm) in $CDCl_3$

6a	0.86 (t, 3H, J = 7.3 Hz, CH_3); 1.51-2.29 (m, 6H, CH_2CH_2 + CH_2); 3.57-3.72 (m, 1H, CH); 3.81-3.94 (m, 1H, CH); 4.25-4.48 (m, 2H, CH_2P); 5.06-5.15 (m, 8H, $2CH_2C_6H_5$ + $2CH_2C_6H_4$); 6.16 (bd, 1H, NH); 6.32 (bd, 1H, NH); 7.18 (bd, 1H, NH); 7.25-7.32 (m, 10H, $2C_6H_5$); 7.41-7.49 (m, 4H, C_6H_4); 8.11-8.18 (m, 4H, C_6H_4)
6b	1.28 (d, 3H, J = 6.9 Hz, CH_3); 2.04-2.29 (m, 4H, CH_2CH_2); 3.60-3.76 (m, 1H, CH); 3.76-3.92 (m, 1H, CH); 4.35-4.46 (m, 2H, CH_2P); 5.06-5.16 (m, 8H, $2CH_2C_6H_5$ + $2CH_2C_6H_4$); 6.20 (bd, 1H, NH); 6.43 (bd, 1H, NH); 7.22 (bd, 1H, NH); 7.29-7.32 (m, 10H, $2C_6H_5$); 7.41-7.49 (m, 4H, C_6H_4); 8.12-8.17 (m, 4H, C_6H_4)
6c	0.90 (t, 3H, J = 7.3 Hz, CH_3); 1.62-2.24 (m, 6H, CH_2CH_2 + CH_2); 4.39-4.54 (m, 2H, 2CH); 4.52 (d, 2H, J_{PH} = 8.2 Hz, OCH_2P); 5.09-5.21 (m, 8H, $2CH_2C_6H_5$ + $2CH_2C_6H_4$); 5.70 (bd, 1H, NH); 6.32 (bd, 1H, NH); 7.26-7.33 (m, 10H, $2C_6H_5$); 7.48-7.52 (m, 4H, C_6H_4); 8.17-8.23 (m, 4H, C_6H_4)
6d	1.36 (d, 3H, J = 8 Hz, CH_3); 1.52-2.32 (m, 4H, CH_2CH_2); 4.30-4.60 (m, 2H, 2CH); 4.53 (d, 2H, J = 8 Hz, OCH_2P); 5.07-5.25 (m, 8H, $2CH_2C_6H_5$ + $2CH_2C_6H_4$); 5.62 (bd, 1H, NH); 6.28 (bd, 1H, NH); 7.25-7.38 (m, 10H, 2 C_6H_5); 7.45-7.55 (m, 4H C_6H_4); 8.18-8.27 (m, 4H, C_6H_4)

TABLE III

Synthetic, analytical and physical data of phosphonic analogues of ophthalmic and norophthalmic acids **7a–d**

No $(M+H)^+$	Formula ^{1}H-NMR (D_2O) δ (ppm)	Yield /%/ M.p. /°C/	$[\alpha]_{546}^{20}$ c 1, H_2O	Molecular formula	Analysis C H N /%/ Calc.	 Found
7a	HO_2C-$\underset{NH_2}{C}HCH_2CH_2$-CONH-$\underset{CH_2CH_3}{C}H$-$CONHCH_2PO_3H_2$	75 213-215	-24.0	$C_{10}H_{20}N_3O_7P$ 325.25	36.92 6.19 12.90	36.60 6.39 12.60
326	0.88 (t, 3H, J = 7.4 Hz, CH_3); 1.55-1.86 (m, 2H, CH_2); 2.05-2.20 (m, 2H, CH_2); 2.51 (t, 2H, J = 7.4 Hz, CH_2); 3.40 (d, 2H, J = 12.6 Hz, CH_2P); 3.88 (t, 1H, J = 6.4 Hz, CH); 4.08-4.20 (m, 1H, CH)					
7b	HO_2C-$\underset{NH_2}{C}HCH_2CH_2$-CONH-$\underset{CH_3}{C}H$-$CONHCH_2PO_3H_2$	78 212-213	-28.0	$C_9H_{18}N_3O_7P$ 311.22	34.73 5.82 13.50	34.55 6.12 13.25
312	1.38 (d, 3H, J = 7.2 Hz, CH_3); 2.11-2.22 (m, 2H, CH_2); 2.51 (t, 2H, J = 7.3 Hz, CH_2); 3.45 (d, 2H, J = 12.5 Hz, CH_2P); 3.88 (t, 1H, J = 6.3 Hz, CH); 4.31 (q, 1H, J = 7.2 Hz, CH)					

7c	$HO_2C-\underset{NH_2}{\underset{\vert}{C}}HCH_2CH_2-CONH-\underset{CH_2CH_3}{\underset{\vert}{C}}H-COOCH_2PO_3H_2$	60 210-212	-30.0	$C_{10}H_{19}N_2O_8P \times \frac{1}{2} H_2O$ 335.24	35.79 5.96 8.35	35.96 5.88 8.07
327	0.84 (t, 3H, J = 7.4 Hz, CH_3); 1.59-1.89 (m, 2H, CH_2); 2.06-2.16 (m, 2H, CH_2); 2.46 (t, 2H, J = 7.2 Hz, CH_2); 3.91 (t, 1H, J = 6.5 Hz, CH); 4.15 (d, 2H, J = 8.5 Hz, OCH_2P); 4.24-4.31 (m, 1H, CH)					
7d	$HO_2C-\underset{NH_2}{\underset{\vert}{C}}HCH_2CH_2-CONH-\underset{CH_3}{\underset{\vert}{C}}H-COOCH_2PO_3H_2$	60 204-206	-38.0	$C_9H_{17}N_2O_8P \times \frac{1}{2} H_2O$ 321.22	33.62 5.60 8.71	33.65 5.74 8.57
313	1.33 (d, 3H, J = 7.3 Hz, CH_3); 2.06-2.16 (m, 2H, CH_2); 2.44 (t, 2H, J = 7.2 Hz, CH_2); 3.93 (t, 1H, J = 6.4 Hz, CH); 4.15 (d, 2H, J = 8.5 Hz, OCH_2P); 4.36 (q, 1H, J = 7.2 Hz, CH)					

Di-p-nitrobenzyl aminomethylphosphonate trifluoroacetat, **3**. To Di-*p*-nitrobenzyl *N-t*-butoxycarbonylaminomethylphosphonate (4.81 g, 10 mmol), 6 ml of trifluoroacetic acid is added at 0°C. The mixture is kept for 30 min. at 20°C and the solution is evaporated at room temperature under reduced pressure. The residue crystallizes after addition of ethyl ether. Yield 4.7 g (95%); m.p. 127–128°C.

^{1}H NMR (TFA) δ: 3.00–3.66 (*m*, 2H, CH_2P); 4.80 (*d*, 4H, J_{PH} = 10 Hz, 2 $POCH_2$); 7.00–8.00 (*m*, 11H, NH_3 + 8H arom.).

$C_{17}H_{17}N_3O_9PF_3$ (493.30) calc.: C 41.39 H 3.47 N 8.52%
found: C 41.35 H 3.29 N 8.22%

Trifluoroacetates of P-terminal Di-p-nitrobenzyl Phosphonodipeptides, **5a**, **5b**. *N-t*-butoxycarbonyl-*L*-amino acid (*L*-α-aminobutyric acid or *L*-Ala) (2 mmol) is dissolved in dry $CHCl_3$ (6 ml) containing NEt_3 (0.28 ml, 2 mmol) and the solution is cooled to −5°C. Then ethyl chloroformate (0.2 ml, 0.22 mmol) is added and the mixture is kept at −5°C for 30 min. Next a solution of di-*p*-nitrobenzyl aminomethylphosphonate trifluoroacetat (0.987 g, 2 mmol) in dry $CHCl_3$ (4 ml) containing NEt_3 (3 ml) is added. The mixture is kept at room temperature for 12 h. The resulting solution is washed successively with water (6 ml), 1M $KHSO_4$ (2 × 6 ml), water (6 ml), 5% $NaHCO_3$ solution (2 × 6 ml), water (6 ml) and dried over $MgSO_4$. The solvent is distilled off and the oily residue representing chromatographically pure peptides **4a** (yield 1.1 g, 97%) or **4b** (yield 1.04 g, 95%) is dissolved in 3 ml of trifluoroacetic acid and left to stand at room temperature for 40 min. The reaction mixture is evaporated in vacuo. Trifluoroacetates of *P*-protected phosphonodipeptides **5a** and **5b** precipitate by addition of ethyl ether.

Compound **5a**. Yield 1.1 g (96%); m.p. 145–147°C.

^{1}H-NMR (TFA) δ: 0.50 (*t*, 3H, *J* = 7 Hz, CH_3); 1.17–1.90 (*m*, 2H, CH_2); 3.23–4.10 (*m*, 3H, CH_2P + CH); 4.80 (*d*, 4H, J_{PH} = 10 Hz, 2 $POCH_2$); 6.50–8.00 (*m*, 8H arom. + 3H, NH_3).

$C_{21}H_{24}N_4O_{10}PF_3$ (580.40) calc.: C 43.45 H 4.16 N 9.65%
found: C 43.36 H 4.07 N 9.40%

Compound **5b**. Yield 1.0 g (95%); m.p. 174–177°C.

^{1}H-NMR (TFA) δ: 1.33 (*d*, 3H, *J* = 7 Hz, CH_3); 3.50–3.95 (*m*, 2H, CH_2P); 4.00–4.40 (*m*, 1H, CH); 4.90 (*d*, 4H, J_{PH} = 10 Hz, 2 $POCH_2$); 6.65–8.00 (*m*, 8H arom. + 3H, NH_3).

$C_{20}H_{22}N_4O_{10}PF_3$ (566.38) calc.: C 42.40 H 3.91 N 9.89%
found: C 42.27 H 3.74 N 9.84%

Di-p-nitrobenzyl esters of P-terminal N-t-butoxycarbonylphosphonodidepsipeptides, **4c**, **4d**. To a solution of *N-t*-butoxycarbonyl-*L*-amino acid (*L*-α-aminobutyric or *L*-Ala) (1.1 mmol) and 4-(*N*,*N*-dimethylamino)pyridine (0.132 g, 1.1 mmol) in 12 ml CH_2Cl_2, di-*p*-nitrobenzyl hydroxymethylphosphonate[10] (0.382 g, 1 mmol), 1-hydroxybenzotriazole (0.140 g, 1 mmol) and DCC (0.226 g, 1.1 mmol) is added. The reaction mixture is kept at 20°C for 18 h. *N*,*N*-dicyclohexylurea (DCU) is filtered off and the filtrate evaporated to dryness. The residue is dissolved in ethyl acetate (20 ml). The solution is washed successively with 1 M $KHSO_4$ (2 × 15 ml), water (1 × 15 ml), 5% $NaHCO_3$ solution (2 × 15 ml), dried with $MgSO_4$ and evaporated to dryness. The residue is purified by flash chromatography on silica gel (eluent-benzene). The solvent is evaporated and the product is crystallized from ethyl ether/hexane.

Compound **4c**. Yield 70%; m.p. 92–94°C.

^{1}H-NMR ($CDCl_3$) δ: 1.00 (*t*, 3H, *J* = 6 Hz, CH_3); 1.40 (*s*, 9H, $(CH_3)_3C$); 1.60–2.20 (*m*, 2H, CH_2); 4.10–4.50 (*m*, 1H, CH); 4.67 (*d*, 2H, J_{PH} = 8 Hz, CH_2P); 4.75–5.20 (*m*, 1H, NH); 5.36 (*d*, 4H, J_{PH} = 8 Hz, 2 $POCH_2$); 7.70, 8.40 (two *d*, 8H arom.).

$C_{24}H_{30}N_3O_{11}P$ (567.47) calc.: C 50.79 H 5.33 N 7.40%
found: C 50.94 H 5.29 N 7.64%

Compound **4d**. Yield 70%; m.p. 70–72°C.

^{1}H-NMR ($CDCl_3$) δ: 1.40 (*d*, 3H, *J* = 7 Hz, CH_3); 1.42 (*s*, 9H, $(CH_3)_3C$); 4.00–4.50 (*m*, 1H, CH); 4.57 (*d*, 2H, J_{PH} = 10 Hz CH_2P); 4.72–5.18 (*m*, 1H, NH); 5.27 (*d*, 4H, 2 $POCH_2$); 7.78, 8.36 (two *d*, 8H arom.).

$C_{23}H_{28}N_3O_{11}P$ (553.44) calc.: C 49.91 H 5.09 N 7.59%
found: C 50.05 H 5.10 N 7.90%

Oxalates of P-terminal di-p-nitrobenzyl phosphonodidepsipeptides, **5c**, **5d**. Compound **4c** or **4d** (2.25 mmol) is treated with 1.4 ml of trifluoroacetic acid at 0°C and allowed to stand for 30 min. at room

temperature. The reaction mixture is evaporated in vacuo and the oily residue is suspended in ethyl acetate (15 ml). The mixture is washed with saturated sodium hydrogen carbonate (2 × 5 ml), saturated aqueous sodium chloride and dried with magnesium sulfate. The resultant solution is poured into a vigorously stirred solution of anhydrous oxalic acid (0.19 g, 2.2 mmol) in ethyl ether (15 ml). The mixture is allowed to stand 2 hours in a refrigerator and the product is collected by filtration.

Compound **5c**. Yield 85%; m.p. 98–100°C.

^{1}H-NMR (TFA) δ: 0.66 (*t*, 3H, J = 7 Hz, CH_3); 1.36–2.10 (*m*, 2H, CH_2); 3.72–4.21 (*m*, 1H, CH); 4.50 (*d*, 2H, J_{PH} = 10 Hz, CH_2P); 5.00 (*d*, 4H, J = 10 Hz, 2 $POCH_2$); 6.70–8.16 (*m*, 11H, NH_3 + 8H arom.).

$C_{21}H_{24}N_3O_{13}P/H_2O$ (575.39)	calc.:	C 43.83	H 4.55	N 7.30%
	found:	C 43.90	H 4.59	N 7.20%

Compound **5d**. Yield 84%; m.p. 93–5°C.

^{1}H-NMR [$(CD_3)_2C{=}O$] δ: 1.66 (*d*, 3H, J = 7 Hz, CH_3); 4.21–5.54 (*m*, 1H, CH); 4.72 (*d*, 2H, J = 8 Hz, CH_2P); 5.24 (*d*, 4H, J = 10 Hz, 2 $POCH_2$); 7.00–8.36 (*m*, 11H, NH_3 + 8H arom.).

$C_{20}H_{22}N_3O_{13}P/H_2O$ (561.37)	calc.:	C 42.79	H 4.30	N 7.48%
	found:	C 42.90	H 4.30	N 7.23%

General procedure for the synthesis of protected γ-glutamylphosphonotripeptides, **6a**, **6b**. Triethylamine (0.28 ml, 2 mmol) is added at 0°C to a suspension of *N*-benzyloxycarbonyl-*L*-glutamic acid α-benzyl ester[14] (408 mg, 1.1 mmol), *P*-terminal di-*p*-nitrobenzyl phosphonodipeptide trifluoroacetate **5a** or **5b** (1 mmol) and benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP reagent) (442 mg, 1 mmol) in methylene chloride (8 ml). The mixture is stirred at room temperature for 8 h and evaporated to dryness. Ethyl acetate (15 ml) is added to the residue. The solution is washed successively with saturated potassium hydrogen sulfate (2 × 15 ml) water (1 × 15 ml), 5% sodium hydrogen carbonate (2 × 15 ml), water (15 ml) and dried with magnesium sulfate. The solvent is removed under reduced pressure and the crude product is purified by crystallization (Tables I and II).

General procedure for the synthesis of protected γ-glutamylphosphonotridepsipeptides, **6c**, **6d**. *N*-benzyloxycarbonyl-L-glutamic acid α-benzyl ester (408 mg, 1.1 mmol) is dissolved in dry methylene chloride (4 ml) containing NEt_3 (0.14 ml, 1 mmol) and cooled to −5°C. Ethyl chloroformate (0.1 ml, 0.11 mmol) is added and the mixture is kept at −5°C for 30 min. A solution of di-*p*-nitrobenzyl phosphonodidepsipeptide oxalate **5c** or **5d** (1 mmol) in dry methylene chloride (4 ml) containing NEt_3 (0.28 ml) is added. The mixture is kept at room temperature overnight and then evaporated to dryness. Ethyl acetate (10 ml) is added to the residue. The solution is washed successively with saturated potassium hydrogen sulfate (2 × 15 ml), water (15 ml), 5% sodium hydrogen carbonate (2 × 15 ml), water (15 ml), and dried with magnesium sulfate. The solvent is removed under reduced pressure and the crude product crystallizes after addition of ethyl ether (Tables I and II).

General procedure for the synthesis of γ-glutamylphosphonotripeptides and tridepsipeptides, **7a–d**. To a solution of compound **6b** (0, 5 mmol) in methanol (20 ml) or compounds **6a**, **6c**, **6d** in ethanol (20 ml), 10% palladium on charcoal (150 mg) is added. The mixture is hydrogenated at ambient temperature and pressure for 4 h. The catalyst is filtered off and washed with ethyl alcohol and water. The filtrate is evaporated to dryness. The residue is dissolved in water (5 ml) and passed through Zerolite 225/H^+. The combined fractions are evaporated and the residue crystallizes after addition of ethanol. Yields and properties of free phosphonotripeptides **7a**, **7b** and phosphonotridepsipeptides **7c**, **7d** are presented in Table III.

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