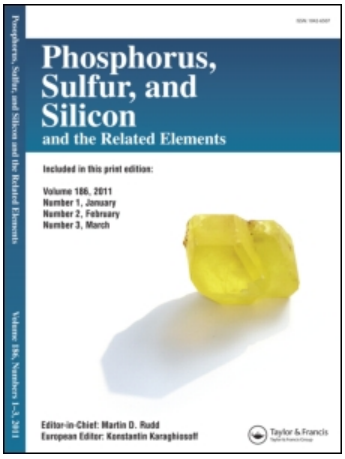


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

SYNTHESIS OF γ-GLUTAMYLPHOSPHONODIDEPEPTIDES

Maria Hoffmann[a]; Czeslaw Wasielewski[a]
[a] Department of Organic Chemistry, Technical University of Gdańsk, Gdańsk, Poland

To cite this Article Hoffmann, Maria and Wasielewski, Czeslaw(1990) 'SYNTHESIS OF γ-GLUTAMYLPHOSPHONODIDEPEPTIDES', Phosphorus, Sulfur, and Silicon and the Related Elements, 53: 1, 69 — 73
To link to this Article: DOI: 10.1080/10426509008038013
URL: http://dx.doi.org/10.1080/10426509008038013

Phosphorus, Sulfur, and Silicon, 1990, Vol. 53, pp. 69–73
Reprints available directly from the publisher
Photocopying permitted by license only

SYNTHESIS OF γ-GLUTAMYLPHOSPHONODIDE-PEPTIDES

MARIA HOFFMANN* and CZESŁAW WASIELEWSKI
Department of Organic Chemistry, Technical University of Gdańsk 80-952 Gdańsk, Poland

(Received November 21, 1989)

γ-Glutamylphosphonodidepsipeptides **3a–f** were obtained by condensation of α-t-butyl or α-benzyl ester of optically active *N*-benzyloxycarbonyl-glutamic acid with di-*p*-nitrobenzyl 1-hydroxymethanephosphonate, (+) dibenzyl 1-hydroxy-2-methylpropanephosphonate and (−) dibenzyl 1-hydroxy-3-methylbutanephosphonate. Dicyclohexylcarbodiimide in the presence of 4-(*N,N*-dimethylamino)-pyridine and 1-hydroxybenzotriazole in methylene chloride was used as a condensing agent for compounds **3a–c**. Compounds **3d–f** were obtained by means of the dicyclohexylcarbodiimide method in the presence of 4-(*N,N*-dimethylamino)pyridine in carbon tetrachloride. Protecting groups were removed by conventional methods.

Key words: 1-hydroxyalkanephosphonates; glutamic acid; phosphonodidepsipeptides.

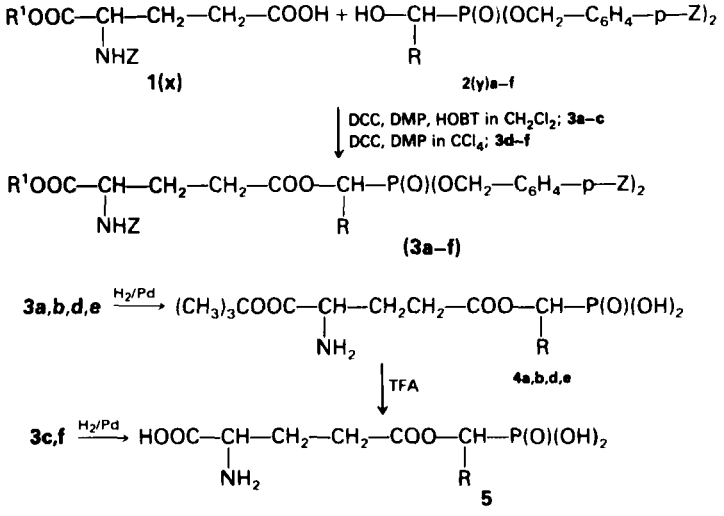
In earlier papers[1,2] we reported the preparation of dibenzyl and di-p-nitrobenzyl 1-hydroxyalkanephosphonates by alkylation of 1-hydroxyalkanephosphonic acids with *O*-benzyl or *O*-p-nitrobenzyl-*N,N'*-dicyclohexylisoureas. We found the method suitable for the synthesis of optically active 1-hydroxyalkanephosphonates. In this paper we describe the use of dibenzyl and di-p-nitrobenzyl 1-hydroxyalkanephosphonates for the synthesis of γ-glutamylphosphonodidepsipeptides. These compounds as analogues of γ-glutamylphosphonodipeptides[3,4] are expected to exhibit neuroactive properties.

Protected P-terminal γ-glutamylphosphonodidepsipeptides were obtained by condensation of α-t-butyl or α-benzyl ester of optically active *N*-benzyloxycarbonylamino-glutamic acid **1(x)** with di-p-nitrobenzyl 1-hydroxymethanephosphonate **2a** or dibenzyl 1-α-hydroxyalkanephosphonates **2(y)d–f.** DCC method in the presence of 4-(*N,N*-dimethylamino)pyridine and 1-hydroxybenzotriazole in methylene chloride as the solvent gave the best results for compounds **3a–c**. Compound **3d–f** were obtained in good yields by means of the DCC method in the presence of 4-(*N,N*-dimethylamino)pyridine in carbon tetrachloride. (Table I). Conventional removal of P and N blocking groups by hydrogenolysis gave crystalline α-t-butyl esters of P-terminal γ-glutamylphosphonodidepsipeptides **4a,b,d,e,** or free amorphous P-terminal γ-glutamylphosphonodidepsipeptides **5**. Compounds **4** could be also transformed into **5** by the action of trifluoroacetic acid.

TABLE I

Protected P-terminal γ-glutamylphosphonodidepsipeptides **3a–f**

Product	Yield (%)	m.p. (°C) solvent	$[\alpha]_D^{20}$ (c, ethyl acetate)	Molecular formula	Analysis C H [%] N Calc.	Found
3a	66	89–91 ether	−4.1 (3)	$C_{32}H_{36}N_3O_{13}P$ 701.6	54.77 5.17 5.98	54.49 5.18 5.68
3b	60	88–90 ether	+3.4 (3)	$C_{32}H_{36}N_3O_{13}P$ 701.6	54.77 5.17 5.98	55.00 4.99 6.25
3c	72	80–82 ethyl acetate n-hexane	−4.2 (3)	$C_{35}H_{34}N_3O_{13}P$ 735.6	57.14 4.65 5.71	57.19 4.63 5.72
3d	76	oil	+2.6 (4)	$C_{35}H_{44}NO_9P$ 653.7	64.30 6.78 2.14	64.55 6.81 2.26
3e	87	oil	−18.5 (2)	$C_{36}H_{46}NO_9P$ 667.7	64.75 6.94 2.09	64.98 7.22 2.15
3f	84	oil	−19.4 (3)	$C_{39}H_{44}NO_9P$ 701.7	66.74 6.32 1.99	66.94 6.15 1.90



3	(x)	R¹	(y)	R	Z	3	(x)	R¹	(y)	R	Z
a	L	$(CH_3)_3C$		H	NO_2	**d**	L	$(CH_3)_3C$	(+)	$(CH_3)_2CH$	H
b	D	$(CH_3)_3C$		H	NO_2	**e**	L	$(CH_3)_3C$	(−)	$(CH_3)_2CHCH_2$	H
c	L	$C_6H_5CH_2$		H	NO_2	**f**	L	$C_6H_5CH_2$	(−)	$(CH_3)_2CHCH_2$	H

DCC = *N,N*-dicyclohexylcarbodiimide; DMP = 4-(*N,N*-dimethylamino) pyridine; HOBT = 1-hydroxybenzotriazole.

EXPERIMENTAL

All melting points are uncorrected. IR spectra were recorded on Zeiss-Jena UR-10 apparatus, ^{1}H-NMR spectra on the Varian EM-360A spectrometer at 60 MHz. Optical rotations were determined with Carl Zeiss Polamat A polarimeter. TLC was done using Merck silica gel on glass in systems: S_1-n-butanol-acetic acid–water (2:1:1), S_2-n-butanol-acetic acid-water-pyridine (15:3:12:10), indicator 0.5% ninhydrin in ethanol. α-t-Butyl ester of *N*-benzyloxycarbonyl-L-glutamic acid $[\alpha]_D^{20} = -26.0$ (c, 1, MeOH) and α-t-butyl ester of *N*-benzyloxycarbonyl-D-glutamic acid $[\alpha]_D^{20} = +23.0$ (c, 1, MeOH) were obtained according to Reference 5. α-Benzyl ester of *N*-benzyloxycarbonyl-L-glutamic acid $[\alpha]_D^{20} = -23.8$ (c, 1, MeOH) was obtained according to Reference 6. Di-p-nitrobenzyl 1-hydroxymethanephosphonate, (+)dibenzyl 1-hydroxy-2-methylpropanephosphonate—yield 83%, m.p. 76–78°C, $[\alpha]_D^{20} = +4.66$ (c, 3, acetone) and (−)dibenzyl 1-hydroxy-3-methylbutanephosphonate $[\alpha]_D^{20} = -18.3$ (c, 1, acetone) were obtained according to References 1, 2, 7.

Protected P-terminal γ-glutamylphosphonodidepsipeptides **3a–c**. To a solution of α-t-butyl ester of *N*-benzyloxycarbonyl L or D-glutamic acid (1.1 mmol) or α-benzyl ester of *N*-benzyloxycarbonyl-L-glutamic acid (1.1 mmol) and 4(*N*,*N*-dimethylamino)pyridine (0.132 g, 1.1 mmol) in 10 ml CH_2Cl_2, was added di-p-nitrobenzyl 1-hydroxymethanephosphonate (0.382 g, 1 mmol), 1-hydroxybenzotriazole (0.140 g, 1 mmol) and DCC (0.226 g, 1.1 mmol). The reaction mixture was kept at 23°C for 18 h. *N*,*N*-dicyclohexylurea (DCU) was filtered off and the filtrate evaporated to dryness. The residue was dissolved in ethyl acetate (20 ml). The solution was washed successively with 1 M $KHSO_4$ (2 × 15 ml), water (1 × 15 ml), 5% $NaHCO_3$ (2 × 15 ml), dried with $MgSO_4$ and evaporated to dryness. The residue was purified by column chromatography on silica gel (eluent: benzene–acetone 5:1).

Protected P-terminal γ-glutamylphosphonodidepsipeptides **3d–f**. To a solution of α-t-butyl or α-benzyl ester of *N*-benzyloxycarbonyl-L-glutamic acid (1.1 mmol) and (+)dibenzyl 1-hydroxy-2-methylpropanephosphonate or (−1)dibenzyl 1-hydroxy-3-methylbutanephosphonate (1 mmol) in 14 ml of CCl_4, was added DCC (0.226 g, 1.1 mmol) and 4-(*N*,*N*-dimethylamino)pyridine (0.132 g, 1.1 mmol). The reaction mixture was kept at 23°C for 18 h. *N*,*N*-dicyclohexylurea (DCU) was filtered off and the filtrate evaporated to dryness. The residue was dissolved in ethyl acetate (20 ml), washed 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 was purified by column chromatography on silica gel (eluent: benzene–acetone 5:1). (Tables I, II).

α-t-Butyl esters of P-terminal γ-glutamylphosphonodidepsipeptides **4a,b,d,e.** To a solution of compound **3a** or **3b** (1 mmol) in ethyl acetate (30 ml) and compound **3d** or **3e** in ether (50 ml), 10% palladium on charcoal was added. The mixture was hydrogenated at ambient temperature and pressure for 3 h. In the case of compound **3a** and **3b** the catalyst and precipitated compounds **4a** or **4b** were filtered off and washed with ethyl acetate and acetone. The filtrate was removed and the precipitate was washed with water. The water filtrate was evaporated to dryness and the residue crystallized after addition of acetone. In the case of compound **3d** and **3e**, the catalyst and compounds **4d** or **4e** were filtered off and washed with acetone and water. The filtrates were evaporated to dryness and crystallized after addition of acetone and ether.

Compound **4a.** Yield 81%; m.p. = 149–150°C; $R_f = 0.33$ in S_1, R_f—0.32 in S_2; $[\alpha]_D^{20} = +14.2$°C (c, 1, H_2O); IR (KBr) cm^{-1} 1040 (POC), 1260 (PO), 1760 (CO); ^{1}H-NMR (TFA) δ 1.20 (s, 9H, $(CH_3)_3C$); 1.90–2.76 (m, 4H, CH_2CH_2); 3.90–4.50 (m, 1H, CH—N); 4.40 (d, 2H, $J_{P-H} = 8$ Hz, CH_2P); 7.20 (bs; NH_3^+). Analysis calcd. for $C_{10}H_{20}NO_7P$: C 40.43; H 6.77; N 4.71. Found: C 40.13; H 6.87; N 4.95.

Compound **4b**. Yield 81%; m.p. = 147–149°C; $R_f - 0.33$ in S_1 $R_f - 0.32$ in S_2; $[\alpha]_D^{20} = -15.6$ (c, 1, H_2O); IR (KBr) cm^{-1} 1040 (POC), 1260 (PO), 1760 (CO); ^{1}H-NMR (TFA) δ 1.20 (s, 9H, $(CH_3)_3C$); 1.90–2.76 (m, 4H, CH_2CH_2); 3.90–4.50 (m, 1H, CH—N); 4.40 (d, 2H, $J_{P-H} = 8$ Hz, CH_2P); 7.20 (bs, NH_3^+). Analysis calcd. for $C_{10}H_{20}NO_7P$: C 40.43; H 6.77; N 4.71. Found: C 40.13; H 6.87; N, 4.95.

Compound **4d**. Yield 80%; m.p. = 147–148°C; R_f—0.43 in S_1; R_f—0.52 in S_2; $[\alpha]_D^{20} = +27.2$ (c, 1, H_2O); IR (KBr) 1070 (POC), 1260 (PO), 1760 (CO). ^{1}H-NMR (TFA) 0.60 (d, 6H $J_{H-H} = 6$ Hz, $(CH_3)_2C$); 1.15 (s, 9H, $(CH_3)_3C$); 1.50–2.50 (m, 5H, CH_2CH_2, CH); 3.70–4.26 (m, 1H, CH—N), 4.50–5.10 (m, 1H, CH—P); 6.60–7.33 (bs, NH_3^+). Analysis calcd. for $C_{13}H_{26}NO_7P \cdot 2H_2O$: C 41.59; H 8.05; N 3.73. Found: C 42.00; H 7.80; N 3.54.

Compound **4e**. Yield 80%; m.p. 136–138°C; R_f—0.43 in S_1; R_f—0.51 in S_2; $[\alpha]_D^{20} = -18.3$ (c, 1, H_2O); IR (KBr) cm^{-1} 1070 (POC), 1260 (PO), 1760 (CO). ^{1}H-NMR (TFA) 0.30–0.70 (m, 6H, $(CH_3)_2C$); 1.20 (s, 9H, $C(CH_3)_3$); 1.23–1.73 (m, 3H, $CHCH_2$): 1.90–2.76 (m, 4H, CH_2CH_2);

TABLE II

^{1}H-NMR of compounds of **3a–f**

Compound	^{1}H-NMR solvent (ppm)
3a ($CDCl_3$)	1.36 (s, 9H, $(CH_3)_3C$); 1.80–2.56 (m, 4H, CH_2CH_2); 3.90–4.40 (m, 1H, CH—N); 4.40 (d, 2H, J_{P-H} = 8 Hz, CH_2—P); 5.00 (s, 2H, $CH_2C_6H_5$); 5.10 (d, 4H, J_{P-H} = 10 Hz, $P(OCH_2)_2$); 5.20–5.56 (m, 1H, NH); 7.00–8.20 (m, 13H, $2C_6H_4$ + C_6H_5)
3b ($CDCl_3$)	1.36 (s, 9H, $(CH_3)_3C$); 1.70–2.60 (m, 4H, CH_2CH_2); 4.00–4.50 (m, 1H, CH—N); 4.40 (d, 2H, J_{P-H} = 8 Hz, CH_2—P); 5.00 (s, 2H, $CH_2C_6H_5$); 5.10 (d, 4H, J_{P-H} = 10 Hz, $P(OCH_2)_2$; 5.20–5.56 (m, 1H, NH); 7.10–8.30 (m, 13H, $2C_6H_4$, C_6H_5)
3c ($CDCl_3$)	1.77–2.66 (m, 4H, CH_2CH_2); 4.47 (d, 2H, J = 10 Hz, CH_2—P); 4.23–4.66 (m, 1H, CH—N); 5.00–5.66 (m, 9H, $2POCH_2$, $2COCH_2$ + NH); 7.19–8.57 (m, 18H arom.)
3d ($CDCl_3$)	0.90 (d, 6H, J_{H-H} = 6 Hz, $(CH_3)_2C$); 1.36 (s, 9H, $(CH_3)_3C$); 1.50–2.60 (m, 5H, CH, CH_2CH_2); 4.00–4.60 (m, 1H, CH—N); 5.00 (d, 4H, J_{P-H} = 10 Hz, $P(OCH_2)_2$); 5.08 (s, 2H, $CH_2C_6H_5$); 5.15–5.66 (m, 2H, CH—P, NH); 7.30 (s, 15H, C_6H_5)
3e (CCl_4)	0.60–1.00 (m, 6H, $(CH_3)_2C$); 1.36 (s, 9H $(CH_3)_3$); 1.40–2.60 (m, 7H, $CHCH_2$, CH_2CH_2); 3.80–4.30 (m, 1H, CH—N); 4.90 (d, 4H, J_{P-H} = 10 Hz, $P(OCH_2)_2$); 5.00 (s, 2H, $CH_2C_6H_5$); 5.10–5.50 (m, 2H, CH—P, NH); 7.23 (s, 15H, C_6H_5)
3f (CCl_4)	0.57–0.90 (m, 6H, $(CH_3)_2C$; 1.10–2.43 (m, 7H, CH_2CH, CH_2CH_2); 3.80–4.36 (m, 1H, CH—N); 4.66–5.50 (m, 9H, $2POCH_2$ + $2COCH_2$ + NH); 7.17 (s, 2OH arom.)

3.56–4.23 (m, 1H, CH—N), 4.90–5.40 (m, 1H, CH—P); 6.80–7.40 (m, 3H, NH_3^+). Analysis calcd. for $C_{14}H_{28}NO_7P$: C 47.58; H 7.98; N 3.96. Found: C 47.87; H 8.22; N, 3.98.

Free P-terminal γ-glutamylphosphonodidepsipeptides **5**. a. To a solution of compound **3c** (0.5 mmol) in ethyl acetate (20 ml) or compound **3f** in ether (30 ml) was added 10% palladium on charcoal (0.2 g). The mixture was hydrogenated at ambient temperature and pressure for 4 h. The catalyst was filtered off and in the case of compound **4c** washed with ethyl acetate and acetone. The filtrate was removed and the precipitate was washed with water. The water filtrate was evaporated to dryness. In the case of compound **3f** the catalyst was washed with acetone and water and the collected filtrates were evaporated to dryness.

Compound **5c**. Yield 75%, R_f = 0.09 in S_1, 0.13 in S_2. ^{1}H-NMR (TFA) δ = 1.90–2.00 (m, 4H, CH_2CH_2); 4.00–4.72 (m, 1H, CH—N); 4.39 (d, 2H, J = 8 Hz, CH_2P); 7.00–7.72 (m, 3H, NH_3^+).

Compound **5f**. Yield 76%, R_f = 0.23 in S_1, 0.27 in S_2. ^{1}H-NMR (TFA) δ = 0.29–0.82 (m, 6H, $(CH_3)_2C$); 1.10–1.76 (m, 3H, CH_2CH); 2.00–2.76 (m, 4H, CH_2CH_2); 3.85–4.42 (m, 1H, CH—N); 4.75–5.50 (m, 1H, CH—P); 6.76–7.50 (m, 3H, NH_3^+).

b. Compounds **3a,b,d,e** were dissolved in 2 ml of trifluroacetic acid and the solutions were kept at room temperature for 1 h. The solvent was evaporated to dryness. Yield 95–100% of **5**; white amorphous solids which exhibited a single TLC spot in systems S_1 and S_2. ^{1}H-NMR (TFA): similar to those of the corresponding compounds **4** but without $OC(CH_3)_3$ singlet.

This research was supported by a grant from the Polish Academy of Sciences (CPBP 01.13).

REFERENCES

1. M. Hoffmann, *Synthesis*, 66 (1988).
2. M. Hoffmann, *J. Prakt. Chem.*, in press.
3. J. Davies, R. H. Evans, A. W. Jones, D. A. S. Smith and J. C. Watkins, *Comp. Biochem. Physiol.*, **72b** 211 (1982).

4. R. H. Evans and J. C. Watkins, *Life Sci.*, **28,** 1303 (1981).
5. E. Taschner, C. Wasielewski, T. Sokołowska and J. F. Biernat, *Liebigs Ann. Chem.*, **646,** 127 (1961).
6. W. J. Le Quesne and G. T. Young, *J. Chem. Soc.*, **1950,** 1954.
7. M. Hoffmann, *Pol. J. Chem.*, **59,** 385 (1985).