Phosphorus-containing derivatives of L-aspartic and L-glutamic acids

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Phosphorylureas (including those with the 1,3,2-oxazaphosphinane ring) containing L-aspartate and L-glutamate fragments, as well as 1,3,2-oxazaphosphinane derivatives of phosphorylacetic acid with an L-aspartate fragment and of phosphamide with an L-glutamate fragment, were obtained in a search for structural analogs of aspartate transcarbamoylase and glutamate carboxypeptidase inhibitors.

Key words: phosphoryl isocyanates, amino acids, phosphorylcarbamoyl-L-aspartates, phosphorylcarbamoyl-L-glutamates, 1,3,2-oxazaphosphinanes, the Arbuzov reaction, carcinolytics.

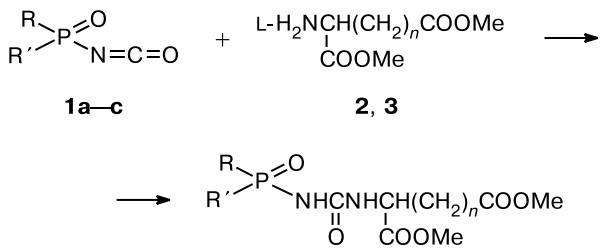
N-Phosphonoacetyl-L-aspartic acid (the drug PALA), which is a phosphorylated derivative of L-aspartic acid, exhibits high carcinolytic activity.[1] Its analogs (*e.g.*, aspartate derivatives) are also aspartate transcarbamoylase inhibitors, some of them being even more cytotoxic.[2—4] It is also known that phosphorylamides of glutamic acid inhibit glutamate carboxypeptidase.[5] For this reason, we deemed it interesting to obtain P,N-containing L-aspartate- and L-glutamate-based structural analogs of the aforementioned enzyme inhibitors, including 1,3,2-oxazaphosphinane derivatives (by analogy with the carcinolytic cyclophosphamide, their oxazaphosphinane ring can deliver a pharmacophore group inside a cell across cell membranes[6]).

One of the potentially most attractive ways of PALA modification could involve replacement of the methylene linker, which binds the phosphoryl group to the amino acid residue, by an amino group. According to the literature data,[7] biologically active compounds are very likely to be found among the corresponding phosphorylureas.

Starting from diethoxy- (**1a**), methyl(phenoxy)- (**1b**), and diphenylphosphoryl isocyanate (**1c**) (typical representatives of phosphoryl, phosphonoyl, and phosphinoyl isocyanates), dimethyl L-aspartate (**2**), and dimethyl L-glutamate (**3**), we obtained phosphorylureas **4a—c** and **5a** (Scheme 1). At room temperature, the reactions proceeded with high rates in benzene or acetonitrile to give the corresponding phosphorylureas in 70—90% yields (Table 1).

With urea (**4d**) (R = R^1 = MeO) as an example, we demonstrated that this type of dialkoxyphosphoryl-containing compounds can also be synthesized from isocyanatophosphorodichloridate (**6**). Its reaction with ester **2** gave intermediate dichlorophosphorylurea **7**, which was treated[8] *in situ* with methanolic MeONa (Scheme 2). Dimethoxy derivative **4d** was converted into the corresponding acid **8** and further into its disodium salt **9** (see Scheme 2). 1,3,2-Oxazaphosphinane derivative **10** was obtained from urea **7** and 3-aminopropan-1-ol in the presence of Et_3N (see Scheme 2).

Scheme 1



Reaction conditions: $MeCN(C_6H_6)$, 20 °C.
n = 1 (**2**, **4**), 2 (**3**, **5**)
R = R′ = EtO (**1a**, **4a**, **5a**), Ph (**1c**, **4c**)
R = Me, R′ = PhO (**1b**, **4b**)

Another oxazaphosphinane derivative of L-aspartic acid, whose monooxygenase-catalyzed metabolism should produce a close analog of PALA,[6] was obtained from 2-methoxy-1,3,2-oxazaphosphinane (**11**) and dimethyl *N*-chloroacetyl-L-aspartate (**12**) as described earlier[9] (Scheme 3). As in the previous cases,[9] the reaction yields not only the target cyclic product **13**, but also acyclic product **14**; the ratio **13** : **14** is 100 : 28 (^{31}P NMR data). Product **13** was isolated by column chromatography as a stable solvate with chloroform (**13**·0.3$CHCl_3$).

Compound **13** is easily hydrolyzed with cleavage of the P—N bond to yield betaine **15**, a close analog of PALA (Scheme 4).

An oxazaphosphinane derivative of L-glutamic acid **16**, an analog of glutamate carboxypeptidase inhibitors,[5] was

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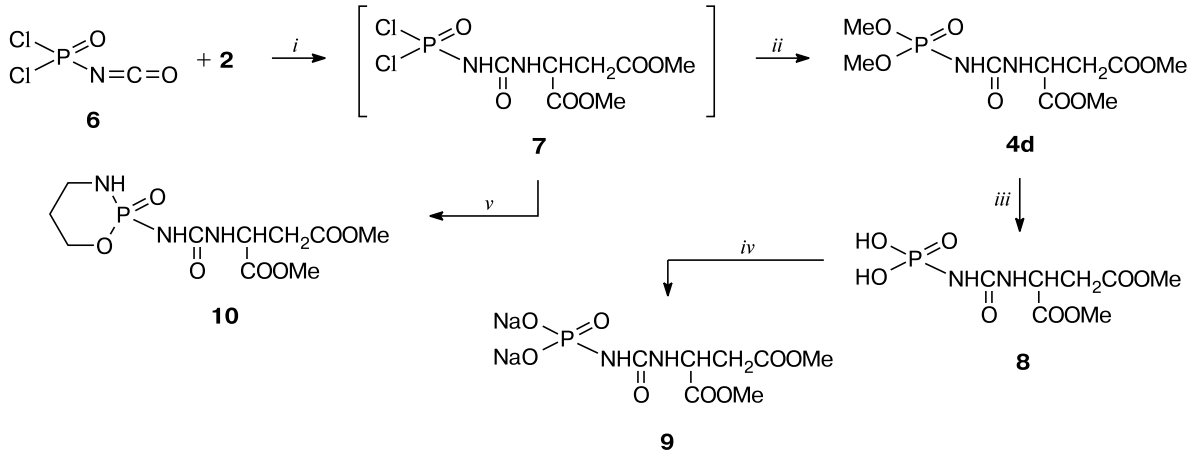
Table 1. Yields, melting points, and elemental analysis data for the compounds obtained

Compound	Yield (%)	M.p. /°C	Found / Calculated (%)				Molecular formula
			C	H	N	P	
4a	89.5	136—137	38.74	6.24	8.20	9.10	$C_{11}H_{21}N_2O_8P$
			38.83	6.22	8.23	9.10	
4b	76.8	105—107	46.69	5.31	7.71	8.64	$C_{14}H_{19}N_2O_7P$
			46.93	5.34	7.82	8.64	
4c	97.8	180—182	56.38	5.18	6.82	7.64	$C_{19}H_{21}N_2O_6P$
			56.44	5.23	6.93	7.66	
4d	53.5	140—141	34.60	5.46	8.94	9.67	$C_9H_{17}N_2O_8P$
			34.62	5.49	8.97	9.92	
5a	96.0	129.5—131	40.61	6,59	7.91	8.75	$C_{12}H_{23}N_2O_8P$
			40.68	6.54	7.91	8.74	
8	62.7	122—124 (decomp.)	29.37	4.63	9.74	—	$C_7H_{13}N_2O_8P$
			29.59	4.61	9.86		
10	6.5	188—189	37.27	5.68	12.94	—	$C_{10}H_{18}N_3O_7P$
			37.16	5.61	13.00		
13	55.3	—[a]	37.85	5.44	7.58	8.55	$C_{11}H_{19}N_2O_7P \cdot 0.3CHCl_3$
			37.90	5.43	7.82	8.65	
15	98.6	—[b]	38.87	6.29	8.07	—	$C_{11}H_{21}N_2O_8P$
			38.83	6.22	8.23		
16	51.0	102—107[c]	40.87	6.54	9.54	—	$C_{10}H_{19}N_2O_6P$
			40.82	6.51	9.52		

[a] A glassy mass.
[b] Softens at 50—60 °C.
[c] For a 10 : 4 mixture of diastereomers.

Scheme 2



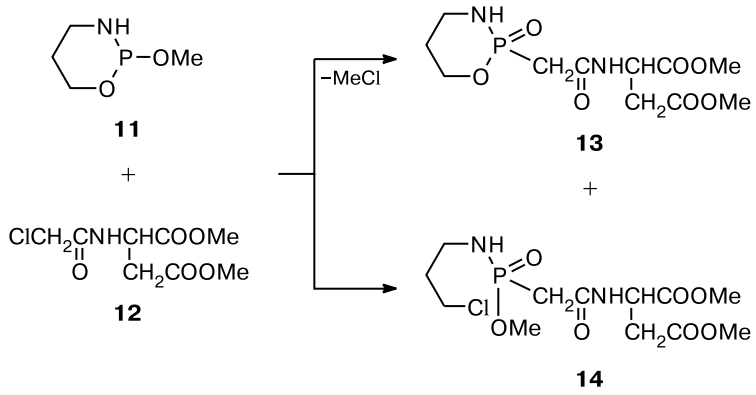
Reaction conditions: *i.* MePh (MeCN), −5 °C; *ii.* MeONa—MeOH, −5 °C; *iii.* 1) Me_3SiBr, 2) MeOH; *iv.* $NaHCO_3$, H_2O; *v.* $H_2N(CH_2)_3OH$, Et_3N, MeCN, −7 °C.

synthesized from 2-chloro-2-oxo-1,3,2λ^5-oxazaphosphinane (**17**) and ester **3** in the presence of Et_3N (Scheme 5).

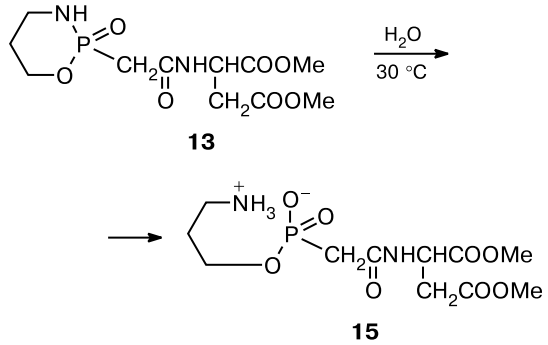
The compositions and structures of the compounds obtained were confirmed by elemental analysis data (see Table 1) and $^{31}P\{^1H\}$ and ^1H NMR spectra (Table 2). The NMR spectra of compounds **4b**, **13**, **14**, and **16** containing two chiral centers (the C and P atoms) show diastereomeric anisochronism.

Biological *in vitro* tests revealed that the compounds obtained at a concentration of 10^{-4} mol L^{-1} do not cause death of 50% of cells of the human tumor lines Caov3 (ovarian carcinoma) and A549 (non-small cell lung carci-

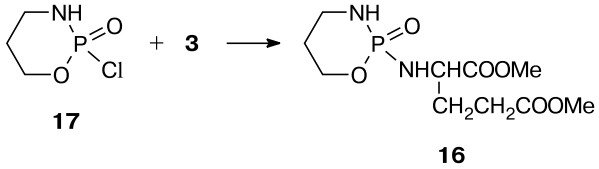
Scheme 3



Scheme 4



Scheme 5



Reaction conditions: Et_3N, MeCN, –3—0 °C.

noma). Thus, they are not cytotoxic *in vitro* in this concentration. However, proliferation of the above cell lines was substantially inhibited (note that PALA itself is active in concentrations of ~10^{-4} mol L^{-1}).[2] Taking into account that other 1,3,2-oxazaphosphinane derivatives (*e.g.*, cyclophosphamide) kill no tumor cells *in vitro* as well,[10] yet being highly efficient against them *in vivo*, one can assume that new 1,3,2-oxazaphosphinane derivative **10** will exhibit biological activity in *in vivo* tests. The results of these tests will be published elsewhere.

Experimental

NMR spectra were recorded on Bruker Avance 400 (400.13 (^{1}H) and 161.98 MHz (^{31}P)) and Bruker Avance 300 instruments (300.13 (^{1}H) and 121.50 MHz (^{31}P)) in $CDCl_3$, CD_3OD, DMSO-d_6, and D_2O with the signals for residual protons of the deuterated solvent as the internal standard (^{1}H) and in C_6H_6, $CDCl_3$, DMSO-d_6, and D_2O with 85% H_3PO_4 as the external standard (^{31}P).

Phosphoryl isocyanate **1a** (Aldrich) was distilled *in vacuo* before use. Phosphoryl isocyanates **1b**,[11] **1c**,[11] and **6**,[12] 2-methoxy-1,3,2-oxazaphosphinane (**11**),[13] and 2-chloro-2-oxo-1,3,2λ^5-oxazaphosphinane[14] were prepared as described earlier.

In some cases, the reaction products were isolated by column chromatography on SiO_2 (Aldrich, 130—270 mesh; product : sorbent = 1 : 16 (w/w); $CHCl_3$—MeOH as an eluent, gradient elution from 100 : 1 to 10 : 1). The fractions were inspected by TLC on SiO_2 in $CHCl_3$—MeOH (10 : 1).

Dimethyl *N*-[*N*-(diethoxyphosphoryl)carbamoyl]-L-aspartate (4a). A solution of ester **2** (0.913 g, 5.58 mmol) in MeCN (5 mL) was added dropwise at room temperature to a stirred solution of isocyanate **1a** (1.00 g, 5.58 mmol) in anhydrous MeCN (7 mL). The reaction mixture was stirred for 5 h and kept for 16 h. The precipitate was filtered off and washed with ether. The yield of compound **4a** was 1.70 g (89.5%).

Dimethyl *N*-[*N*-(methylphenoxyphosphoryl)carbamoyl]-L-aspartate (4b) was obtained analogously from isocyanate **1b** (1.97 g, 10 mmol) in benzene (10 mL) and ester **2** (1.64 g, 10 mmol) in benzene (5 mL). The solvent was removed *in vacuo*, the viscous residue was triturated with ether, and the resulting precipitate was filtered off. The yield of the product was 2.50 g. The filtrate was concentrated *in vacuo* and the residue was triturated with acetone to give additional crop of the product (0.25 g). The total yield of compound **4b** was 2.75 g (76.8%).

Dimethyl *N*-[*N*-(diphenylphosphoryl)carbamoyl]-L-aspartate (4c) was obtained analogously from isocyanate **1c** (1.042 g, 4.3 mmol) in anhydrous benzene (10 mL) and ester **2** (0.722 g, 4.3 mmol) in benzene (10 mL). The precipitate was filtered off and washed with anhydrous hexane (2×10 mL). The yield of compound **4c** was 1.70 g (97.8%).

Dimethyl *N*-[*N*-(diethoxyphosphoryl)carbamoyl]-L-glutamate (5a) was obtained under the same conditions from isocyanate **1a** (0.506 g, 2.825 mmol) in MeCN (3.5 mL) and ester **3** (0.494 g, 2.825 mmol) in MeCN (3.5 mL). The yield of compound **5a** was 0.96 g (96.0%).

Dimethyl *N*-[*N*-(dimethoxyphosphoryl)carbamoyl]-L-aspartate (4d). A solution of ester **2** (1.61 g, 10 mmol) in toluene (15 mL) was added dropwise at –5 °C for 1 h 45 min to a stirred

Table 2. $^{31}P\{^1H\}$ and ^1H NMR spectra of the compounds obtained

Compound	^{31}P, δ (solvent)	^1H, δ, J/Hz ($CDCl_3$)
4a	−1.31 ($CDCl_3$)	1.36 (t, 6 H, C<u>H</u>$_3$CH$_2$, $^3J_{H,H}$ = 7.1); 2.86 (AB system, 1 H, H$_B$, C<u>H</u>$_2$CH, $^3J_{H,H_B}$ = 4.9, $^2J_{H_A,H_B}$ = 16.9); 3.00 (AB system, 1 H, H$_A$, C<u>H</u>$_2$CH, $^3J_{H,H_A}$ = 5.0, $^2J_{H_A,H_B}$ = 16.9); 3.69, 3.74 (both s, 3 H each, C<u>H</u>$_3$O); 4.09—4.26 (m, 4 H, C<u>H</u>$_2$CH$_3$); 4.76 (dt, 1 H, NHC<u>H</u>CH$_2$, $^3J_{H,H}$ = 5.0, $^3J_{H,H}$ = 8.2); 6.26 (d, 1 H, N<u>H</u>P, $^2J_{H,H}$ = 4.56); 7.56 (d, 1 H, N<u>H</u>CH, $^2J_{H,H}$ = 8.5)
4b	28.10 ($CHCl_3$); 28.65, 29.09 (C_6H_6)	<u>Diastereomer α:</u> 1.85 (d, 3 H, C<u>H</u>$_3$P, $^2J_{H,P}$ = 9.0); 2.82 (AB system, 1 H, H$_B$, C<u>H</u>$_2$CH, $^3J_{H,H_B}$ = 4.8, $^2J_{H_A,H_B}$ = 17.3); 2.98 (AB system, 1 H, H$_A$, C<u>H</u>$_2$CH, $^3J_{H,H_B}$ = 4.7, $^2J_{H_A,H_B}$ = 17.3); 3.66, 3.71 (both s, 3 H each, C<u>H</u>$_3$O); 4.68—4.74 (m, 1 H, NHC<u>H</u>CH$_2$); 6.80 (d, 1 H, N<u>H</u>P, $^2J_{H,P}$ = 8.6); 7.11—7.27 (m, 5 H, C$_6$H$_5$); 7.95 (br.s, 1 H, N<u>H</u>CH) <u>Diastereomer β:</u> 1.85 (d, 3 H, C<u>H</u>$_3$P, $^2J_{H,P}$ = 9.0); 2.74 (AB system, 1 H, H$_B$, C<u>H</u>$_2$CH, $^3J_{H,H_B}$ = 4.8, $^2J_{H_A,H_B}$ = 17.1); 2.94 (AB system, 1 H, H$_A$, C<u>H</u>$_2$CH, $^3J_{H,H_B}$ = 4.6, $^2J_{H_A,H_B}$ = 17.1); 3.63, 3.74 (both s, 3 H each, C<u>H</u>$_3$O); 4.68—4.74 (m, 1 H, NHC<u>H</u>CH$_2$); 6.86 (d, 1 H, N<u>H</u>P, $^2J_{H,P}$ = 8.5); 7.11—7.27 (m, 5 H, C$_6$H$_5$); 7.92 (br.s, 1 H, N<u>H</u>CH)
4c	24.18 ($CDCl_3$)	2.75 (AB system, 1 H, H$_B$, C<u>H</u>$_2$CH, $^3J_{H,H_B}$ = 5.0, $^2J_{H_A,H_B}$ = 17.0); 2.88 (AB system, 1 H, H$_A$, C<u>H</u>$_2$CH, $^3J_{H,H_A}$ = 4.8, $^2J_{H_A,H_B}$ = 17.0); 3.58, 3.62 (both s, 3 H each, C<u>H</u>$_3$O); 4.66 (dt, 1 H, NHC<u>H</u>CH$_2$, $^3J_{H,H}$ = 5.0, $^3J_{H,H}$ = 8.1); 7.33—7.59 (m, 8 H, *m*-C$_6$H$_5$ + *p*-C$_6$H$_5$ + 2 NH); 7.71—7.86 (m, 7 H, *o*-C$_6$H$_5$)
4d	−1.56 ($CDCl_3$)	2.86 (AB system, 1 H, H$_B$, C<u>H</u>$_2$CH, $^3J_{H,H_B}$ = 4.7, $^2J_{H_A,H_B}$ = 16.9); 3.00 (AB system, 1 H, H$_A$, C<u>H</u>$_2$CH, $^3J_{H,H_A}$ = 5.1, $^2J_{H_A,H_B}$ = 16.9); 3.69, 3.74 (both s, 3 H each, C<u>H</u>$_3$OC); 3.82, 3.83 (both d, 3 H each, C<u>H</u>$_3$OP, $^3J_{H,P}$ = 6.0); 4.66 (dt, 1 H, NHC<u>H</u>CH$_2$, $^3J_{H,H}$ = 4.8, $^3J_{H,H}$ = 8.3); 7.01 (d, 1 H, N<u>H</u>P, $^2J_{H,P}$ = 6.7); 7.40 (d, 1 H, N<u>H</u>CH, $^3J_{H,H}$ = 8.0)
5a	−1.00 ($CDCl_3$)	1.35 (t, 3 H, C<u>H</u>$_3$CH$_2$, $^3J_{H,H}$ = 7.0); 1.36 (t, 3 H, C<u>H</u>$_3$CH$_2$, $^3J_{H,H}$ = 7.0); 1.94—2.06, 2.16—2.27 (both m, 1 H each, C<u>H</u>$_2$CH); 2.33—2.48 (m, 2 H, C<u>H</u>$_2$C(O)); 3.66, 3.73 (both s, 3 H each, C<u>H</u>$_3$O); 4.09—4.24 (m, 4 H, C<u>H</u>$_2$O); 4.47 (dt, 1 H, NHC<u>H</u>CH$_2$, $^3J_{H,H}$ = 5.4, $^3J_{H,H}$ = 8.0); 6.72 (d, 1 H, N<u>H</u>P, $^2J_{H,P}$ = 6.0); 7.28 (d, 1 H, N<u>H</u>CH, $^3J_{H,H}$ = 7.6)
7	8.19 ($CHCl_3$)	—
8	−1.76 (CD_3OD)	2.89 (AB system, 1 H, H$_B$, C<u>H</u>$_2$CH, $^3J_{H,H_B}$ = 5.0, $^2J_{H_A,H_B}$ = 16.8); 2.99 (AB system, 1 H, H$_A$, C<u>H</u>$_2$CH, $^3J_{H,H_A}$ = 5.5, $^2J_{H_A,H_B}$ = 16.8); 3.72, 3.77 (both s, 3 H each, C<u>H</u>$_3$O); 4.74 (t, 1 H, NHC<u>H</u>CH$_2$, $^3J_{H,H}$ = 5.2)[a]
9	−3.45 (H_2O)	—
10	−0.79 (DMSO-d_6)	1.61—1.70, 1.72—1.85 (both m, 1 H each, CH$_2$C<u>H</u>$_2$CH$_2$); 2.78 (AB system, 1 H, H$_B$, C<u>H</u>$_2$CH, $^3J_{H,H_B}$ = 5.3, $^2J_{H_A,H_B}$ = 17.4); 2.84 (AB system, 1 H, H$_A$, C<u>H</u>$_2$CH, $^3J_{H,H_A}$ = 5.8, $^2J_{H_A,H_B}$ = 17.4); 2.96—3.13, 3.15—3.28 (both m, 1 H each, C<u>H</u>$_2$NHP); 3.62, 3.65 (both s, 3 H each, C<u>H</u>$_3$O); 4.15—4.32 (m, 2 H, C<u>H</u>$_2$OP); 4.59 (dt, 1 H, NHC<u>H</u>CH$_2$, $^3J_{H,H}$ = 5.4, $^3J_{H,H}$ = 8.1); 5.11 (br.s, 1 H, CH$_2$N<u>H</u>P); 7.12, 7.14 (both d, 1 H, N<u>H</u>P, $^3J_{H,P}$ = 9.1); 8.02 (dd, 1 H, N<u>H</u>CH, $^3J_{H,H}$ = 4.9, $^3J_{H,H}$ = 10.0)[b]
13	20.11, 20.22 ($CDCl_3$)	1.73—1.77, 1.96—2.03 (both m, 1 H each, CH$_2$C<u>H</u>$_2$CH$_2$); 2.80—3.08 (m, 4 H, C<u>H</u>$_2$CH, C<u>H</u>$_2$P); 3.24—3.33 (m, 2 H, C<u>H</u>$_2$NHP); 3.6565, 3.6608 (both s, 3 H, CH$_2$COOC<u>H</u>$_3$); 3.7062, 3.7126 (both s, 3 H, CHCOOC<u>H</u>$_3$); 3.81 (d, 1 H, N<u>H</u>P, $^2J_{H,P}$ = 29.0); 4.24—4.42 (m, 2 H, C<u>H</u>$_2$OP); 4.80—4.88 (m, 1 H, C<u>H</u>CH$_2$); 7.69 (d, 0.5 H, N<u>H</u>CH, $^3J_{H,H}$ = 7.9); 7.84 (d, 0.5 H, N<u>H</u>CH, $^3J_{H,H}$ = 8.2)
14	26.87, 27.24 ($CHCl_3$)	—
15	15.62 ($CDCl_3$); 13.67 (DMSO-d_6)	1.76 (br.s, 2 H, CH$_2$C<u>H</u>$_2$CH$_2$); 2.43 (d, 2 H, C<u>H</u>$_2$P, $^2J_{H,P}$ = 19.0); 2.68 (AB system, 1 H, H$_B$, C<u>H</u>$_2$CH, $^3J_{H,H_B}$ = 5.5, $^2J_{H_A,H_B}$ = 16.5); 2.75 (AB system, 1 H, H$_A$, C<u>H</u>$_2$CH, $^3J_{H,H_A}$ = 6.4, $^2J_{H_A,H_B}$ = 16.5); 2.84 (br.s, 2 H, C<u>H</u>$_2$NH$_2$); 3.57, 3.59 (both s, 3 H each, C<u>H</u>$_3$O); 3.78 (br.s, 2 H, C<u>H</u>$_2$O); 4.61 (dt, 1 H, NHC<u>H</u>CH$_2$, $^3J_{H,H}$ = 6,5, $^3J_{H,H}$ = 7.0); 8.26 (br.s, 2 H, <u>H</u>$_2$NCH$_2$); 8.50 (d, 1 H, <u>H</u>NCH, $^3J_{H,H}$ = 7.9)[b]
16	9.49, 9.70 ($CDCl_3$)	1.79 (t, 2 H, C<u>H</u>$_2$C(O), $^3J_{H,H}$ = 5.2); 1.86—1.97, 2.06—2.16 (both m, 1 H each, CH$_2$C<u>H</u>$_2$CH$_2$); 2.36—2.52 (m, 2 H, C<u>H</u>$_2$CH); 2.83 (broad s, 1 H, CHN<u>H</u>P); 3.13—3.23, 3.30—3.39 (both m, 1 H each, C<u>H</u>$_2$NH); 3.48 (broad d, 1 H, CH$_2$N<u>H</u>P, $^2J_{H,P}$ = 26.1); 3.64, 3.70 (both s, 3 H each, C<u>H</u>$_3$O); 3.91 (br.s, 1 H, NHC<u>H</u>CH$_2$); 4.16—4.24, 4.31—4.39 (both m, 1 H each, C<u>H</u>$_2$OP)

[a] In CD_3OD.
[b] In DMSO-d_6.

solution of isocyanate **6** (1.60 g, 10 mmol) in anhydrous toluene (15 mL); a precipitate of urea **7** was formed (see Table 2). The mixture was stirred at room temperature for 40 min and then cooled to −5 °C. A solution of MeONa (from metallic Na (0.58 g, 25 mmol)) in MeOH (15 mL) was added dropwise with stirring. The mixture was kept for 16 h and centrifuged to remove a precipitate of NaCl (20 min, 5500 rpm). The supernatant was concentrated *in vacuo*. The residue was dissolved in acetone (30 mL) and the solution was again centrifuged and concentrated *in vacuo*. The crude product (2.93 g) was purified by column chromatography on SiO_2 and recrystallized from acetone—ether. The yield of compound **4d** was 1.67 g (53.5%).

Dimethyl *N*-(*N*-phosphonocarbamoyl)-L-aspartate (8). Trimethylsilyl bromide (1.28 g, 8.33 mmol) was added to a solution of ester **4d** (1.04 g, 3.33 mmol) in anhydrous $CHCl_3$ (15 mL). After 24 h, the solution was concentrated *in vacuo* at room temperature. The residue was dissolved in MeOH (20 mL) and the solution was stirred for 1 h, filtered, and concentrated *in vacuo*. The crude solid product (1.01 g; calcd 0.95 g) was triturated with acetone. The resulting precipitate was filtered off, washed with acetone and ether, and dried *in vacuo*. The yield of compound **8** was 0.60 g (62.7%).

Dimethyl *N*-(*N*-phosphonocarbamoyl)-L-aspartate, disodium salt (9). A mixture of compound **8** (0.100 g, 0.3519 mmol) and dried $NaHCO_3$ (0.059 g, 0.7038 mmol) was dissolved in water (3 mL) (foaming) and the solution was repeatedly concentrated *in vacuo* with addition of $CHCl_3$ and anhydrous MeOH for complete removal of water. The solid residue was dried *in vacuo* over P_2O_5. The yield of hygroscopic salt **9** was 0.11 g (100%).

Dimethyl *N*-[*N*-(2-oxo-1,3,2λ^5-oxazaphosphinan-2-yl)carbamoyl]-L-aspartate (10). Ester **2** in MeCN (10 mL) was added dropwise at −5 °C for 1 h to a stirred solution of isocyanate **6** (1.60 g, 10 mmol) in anhydrous MeCN (15 mL). The mixture was allowed to warm to room temperature, kept for 1 h, and then cooled to −5 °C. A mixture of 3-aminopropan-1-ol (0.75 g, 10 mmol) and Et_3N (1.06 g, 10.5 mmol) in MeCN (10 mL) was added dropwise for 2 h. The resulting mixture was allowed to warm to 0 °C and another portion of Et_3N (1.06 g, 10.5 mmol) in MeCN (5 mL) was added over 30 min. Stirring was continued at room temperature for 2.5 h. The mixture was left for 16 h. The precipitate that formed was filtered off and washed with MeCN. Dilution of the filtrate produced a precipitate (white resin). The solution was decanted and concentrated. The residue (3.60 g) was chromatographed on SiO_2 and recrystallized from anhydrous MeOH. The yield of compound **10** was 0.21 g (6.5%).

Dimethyl *N*-[(2-oxo-1,3,2λ^5-oxazaphosphinan-2-yl)acetyl]-L-aspartate (13). Phosphinane **11** (1.35 g, 10 mmol) was added dropwise under argon at 60 °C to a solution of ester **12** (2.38 g, 10 mmol) in anhydrous MeCN (2 mL). The reaction mixture was heated at 85 °C for 8 h. The final mixture contained products **13** and **14** in a ratio of 100 : 28 (^{31}P NMR data, see Table 2). The solvent was removed *in vacuo*, the residue (3.62 g) was separated by column chromatography. Phosphinane **13** was isolated as a stable solvate with $CHCl_3$. The yield of solvate **13**·0.3$CHCl_3$ was 1.78 g (55.3%), a viscous glassy mass (see Tables 1, 2).

Dimethyl *N*-{[(3-aminopropoxy)hydroxyphosphoryl]acetyl}-L-aspartate (15). A solution of solvate **13**·0.3$CHCl_3$ (0.75 g, 2.1 mmol) in water (15 mL) was stirred at 35—40 °C for 5 h and repeatedly concentrated *in vacuo* with addition of $CHCl_3$ and MeOH. The dry residue was dissolved in anhydrous MeOH and the resulting solution was filtered and concentrated *in vacuo*. The residue (solidified foam) was dried *in vacuo* over P_2O_5. The yield of amorphous solid betaine **15** was 0.70 g (98.6%).

Dimethyl *N*-(2-oxo-1,3,2λ^5-oxazaphosphinan-2-yl)-L-glutamate (16). A mixture of ester **3** (0.88 g, 5 mmol) and Et_3N (0.51 g, 5 mmol) in MeCN (10 mL) was added dropwise at −3—0 °C for 25 min to a solution of chloride **17** (0.78 g, 5 mmol) in MeCN (10 mL). The reaction mixture was stirred at room temperature for 3 h and kept for 16 h. The precipitate that formed was filtered off and the filtrate was concentrated *in vacuo*. The residue was dissolved in dry acetone and the resulting solution was filtered again and concentrated. The residue (1.13 g) was purified by column chromatography on SiO_2. The product was recrystallized from benzene with a small amount of hexane. The yield of compound **16** was 0.75 g (51.0%).

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