PERKIN 1

Synthesis of model compounds for potential contrast agents containing phosphonate and peptide moieties

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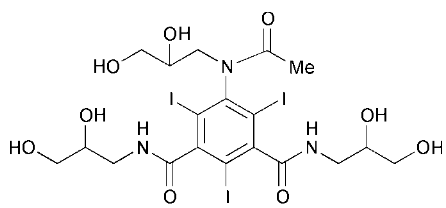
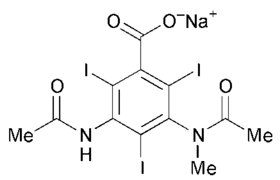
Received (in Cambridge, UK) 16th November 1999, Accepted 19th April 2000
Published on the Web 7th July 2000

The synthesis of dimethyl 2-acetoxy-2-(2,4-diiodo-5-aminophenyl)ethylphosphonate and dimethyl 2-acetoxy-2-(2,4,6-triiodo-3,5-diaminophenyl)ethylphosphonate is described. Several amido and peptidic derivatives of these two compounds were prepared. These products are composed of a combination of structural/functional moieties which pave the way for their potential application as non-ionic selective X-ray contrast agents.

X-Ray contrast agents for medical diagnosis available today are hydrophilic, water-soluble derivatives of iodinated benzene containing at least three iodine atoms, such as Iopamidol[1] and Iohexol.[2] An ideal contrast agent should be completely biologically inert, namely, stable, pharmacologically inactive and efficiently and innocuously excretable. Generally, the clarity of a contrast-enhanced diagnostic examination depends upon the ability of the contrast agent to reach the targeted tissues and/or organs, and on the amount of the X-ray energy absorbed in the targeted region. In the case of ionic contrast agents, encapsulating water-soluble contrast media (CM), into liposomes[3] could be an alternative way towards a truly inert particular CM which would not be rapidly filtered from the blood pool. Moreover, a phospholipid-based compound covalently linked to an X-ray contrast-giving moiety in the form of liposomes, which is used i.v. for X-ray examination of the reticuloendothelial system (especially the liver), has been recently reported.[4] Thus, it might be possible, based on a liposome system and on phospholipids covalently linked to an X-ray contrast agent, that moieties of phosphonic acids or esters thereof that are part of iodinated aromatic compounds could enhance the ability of the contrast agent to reach targeted tissues.[5] In addition, incorporation of such compounds (iodinated aromatic phosphonates) into short peptides might enable the development of new potential contrast agents containing both phosphonic and peptidic moieties. The peptidic moiety could affect the selective affinity of such molecules towards specific tissues.[6] During the last decade, the use of non-ionic contrast agents (*e.g.* Iohexol) has increased at the expense of the ionic ones (*e.g.* sodium metrizoate). This is due to the reduced osmolality, reduced toxicity and improved saftey of the non-ionic contrast agents.[2b,7]



Iohexol



Sodium metrizoate

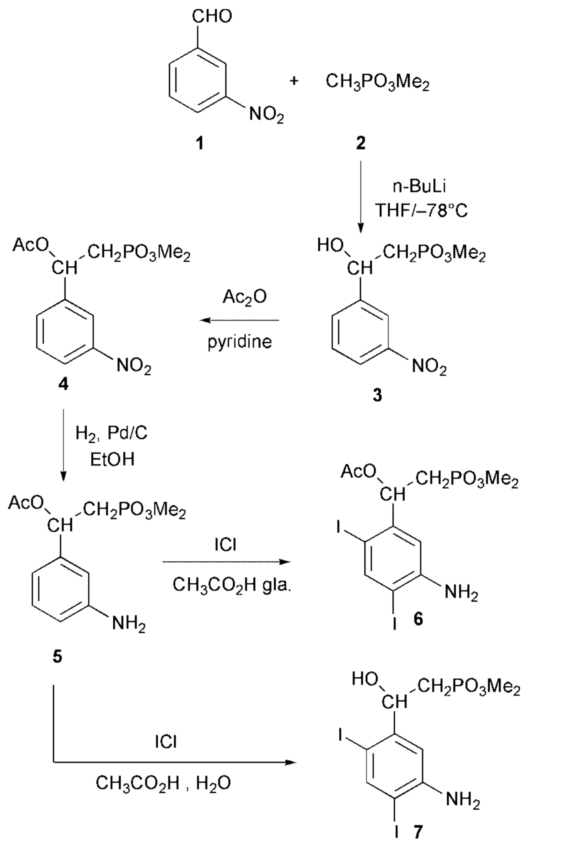
It was the purpose of the present research to design a novel class of X-ray contrast agents (in potential), which both phosphonic acid and peptidic structural moieties are part of, and to develop a synthetic approach for preparing model compounds of this class.

Results and discussion

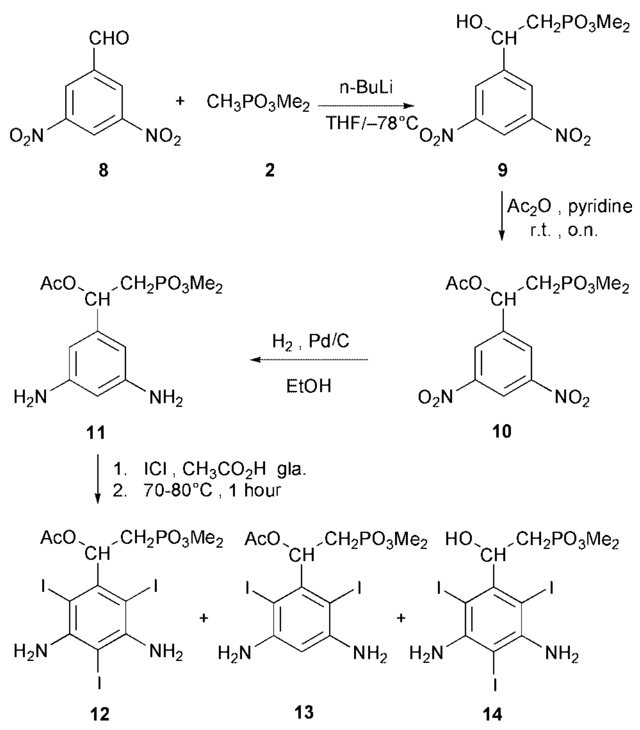
We report herein on a synthetic route to iodinated compounds containing moieties of 2-(aminophenyl or amidophenyl)-2-acetoxyethyl phosphonate, and on 2-acetoxy-2-(2,4,6-triiodo-3,5-diaminophenyl)ethylphosphonate **12**, as well as on some of their amido and peptidic derivatives. These compounds might pave the way, as model compounds, for developing selective and efficient non-ionic contrast agents. The synthesis of the 2,4-diiodo-5-aminophenyl derivative **6** is outlined in Scheme 1. 3-Nitrobenzaldehyde **1** was used as a starting material for the synthesis of the iodinated aromatic phosphonates. The first step consisted of an addition reaction of the lithium salt of dimethyl methylphosphonate **2** to the aldehydic function of **1**. This resulted in a racemic mixture of the hydroxynitrophosphonate (*rac*-**3**) in a 97% yield.[8]

Acetylation of the hydroxy group of **3** to an acetate group in **4** was carried out by reacting it with acetic anhydride in pyridine as a solvent. Compound **4** was obtained in a quantitative yield. The nitro compound **4** was reduced to the amino compound **5**, which provides the activation of the benzene ring needed for introduction of the iodine atoms. The reduction, which was carried out by catalytic hydrogenation, was quantitative. Iodination of the aminophosphonate **5** was accomplished in an acetic acid solution with iodine monochloride[9] to give the diiodinated compound **6** in 81% yield. The product was water-insoluble, and it could therefore be easily isolated and purified. Attempts to form the triiodinated compound failed. On carrying out the iodination of **5** in the presence of water, the iodinated aminohydroxyphosphonate **7** was obtained in a yield of 80%.

The 2,4,6-triiodo-3,5-diaminophenyl derivative **12** was similarly prepared using 3,5-dinitrobenzaldehyde[10] **8** as the starting material (Scheme 2). The first step consisted of an addition reaction of the lithium salt of dimethyl methylphosphonate **2** to the aldehydic function of **8**. This resulted in a racemic mixture of the hydroxydinitrophosphonate (*rac*-**9**) in 50–60% yield.



Scheme 1



Scheme 2

Acetylation of the hydroxy group of **9** yielding the acetate derivative **10** was carried out by reacting it with acetic anhydride in pyridine as a solvent. The mixed ester **10** was obtained in a quantitative yield. The dinitro compound **10** was reduced by a catalytic hydrogenation to the derived diamino phosphonate **11** which was obtained as a spongy solid in 95% yield. Iodination of the diaminophosphonate **11** was accomplished in acetic acid using iodine monochloride[9] as the iodinating agent, to give the triiodo compound **12** in 30% yield. Compounds **13** and **14** are two additional products formed in this iodination reaction mixture, which were isolated by chromatography in 8% and 2% yields, respectively.

Each of the two compounds **6** and **12** was converted into several amido derivates, thus introducing into these molecules structural/functional features which could increase the potential activity of these derived products, as both selective and effective contrast agents.

Several bis compounds, having the general structure **15** (**15a**–**15d**) were prepared by reacting the 5-aminophenyl derivative **6** with each of several aliphatic diacyl chlorides, using pyridine as a solvent [eqn. (1) and Table 1].

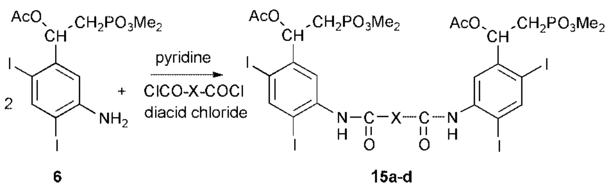
 (1)

Table 1

	n of X = $(–CH_2–)_n$	Yield of **15** (%)
a	0	78
b	2	46
c	4	89
d	6	80

It is noteworthy that each of the compounds **15a**–**15d**, contains two phosphonic acid ester groups, two (acetyl protected) alcoholic functions and four iodine atoms. Basic hydrolysis[11] of the acetate groups in compounds **15a**, **15b** and **15d**, using 1 M NaOH solution in methanol, gave the following dihydroxy bis compounds of type **16** listed in Table 2.

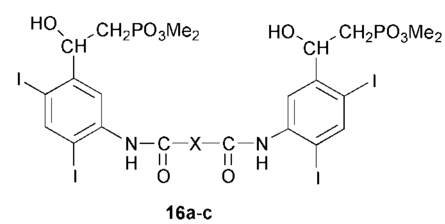
Compounds **16a**–**16c** were obtained in quantitative yields.

The diiodinated phosphonate **6** was coupled with N-protected amino acids or with N-protected dipeptides to yield iodinated aromatic compounds of type **17** containing a peptidic moiety. The coupling reactions were carried out in THF, by using isobutyl chloroformate[12] (mixed anhydride method) as a coupling reagent, in presence of *N*-methylmorpholine.

The synthesized target compounds of type **17** (Table 3) contain an appropriate combination of functional moieties which could significantly increase the efficiency and selectivity of contrast agents, namely: diiodinated aromatic ring, a (protected) alcoholic function, a phosphonic acid ester moiety and a peptidic moiety.

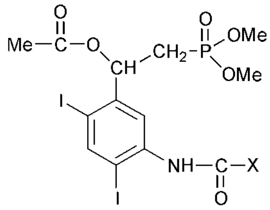
The diiodinated phosphonate **13** and the triiodinated phosphonate **12** were coupled with N-protected amino acid (t-Boc-alanine or *N*-Cbz-glycine) to yield the corresponding iodinated aromatic compounds of types **18**, **19** and **20** containing a peptidic moiety (Table 4). The coupling reactions were carried

Table 2



	n of X = $(–CH_2–)_n$
a	0
b	2
c	6

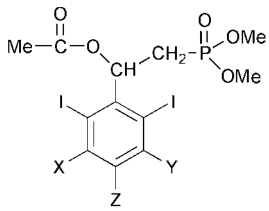
Table 3



17a-g

	X	Yield of **17** (%)
a	$CH(Me)NHCO_2CMe_3$	30
b	$CH_2NHCO_2CH_2Ph$	60
c	$CH(Me)NHCOCH(Me)NHCO_2CMe_3$	30
d	$CH_2NHCOCH_2NHCO_2CH_2Ph$	28
e	$CH_2NHCO–CH(CH_2CHMe_2)NHCO_2CH_2Ph$	20
f	$CH(Me)NHCOCH_2NHCO_2CH_2Ph$	17
g	$CH(CHMe_2)NHCOCH(Me)NHCO_2CH_2Ph$	50

Table 4



18-21

	X	Y	Z
18	$NHCOCH_2NHCO_2CH_2Ph$	$NHCOCH_2NHCO_2CH_2Ph$	H
19	NH_2	$NHCOCH_2NHCO_2CH_2Ph$	I
20	$NHCOCH(Me)NHCO_2CMe_3$	$NHCOCH(Me)NHCO_2CMe_3$	I
21	NHCOMe	NHCOMe	H

out in THF, using isobutyl chloroformate[12] (mixed anhydride method) as a coupling reagent, in the presence of *N*-methylmorpholine.

The two aromatic amino groups in compound **13** were acetylated to the corresponding acetamide derivative **21** in an 80% yield, by reaction with acetic anhydride in pyridine as a solvent. It should be noted that amides, as functional groups in contrast agents, proved to form effective linkages due to their stability and high capacity to form transient bonds with hydrogens of the aqueous milieu.[13] Compounds **18**–**20**, which contain a polyiodinated aromatic ring (contrast element), a (protected) alcoholic function, a phosphonic acid ester moiety and a peptidic residue might also be model compounds for efficient contrast agents. The peptidic moiety could affect the selective affinity of these potential contrast agents towards specific tissues.[6] The phosphonic ester, being part of the iodinated aromatic compounds, could enhance the ability of the contrast agent to reach targeted tissues.[5]

Experimental

General

Melting points were determined with a Buchi SMP-20 melting point apparatus. IR spectra were recorded with a Nicolet FT-IR 205 spectrometer. ^{1}H-NMR spectra were recorded with a Bruker AC-200E NMR spectrometer at a frequency of 200 MHz in $CDCl_3$ using TMS as internal standard. ^{13}C-NMR spectra were recorded with a Bruker AC-200E NMR spectrometer at a frequency of 50.3 MHz. *J* values are given in Hz. ^{31}P-NMR spectra were recorded with a Bruker ARX-500E NMR spectrometer at a frequency of 202.46 MHz, by using H_3PO_4 as an external standard. A double-focus 21-491B (DuPont) spectrometer and VS Autospsec. M250 were used for mass spectrometry. THF was purified by distillation over metallic sodium. Pyridine was purified by distillation after standing over KOH. Alumina (Merck, Aluminium oxide 90) and silica (Merck, Silica gel 60H) were used for column chromatography.

Dimethyl 2-hydroxy-2-(3-nitrophenyl)ethylphosphonate 3

A precooled (−78 °C) solution of *n*-BuLi (1.6 M in *n*-hexane, 4.55 ml, 7.28 mmol) was added dropwise under dry nitrogen during 15 min to a stirred solution of dimethyl methylphosphonate **2** (0.82 g, 6.62 mmol) in dry tetrahydrofuran (THF) at −78 °C. A solution of the aldehyde **1** (1 g, 6.62 mmol) in 20 ml of dry THF was introduced dropwise over 15 min, and the reaction was allowed to continue for another 30 min at −78 °C, and then another 30 min at room temperature. Water (20 ml) was then added, and the mixture was extracted with three 20 ml portions of diethyl ether, followed by extraction with two 20 ml portions of CH_2Cl_2. The combined extracts were dried with anhydrous $MgSO_4$, and the residue which was obtained after removal of the solvent was crystallized from dichloromethane–petroleum ether (9 : 1) to give 3.53 g (97%) of **3** as a yellow solid, mp 82 °C (Found: C, 43.28; H, 5.47; N, 5.02; P, 11.01. $C_{10}H_{14}NO_6P$ requires C, 43.65; H, 5.13; N, 5.05; P, 11.26%); IR(KBr), ν/cm^{-1} 3338, 1532, 1244, 1038; δ_H 2.12–2.24 (2 H, m), 3.75 (3 H, d, *J* 10), 3.81 (3 H, d, *J* 10), 4.27 (1 H, br s), 5.14–5.29 (1 H, m), 7.53 (1 H, t, *J* 8), 7.75 (1 H, d, *J* 8), 8.14 (1 H, d, *J* 8), 8.25 (1 H, s); δ_C 35.12 (dt, J_{C-P} 137.31), 52.42–52.89 (2q), 67.76 (dd, J_{C-P} 4.07), 120.72 (d), 122.62 (d), 129.44 (d), 131.58 (d), 146.08 (d, J_{C-P} 17.10), 148.51 (s); δ_P 31.62; *m*/*z* (%) 257 (10) [M$^+$ − 18], 152 (17), 124 (100), 109 (10).

Dimethyl 2-acetoxy-2-(3-nitrophenyl)ethylphosphonate 4

Acetic anhydride (0.68 ml, 7.27 mmol) was added to a stirred solution of compound **3** (1 g, 3.63 mmol) in dry pyridine. The reaction mixture was stirred overnight at room temperature. The solvent was evaporated under reduced pressure. The residue was dissolved in chloroform, washed twice with a cold solution of 2 M HCl, dried with anhydrous $MgSO_4$, filtered and the solvent was evaporated under reduced pressure to give 2.3 g (quantitative yield) of **4** as a yellow oil (Found: C, 45.81; H, 5.18; N, 4.28. $C_{12}H_{16}NO_7P$ requires C, 45.43; H, 5.08; N, 4.42; P, 9.76%); IR(neat), ν/cm^{-1} 1750, 1548, 1222, 1037; δ_H 2.11 (3 H, s), 2.18–2.62 (2 H, m), 3.66 (3 H, d, *J* 10), 3.69 (3 H, d, *J* 10), 6.10 (1 H, m), 7.55 (1 H, t, *J* 8), 7.72 (1 H, d, *J* 8), 8.18 (1 H, d, *J* 8), 8.24 (1 H, s); δ_C 20.83 (q), 32.42 (dt, J_{C-P} 140.84), 52.25–52.46 (2q), 69.61 (d), 121.41 (d), 123.30 (d), 129.50 (d), 132.79 (d), 141.79 (d, J_{C-P} 7.64), 148.47 (s), 168.90 (s); δ_P 27.53; *m*/*z* (%) 274 (50) [M$^+$ − Ac], 258 (100) [M$^+$ − OAc], 228 (6), 124 (5).

Dimethyl 2-acetoxy-2-(3-aminophenyl)ethylphosphonate 5

A catalytic amount of Pd/C (10% Pd) was added to a medium-pressure hydrogenation flask which contained a solution of **4** (1.5 g, 4.73 mmol) in ethanol. The hydrogenation was carried out at a pressure of 5 atm for 4 h. The solution was filtered and dried with anhydrous $MgSO_4$. The solvent was removed under reduced pressure to give 1.34 g (99%) of **5** as a yellow oil (Found: C, 49.84; H, 6.01; N, 5.03. $C_{12}H_{18}NO_5P$ requires C, 50.18; H, 6.32; N, 4.88; P, 10.78%); IR(neat) ν/cm^{-1} 3388, 1652, 1211, 1043; δ_H 2.06 (3 H, s), 2.15–2.58 (2 H, m), 3.64 (3 H, d, *J* 10), 3.66 (3 H, d, *J* 10), 5.96 (1 H, m), 6.64 (1 H, d, *J* 8), 6.73 (1 H, s), 6.75 (1 H, d, *J* 8), 7.11 (1 H, t, *J* 8); δ_C 21.08 (q), 32.46 (dt, J_{C-P} 139.83), 52.16–52.58 (2q), 70.37 (d), 114.17 (d), 116.02 (d), 117.41 (d), 129.63 (d), 141.00 (d, J_{C-P} 11.06), 144.93 (s), 169.24 (s); δ_P 27.71; *m*/*z* (%) 287 (99) [M$^+$], 245 (25) [MH$^+$ − Ac], 288 (15) [M$^+$ − OAc], 124 (6).

Dimethyl 2-acetoxy-2-(2,4-diiodo-5-aminophenyl)ethylphosphonate 6

A solution of iodine monochloride (1.41 g, 8.71 mmol) in 5 ml of glacial acetic acid was added dropwise to a stirred solution of **5** (1 g, 3.48 mmol) in 10 ml of glacial acetic acid, over a period of 1.5 h. The reaction mixture was stirred at room temperature for an additional 1–1.5 h. It was then heated to 80 °C, kept at that temperature for 40 min and then allowed to cool to room temperature. The excess of iodine monochloride was eliminated by addition of solid sodium bisulfite followed by sodium bicarbonate to pH 7. The reaction mixture was extracted with three 20 ml portions of CH_2Cl_2. The combined extracts were dried with anhydrous $MgSO_4$, filtered, and the solvent was evaporated under reduced pressure. The residue was purified by chromatography (silica gel 60H) using methylene chloride as the eluent. 3.37 g (60%) of **6** were obtained as a yellow solid, mp 128–129 °C (Found: C, 27.00; H, 3.14; N, 2.44. $C_{12}H_{16}I_2NO_5P$ requires C, 26.74; H, 2.99; I, 47.08; N, 2.60; P, 5.75%); IR(KBr): ν/cm^{-1} 3448, 1750, 1625, 1238, 1035, 762; δ_H 2.12 (3 H, s), 2.19–2.33 (2 H, m), 3.71 (3 H, d, *J* 11), 3.77 (3 H, d, *J* 12), 6.03 (1 H, m), 6.78 (1 H, s), 7.97 (1 H, s); δ_C 20.91 (q), 31.14 (dt, $J_{C\text{-}P}$ 139.33), 52.46–52.79 (2q), 73.20 (d), 80.99 (s), 84.48 (s), 112.25 (d), 143.35 (d, $J_{C\text{-}P}$ 14.08), 147.50 (s), 147.71 (d), 169.15 (s); δ_P 27.85; *m*/*z* (%) 539 (28) [M$^+$], 412 (100) [M$^+$ − I], 352 (41) [M$^+$ − OAc − 1].

Dimethyl 2-hydroxy-2-(2,4-diiodo-5-aminophenyl)ethylphosphonate 7

This compound was prepared from **5** (0.5 g, 1.74 mmol) and ICl (0.7 g, 4.35 mmol) in analogy to the preparation of compound **6**, in 5 ml of glacial acetic acid. Iodine monochloride was added to the reaction mixture and stirring was continued for an additional 1–1.5 h. Water (5–10 ml) was added, the reaction mixture was further stirred for 30 min, and was slowly heated to 80 °C. The crude residue isolated after workup was crystallized from CH_2Cl_2–petroleum ether (9:1) to give 1.29 g (50%) of **7** as a yellow-brown solid, mp 148–149 °C (Found: C, 24.32; H, 3.00; N, 2.63. $C_{10}H_{14}I_2NO_4P$ requires C, 24.17; H, 2.84; I, 51.07; N, 2.82; P, 6.23%). IR(KBr): ν/cm^{-1} 3363, 3020, 1605, 1216, 1023, 757; δ_H 1.77–2.41 (2 H, m), 3.73 (3 H, d, *J* 10), 3.84 (3 H, d, *J* 10), 4.22 (2 H, br s), 5.03 (1 H, m), 7.07 (1 H, s), 7.92 (1 H, s); δ_C 33.19 (dt, $J_{C\text{-}P}$ 135.30), 51.58–52.33 (2q), 70.65 (dd, $J_{C\text{-}P}$ 5.03), 79.44 (s), 82.78 (s), 112.75 (d), 146.01 (s), 147.79 (d, $J_{C\text{-}P}$ 16.04), 149.08 (d); δ_P 31.35; *m*/*z* (%) 497.8 (45) [MH$^+$], 479.8 (100) [MH$^+$ − 18], 387.9 (12) [M$^+$ − 109], 369.9 (50) [M$^+$ − I].

Dimethyl 2-hydroxy-2-(3,5-dinitrophenyl)ethylphosphonate 9

A precooled (−78 °C) solution of *n*-BuLi (1.6 M in *n*-hexane, 7.01 ml, 11.22 mmol) was added dropwise under dry nitrogen for 15 min to a stirred solution of dimethyl methylphosphonate **2** (1.26 g, 10.20 mmol) in dry tetrahydrofuran (THF) at −78 °C. A solution of the aldehyde **8** (2 g, 10.20 mmol) in 40 ml of dry THF was introduced dropwise over 5 min, and the reaction was allowed to continue for another 30 min at −78 °C, and then another 30 min at room temperature. Water (40 ml) was then added and the mixture was extracted with three 40 ml portions of diethyl ether, followed by extraction with two 40 ml portions of CH_2Cl_2. The combined extracts were dried with anhydrous $MgSO_4$ and the residue, obtained after removal of the solvent, was crystallized from dichloromethane–petroleum ether (8:2) to give 3.59 g (55%) of **9** as a white solid, mp 88–89 °C (Found: C, 37.66; H, 4.09; N, 8.93. $C_{10}H_{13}N_2O_8P$ requires C, 37.51; H, 4.09; N, 8.75; P, 9.67%); IR(KBr): ν/cm^{-1} 3248, 1535, 1342, 1230, 1032, 856; δ_H 2.13–2.28 (2 H, m), 3.79 (3 H, d, *J* 12), 3.85 (3 H, d, *J* 12), 4.79 (br s, OH), 5.29 (1 H, m), 8.61 (2 H, d, *J* 2), 8.95 (1 H, d, *J* 2); δ_C 33.61 (dt, $J_{C\text{-}P}$ 136.81), 51.68–52.00 (2q), 66.46 (d), 117.26 (d), 126.50 (2d), 147.79 (2s), 149.70 (d, $J_{C\text{-}P}$ 13.53); δ_P 30.44; *m*/*z* (%) 303 (12) [M$^+$ − 17], 302 (10) [M$^+$ − 18], 272 (30) [M$^+$ − OH − OMe], 124 (100).

Dimethyl 2-acetoxy-2-(3,5-dinitrophenyl)ethylphosphonate 10

Acetic anhydride (1.17 ml, 12.5 mmol) was added to a stirred solution of compound **9** (2 g, 6.25 mmol) in dry pyridine. The reaction mixture was stirred overnight at room temperature. The solvent was evaporated under reduced pressure. The residue was dissolved in chloroform, washed twice with a cold solution of 2 M HCl, dried with anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure to give 3.39 g (quantitative yield) of **10** as a yellow oil (Found: C, 39.91; H, 4.21; N, 7.89. $C_{12}H_{15}N_2O_9P$ requires C, 39.79; H, 4.17; N, 7.73; P, 8.55%); IR(neat): ν/cm^{-1} 1747, 1541, 1346, 1228, 1031, 813; δ_H 2.09 (3 H, s), 2.20–2.58 (2 H, m), 3.62 (3 H, d, *J* 12), 3.67 (3 H, d, *J* 12), 6.11 (1 H, m), 8.51 (2 H, d, *J* 2), 8.87 (1 H, d, *J* 2); δ_C 20.77 (q), 32.15 (dt, $J_{C\text{-}P}$ 141.34), 52.58 (2q), 69.24 (d), 118.60 (d), 126.93 (2d), 144.20 (d, $J_{C\text{-}P}$ 9.55), 148.62 (2s), 168.96 (s); δ_P 26.43; *m*/*z* (%) 363 (100) [MH$^+$], 303 (65) [M$^+$ − OAc], 273 (45), 257 (15), 210 (10).

Dimethyl 2-acetoxy-2-(3,5-diaminophenyl)ethylphosphonate 11

An equivalent amount of Pd/C (10% Pd) was added to a medium-pressure hydrogenation flask which contained a solution of **10** (1.5 g, 4.14 mmol) in ethanol. The hydrogenation was carried out at a pressure of 5 atm for 24 h. The solution was filtered and dried with anhydrous $MgSO_4$. The solvent was removed under reduced pressure to give 1.18 g (95%) of **11** as a spongy solid (Found: C, 48.00; H, 6.26; N, 8.92. $C_{12}H_{19}N_2O_5P$ requires C, 47.68; H, 6.34; N, 9.27; P, 10.25%); δ_H 2.06 (3 H, s), 2.10–2.53 (2 H, m), 3.44 (br s), 3.67 (3 H, d, *J* 12), 3.68 (3 H, d, *J* 12), 5.86 (1 H, m), 5.90 (1 H, d, *J* 2), 6.05 (2 H, d, *J* 2); δ_C 21.03 (q), 32.30 (dt, $J_{C\text{-}P}$ 140.33), 52.48 (2q), 70.37 (d), 101.83 (d), 103.94 (2d), 142.11 (d, $J_{C\text{-}P}$ 10.81), 147.62 (2s), 169.44 (s); δ_P 31.73; *m*/*z* (%) 303 (25) [MH$^+$], 302 (35) [M$^+$], 243 (100) [M$^+$ − OAc].

Dimethyl 2-acetoxy-2-(2,4,6-triiodo-3,5-diaminophenyl)ethylphosphonate 12

A solution of iodine monochloride (0.94 g, 5.79 mmol) in 10 ml of glacial acetic acid was added dropwise to a stirred solution of **11** (0.5 g, 1.65 mmol) in 10 ml of glacial acetic acid over a period of 1 h. The reaction mixture was stirred at room temperature for an additional 1–1.5 h. It was then heated to 80 °C, kept at that temperature for 1 h and then allowed to cool to room temperature. The excess of iodine monochloride was eliminated by addition of a 10% solution of sodium bisulfite followed by sodium bicarbonate to pH 7. The reaction mixture was extracted with three 20 ml portions of CH_2Cl_2. The combined extracts were dried with anhydrous $MgSO_4$, filtered, and the solvent was evaporated under reduced pressure. The residue was purified by chromatography (alumina) using ethyl acetate and 5% methanol in ethyl acetate as the eluents. 1.34 g (30%) of **12** were obtained (Found: C, 20.86; H, 2.03; I, 56.32; N, 4.53. $C_{12}H_{16}I_3N_2O_5P$ requires C, 21.20; H, 2.37; I, 55.99; N, 4.12; P, 4.56%); IR(neat): ν/cm^{-1} 3471–3374, 2956, 1743, 1610, 1438, 1241, 1034, 761; δ_H 2.08 (3 H, s), 2.23–2.47 (1 H, m), 2.78–2.98 (1 H, m), 3.73 (3 H, d, *J* 12), 3.75 (3 H, d, *J* 12), 4.51 (br s), 6.65 (1 H, m); δ_C 20.68 (q), 28.26 (dt, $J_{C\text{-}P}$ 141.34), 52.58 (2q), 68.05 (d), 128.31 (2s), 139.69 (s), 169.57 (s); δ_P 28.70; ESMS: *m*/*z* (%) 636 (35) [M$^+$ − Ac], 620 (55) [M$^+$ − OAc].

Dimethyl 2-acetoxy-2-(2,6-diiodo-3,5-diaminophenyl)ethylphosphonate 13. Compound **13** was obtained as a by-product by iodination of **11**, after purification of the crude reaction product by chromatography, in a yield of 8% (0.21 g) (Found: C, 25.67; H, 3.19; I, 46.12; N, 4.83. $C_{12}H_{17}I_2N_2O_5P$ requires C, 26.01; H, 3.09; I, 45.81; N, 5.06; P, 5.59%); IR(neat): ν/cm^{-1} 3460–3320, 2946, 1741, 1620, 1418, 1240, 1033, 759; δ_H 2.13

(3 H, s), 2.31–2.48 (1 H, m), 3.74 (3 H, d, *J* 10), 3.76 (3 H, d, *J* 10), 6.68 (1 H, m), 7.95 (1 H, s); δ_C 20.67 (q), 28.21 (dt, J_{C-P} 140.33), 52.58 (2q), 68.05 (d), 107.41 (d), 111.55 (2s), 133.58 (s), 169.60 (s); δ_P 28.44; *m*/*z* (%) 553 (3) [M^+], 426 (2) [$M^+ - 127$], 317 (90) [$M^+ - 127 - 109$], 274 (29) [317 −43], 109 (40) [-PO_3-Me_2], 43 (100) [-Ac].

Dimethyl 2-hydroxy-2-(2,4,6-triiodo-3,5-diaminophenyl)ethylphosphonate 14. Compound **14** was obtained as a by-product by iodination of **11**, after purification of the crude reaction product by chromatography, in a yield of 2% (0.084 g) (Found: C, 18.76; H, 2.45; N, 4.13; I, 60.02. $C_{10}H_{14}I_3N_2O_4P$ requires C, 18.83; H, 2.21; I, 59.68; N, 4.39; P, 4.86%); δ_H 2.32–2.51 (1 H, m), 2.66–2.86 (1 H, m), 3.68 (3 H, d, *J* 12), 3.72 (3 H, d, *J* 12), 5.83 (1 H, m); δ_C 31.46 (dt, J_{C-P} 148.84), 53.39 (2q), 67.53 (d), 108.32 (s), 136.89 (s), 142.11 (s); δ_P 28.45; *m*/*z* (%) 639.25 (14) [MH^+], 603.36 (29) [$M^+ - 18 - NH_2$], 577.37 (70) [$MH^+ -$ 2(OMe)], 549.34 (100).

N,*N*′-Bis{2,4-diiodo-5-[1-acetoxy-2-(dimethylphosphoryl)-ethyl]phenyl}oxamide 15a

Oxalyl chloride (0.01 ml, 0.13 mmol) was added under nitrogen to a stirred solution of **6** (0.15 g, 0.27 mmol) in dry pyridine (2 ml) at 0 °C. The reaction mixture was stirred for 1 h at that temperature and then was heated to room temperature and further stirred for 4 h. A cold aqueous solution of 10% HCl was then added to the reaction mixture (to pH 7). The reaction mixture was extracted with five 5 ml portions of CH_2Cl_2. The combined organic extracts were washed with water, then with a 2% $NaHCO_3$ solution, and again with water. The organic phase was dried with anhydrous $MgSO_4$ and filtered. The solvent was removed from the filtrate under reduced pressure to give 0.35 g (78%) of **15a** as a yellow oil (Found: C, 27.82; H, 2.86; N, 2.31. $C_{26}H_{30}I_4N_2O_{12}P_2$ requires C, 27.58; H, 2.67; I, 44.84; N, 2.47; P, 5.47%); IR(neat): *ν*/cm^{-1} 3300, 2955, 1745, 1561, 1444, 1372, 1221, 1031, 755; δ_H 2.15 (6 H, s), 2.24–2.36 (4 H, m), 3.75 (6 H, d, *J* 10), 3.76 (6 H, d, *J* 10), 6.07 (2 H, m), 8.24 (2 H, s), 8.43 (2 H, br s), 8.45 (2 H, s); δ_C 17.25 (2q), 30.11 (2dt, J_{C-P} 139.83), 51.67 (4q), 72.58 (2d), 88.64 (2s), 91.18 (2s), 117.34 (2d), 136.59 (2s), 143.42 (2d, J_{C-P} 13.07), 147.32 (2d), 156.12 (2s), 168.36 (2s); δ_P 28.10; *m*/*z* (%) 1132.5 (100) [MH^+], 1072 (5) [$M^+ -$ OAc], 1013 (72) [$M^+ -$ 2OAc].

N,*N*′-Bis{2,4-diiodo-5-[1-acetoxy-2-(dimethoxyphosphoryl)-ethyl]phenyl}succinamide 15b

Succinyl chloride (0.03 ml, 0.27 mmol) was added under nitrogen to a solution of **6** (0.3 g, 0.55 mmol) in dry pyridine. The reaction mixture was stirred for 24 hours at room temperature. The work-up was performed analogously to that used for the preparation of **15a**. The crude residue was purified by chromatography (Alumina) using 2% methanol in ethyl acetate as the eluent. 0.43 g (46%) of **15b** were obtained as a yellow oil (Found: C, 29.11; H, 3.13; I, 44.03; N, 2.21. $C_{28}H_{34}I_4N_2O_{12}P_2$ requires C, 28.99; H, 2.95; I, 43.75; N, 2.41; P, 5.34%); IR(neat): *ν*/cm^{-1} 3290, 2955, 1744, 1683, 1557, 1499, 1371, 1237, 1030, 757; δ_H 2.13 (6 H, s), 2.25–2.37 (4 H, m), 2.88 (4 H, s), 3.75 (6 H, d, *J* 10), 3.76 (6 H, d, *J* 10), 6.08 (2 H, m), 7.74 (2 H, s), 8.20 (2 H, s), 8.33 (2 H, s); δ_C 20.99 (2q), 31.14 (2dt, J_{C-P} 39.33), 32.36 (2t), 52.58 (2q), 52.68 (2q), 73.64 (2d), 89.71 (2s), 90.53 (2s), 119.33 (2d), 138.97 (2s), 144.02 (2d, J_{C-P} 13.58), 147.86 (2d), 169.39 (2s), 169.93 (2s); δ_P 27.67; *m*/*z* (%): 1160.6 (100) [MH^+], 1041 (60) [$M^+ -$ 2OAc], 914 (25) [$M^+ - 2(CH_2PO_3Me_2)$].

N,*N*′-Bis{2,4-diiodo-5-[1-acetoxy-2-(dimethoxyphosphoryl)-ethyl]phenyl}hexanediamide 15c

Adipoyl chloride (0.013 ml, 0.092 mmol) was added under nitrogen to a stirred solution of **6** (0.1 g, 0.185 mmol), in dry pyridine. The reaction mixture was stirred for 1 h at room temperature and then slowly heated to 50 °C, kept at room temperature for 2 h and then allowed to cool to room temperature. The work up was performed analogously to that used for preparation of **15a** to give 0.292 g (89%) of **15c** as a yellow oil (Found: C, 29.98; H, 3.01; I, 43.10; N, 2.09. $C_{30}H_{38}I_4N_2O_{12}P_2$ requires C, 30.33; H, 3.22; I, 42.72; N, 2.36; P, 5.21%); IR(neat): *ν*/cm^{-1} 3305, 2962, 1744, 1690, 1554, 1371, 1260, 1027, 800; δ_H 1.85 (4 H, t, *J* 6), 2.19 (6 H, s), 2.19–2.34 (4 H, m), 2.49 (4 H, t, *J* 6), 3.75 (6 H, d, *J* 12), 3.77 (6 H, d, *J* 12), 6.08 (2 H, m), 7.50 (2 H, s), 8.16 (2 H, s), 8.33 (2 H, s); δ_C 20.93 (2q), 24.71 (2t), 31.31 (2dt, J_{C-P} 138.82), 37.43 (2t), 52.55 (4q), 73.45 (2dd, J_{C-P} 5.03), 89.72 (2s), 90.31 (2s), 119.37 (2d), 139.09 (2s), 144.16 (2s), 147.67 (2d), 169.01 (2s), 170.41 (2s); δ_P 27.72; *m*/*z* (%) 1188.8 (90) [M^+], 1128.6 (10) [$M^+ -$ OAc], 1068.7 (100) [$MH^+ -$ 2OAc], 942.8 (40) [$M^+ - 2(CH_2PO_3Me_2)$].

N,*N*′-Bis{2,4-diiodo-5-[1-acetoxy-2-(dimethoxyphosphoryl)-ethyl]phenyl}octanediamide 15d

This compound was prepared analogously to **15a** from **6** (0.15 g, 0.278 mmol) and suberoyl chloride (0.025 ml, 0.139 mmol) to yield 0.405 g (80%) of **15d** as an oil (Found: C, 31.89; H, 3.73; I, 41.52; N, 2.17. $C_{32}H_{42}I_4N_2O_{12}P_2$ requires C, 31.60; H, 3.48; I, 41.74; N, 2.30; P, 5.09%); IR(neat): *ν*/cm^{-1} 3300, 2953, 1744, 1681, 1498, 1371, 1235, 1034, 753; δ_H 1.47 (4 H, m), 1.78 (4 H, m), 2.14 (6 H, s), 2.25–2.48 (8 H, m), 3.76 (6 H, d, *J* 12), 3.77 (6 H, d, *J* 12), 6.09 (2 H, m), 7.48 (2 H, s), 8.19 (2 H, s), 8.35 (2 H, s); δ_C 20.89 (2q), 25.09 (2t), 28.75 (2t), 31.06 (2dt, J_{C-P} 139.83), 37.71 (2t), 52.58 (4q), 73.59 (2d), 89.83 (2s), 90.14 (2s), 119.13 (2d), 139.01 (2s), 143.98 (2d, J_{C-P} 14.08), 147.61 (2d), 169.39 (2s), 171.16 (2s); δ_P 27.75; *m*/*z* (%) 1216.6 (100) [MH^+], 1098 (73) [$M^+ -$ 2OAc], 970 (25) [$M^+ - 2(CH_2PO_3Me_2)$].

N,*N*′-Bis{2,4-diiodo-5-[1-hydroxy-2-(dimethoxyphosphoryl)-ethyl]phenyl}oxamide 16a

A solution of 1 M NaOH (0.795 ml, 0.795 mmol) was added to a stirred solution of **15a** (0.2 g, 0.176 mmol) in methanol (the amount needed for dissolving **15a**). The reaction mixture was stirred at room temperature for 4 h and the methanol was then evaporated under reduced pressure. The residue left behind was acidified to pH 7 using aqueous 1 M HCl solution. The aqueous reaction mixture was extracted with five 5 ml portions of dichloromethane. The combined extracts were dried with anhydrous $MgSO_4$, filtered, and the solvent evaporated under reduced pressure to give 0.185 g (quantitative yield) of **16a** (Found: C, 24.92; H, 2.83; I, 48.11; N, 2.93. $C_{22}H_{26}I_4N_2O_{10}P_2$ requires C, 25.21; H, 2.50; I, 48.44; N, 2.67; P, 5.91%); IR(neat): *ν*/cm^{-1} 3400, 2360, 1698, 1558, 1372, 1180, 1029; δ_H 1.98–2.37 (4 H, m), 3.74 (6 H, d, *J* 10), 3.78 (6 H, d, *J* 10), 5.15 (2 H, m), 8.25 (2 H, s), 8.32 (2 H, s); δ_C 34.38 (2dt, J_{C-P} 137.82), 53.60 (4q), 73.13 (2d), 92.47 (2s), 93.82 (2s), 122.65 (2d), 140.28 (2s), 149.71 (2d), 150.04 (2d, J_{C-P} 16.09), 162.98 (2s); δ_P 31.58; *m*/*z* (%) 1071 (25) [MNa^+], 1048 (100) [M^+], 1012 (35) [$M^+ - 2H_2O$].

N,*N*′-Bis{2,4-diiodo-5-[1-hydroxy-2-(dimethoxyphosphoryl)-ethyl]phenyl}succinamide 16b

This compound was prepared analogously to **16a** from **15b** (0.2 g, 0.172 mmol) and 1 M NaOH solution (0.775 ml, 0.775 mmol), to give 0.185 g (quantitative yield) of **16b** (Found: C, 26.54; H, 3.00; N, 2.89. $C_{24}H_{30}I_4N_2O_{10}P_2$ requires C, 26.77; H, 2.81; I, 47.17; N, 2.60; P, 5.76%); δ_H 1.98–2.38 (4 H, m), 2.87 (4 H, s), 3.76 (6 H, d, *J* 10), 3.83 (6 H, d, *J* 10), 5.14 (2 H, "t"), 7.74 (2 H, s), 8.17 (2 H, s), 8.39 (2 H, s); δ_C 2.07–2.27 (4 H, m), 2.83 (4 H, s), 3.74 (6 H, d, *J* 12), 3.77 (6 H, d, *J* 12), 5.12 (2 H, m), 7.75 (2 H, s), 8.29 (2 H, s); δ_P 31.36; *m*/*z* (%) 1076.7 (100) [MH^+], 1040.8 (12) [$M^+ -$ 2OH], 951 (32) [$M^+ - 124$].

N,*N*′-Bis{2,4-diiodo-5-[1-hydroxy-2-(dimethoxyphosphoryl)-ethyl]phenyl}octanediamide 16c

This compound was prepared analogously to **16a** from **15d** (0.038 g, 0.031 mmol) and 1 M NaOH solution (0.140 ml, 0.140

mmol), to give 0.035 g (quantitative yield) of **16c** (Found: C, 30.03; H, 3.01; I, 45.12; N, 2.33. $C_{28}H_{38}I_4N_2O_{10}P_2$ requires C, 29.70; H, 3.38; I, 44.84; N, 2.47; P, 5.47%); IR(neat): ν/cm^{-1} 3540, 2963, 1733, 1448, 1370, 1220, 1033, 754; δ_H 1.46 (4 H, m), 1.77 (4 H, m), 2.01–2.46 (8 H, m), 3.78 (6 H, d, *J* 10), 3.83 (6 H, d, *J* 10), 5.14 (2 H, m), 7.49 (2 H, d, *J* 10), 8.15 (2 H, d, *J* 3), 8.34 (2 H, d, *J* 8); δ_C 25.03 (2t), 28.64 (2t), 29.67 (2t), 35.86 (2dt, J_{C-P} 147.37), 52.84 (4q), 71.85 (2d), 90.26 (2s), 90.53 (2s), 120.88 (2d), 139.13 (2s), 147.30 (2d + 2s), 171.33 (2s); δ_P 31.71; *m*/*z* (%) 1155 (15) [MNa$^+$], 1132 (100) [M$^+$].

Dimethyl 2-acetoxy-2-{2,4-diiodo-5-[*N*-(*tert*-butyloxycarbonyl)-alanylamino]phenyl}ethylphosphonate 17a

Isobutyl chloroformate (0.072 ml, 0.555 mmol) was added dropwise to a solution of t-Boc-alanine (1.05 g, 0.555 mmol) and *N*-methylmorpholine (0.66 ml, 0.555 mmol) in dry THF (5 ml) at −20 °C (CO_2/CCl_4 bath) and the reaction mixture stirred for 15 min. A solution of **6** (0.3 g, 0.555 mmol) in dry THF (3 ml) was then introduced dropwise over 15 min, and the reaction mixture was further stirred for another 1 h at −20 °C, followed by additional 15 min at room temperature. The reaction mixture was filtered, and the solvent was evaporated under reduced pressure. The residue was dissolved in 20 ml of CH_2Cl_2, washed with 0.2 M HCl solution, then with 5% $NaHCO_3$ solution and then with brine. The organic phase was dried using anhydrous $MgSO_4$, filtered, and the solvent was evaporated under reduced pressure. The residue was purified by chromatography (alumina) using a 5% methanol solution in ethyl acetate as the eluent, to give 0.236 g (30%) of **17a** as an oil (Found: C, 33.93; H, 4.42; N, 3.58. $C_{20}H_{29}I_2N_2O_8P$ requires C, 33.82; H, 4.12; I, 35.74; N, 3.94; P, 4.36%); IR(neat): ν/cm^{-1} 3400, 1690, 1499, 1371, 1246, 1030; δ_H 1.47–1.50 (9 H + 3 H, s + d), 2.14 (3 H, s), 2.22–2.34 (2 H, m), 3.76 (3 H, d, *J* 12), 3.77 (3 H, d, *J* 12), 4.32 (1 H, br s), 4.92 (1 H, d, *J* 6), 6.07 (1 H, m), 8.18 (1 H, s), 8.39 (1 H, s), 8.42 (1 H, d, *J* 4); δ_H 17.88 (q), 20.95 (q), 28.54 (3q), 31.32 (dt, J_{C-P} 139.83), 51.44 (d), 52.53–52.63 (2q), 73.55 (d), 80.81 (s), 89.38 (s), 90.30 (s), 118.92 (d), 139.17 (s), 144.27 (d, J_{C-P} 15.69), 147.81 (d), 155.33 (s), 169.11 (s), 170.94 (s); δ_C 27.68; *m*/*z* (%) 733 (10) [MNa$^+$], 711 (100) [MH$^+$], 654 (25) [MH$^+$ − 57], 594 (21) [MH$^+$ − 57 − 59].

Dimethyl 2-acetoxy-2-{2,4-diiodo-5-[*N*-(benzyloxycarbonyl)-glycylamino]phenyl}ethylphosphonate 17b

This compound was prepared analogously to **17a** from *N*-Cbz-glycine (0.15 g, 0.74 mmol) and compound **6** (0.2 g, 0.37 mmol) to yield 0.32 g (60%) of **17b** as an oil (Found: C, 35.91; H, 3.81; I, 35.10; N, 4.12. $C_{22}H_{25}I_2N_2O_8P$ requires C, 36.19; H, 3.45; I, 34.76; N, 3.84; P, 4.24%); IR(neat): ν/cm^{-1} 3343, 1720, 1702, 1239, 1030; δ_H 2.12 (3 H, s), 2.20–2.32 (2 H, m), 3.74 (3 H, d, *J* 12), 3.75 (3 H, d, *J* 12), 3.99 (2 H, d, *J* 6), 5.15 (2 H, s), 5.77 (1 H, t, *J* 6), 6.03 (1 H, m), 7.32 (5 H, s), 8.13 (1 H, s), 8.24 (1 H, s), 8.32 (1 H, s); δ_C 20.85 (q), 31.09 (dt, J_{C-P} 137.82), 45.89 (t), 52.53 (q), 52.62 (q), 67.45 (t), 73.42 (d), 89.77 (s), 90.57 (s), 119.09 (d), 128.58 (5d), 136.02 (s), 138.72 (s), 144.02 (d, J_{C-P} 13.58), 147.71 (d), 156.63 (s), 167.64 (s), 169.03 (s); δ_P 27.84; *m*/*z* (%) 735 (5) [MNa$^+$], 731 (100) [MH$^+$], 671 (10) [M$^+$ − OAc].

Dimethyl 2-acetoxy-2-{2,4-diiodo-5-[*N*-(*tert*-butoxycarbonyl)-alanylalanylamino]phenyl}ethylphosphonate 17c

This compound was prepared analogously to **17a** from t-Boc-alanylalanine (0.28 g, 1.11 mmol) and amine **6** (0.3 g, 0.55 mmol). After letting the reaction mixture warm to room temperature, it was slowly heated to 50 °C and allowed to stay at that temperature for 1 h. Work-up was carried out in analogy to that applied for **17a**. The residue obtained after work-up was purified by chromatography (alumina) using a 10% solution of methanol in ethyl acetate as the eluent to give 0.26 g (30%) of **17c** as a yellow oil (Found: C, 35.16; H, 4.01; I, 32.09; N, 5.72. $C_{23}H_{34}I_2N_3O_9P$ requires C, 35.36; H, 4.39; I, 32.48; N, 5.38; P, 3.96%); IR(neat): ν/cm^{-1} 3350, 1702, 1501, 1370, 1240, 1031, 753; δ_H 1.38–1.50 (15 H, m), 2.14 (3 H, s), 2.24–2.36 (2 H, m), 3.76 (3 H, d, *J* 12), 3.77 (3 H, d, *J* 12), 4.24 (1 H, m), 4.63 (1 H, m), 4.91 (1 H, br s), 6.10 (1 H, m), 7.01 (1 H, br s), 8.20 (1 H, s), 8.26 (1 H, s), 8.29 (1 H, br s); δ_C 17.27 (q), 17.57 (q), 20.93 (q), 28.26 (3q), 31.10 (dt, J_{C-P} 139.83), 49.88 (2d), 52.63 (2q), 73.59 (d), 80.67 (s), 90.31 (s), 90.63 (s), 119.66 (d), 139.09 (s), 143.92 (d, J_{C-P} 13.58), 147.94 (d), 155.82 (s), 169.41 (s), 170.28 (s), 173.12 (s); δ_P 27.63; *m*/*z* (%) 804 (10) [MNa$^+$], 781 (23) [M$^+$], 681 (38) [M$^+$ − CO_2CMe_3], 621 (97) [M$^+$ − CO_2CMe_3 − OAc].

Dimethyl 2-acetoxy-2-{2,4-diiodo-5-[*N*-(benzyloxycarbonyl)-glycylglycylamino]phenyl}ethylphosphonate 17d

This compound was prepared analogously to **17c** from *N*-Cbz-glycylglycine (0.49 g, 1.85 mmol) and amine **6** (0.5 g, 0.92 mmol) to yield 0.4 g (28%) of **17d** as an oil (Found: C, 35.15; H, 3.31; I, 31.87; N, 5.08. $C_{24}H_{28}I_2N_3O_9P$ requires C, 36.62; H, 3.58; I, 32.24; N, 5.34; P, 3.93%); IR(neat): ν/cm^{-1} 3350, 1700, 1505, 1237, 1036, 755; δ_H 2.11 (3 H, s), 2.21–2.37 (2 H, m), 3.73 (3 H, d, *J* 12), 3.74 (3 H, d, *J* 12), 3.98 (2 H, d, *J* 6), 4.07 (2 H, d, *J* 6), 5.11 (2 H, s), 5.82 (1 H, br s), 6.07 (1 H, m), 7.33 (5 H, s), 7.38 (1 H, br s), 8.18–8.20 (3 H, s + br s); δ_C 20.88 (q), 30.80 (dt, J_{C-P} 139.33), 44.26 (t), 44.58 (t), 52.75 (2q), 67.34 (t), 73.48 (d), 90.57 (s), 91.14 (s), 119.90 (d), 128.10 (2d), 128.31 (d), 128.53 (2d), 135.84 (s), 138.61 (s), 143.66 (d, J_{C-P} 12.57), 147.92 (d), 158.74 (s), 167.27 (s), 169.42 (s), 170.34 (s); δ_P 27.69; *m*/*z* (%) 788 (100) [MH$^+$], 728 (25) [M$^+$ − OAc].

Dimethyl 2-acetoxy-2-{2,4-diiodo-5-[*N*-(benzyloxycarbonyl)-leucylglycylamino]phenyl}ethylphosphonate 17e

This compound was prepared analogously to **17c** from *N*-Cbz-leucylglycine (0.59 g, 1.85 mmol) and amine **6** (0.5 g, 0.92 mmol) to yield 0.31 g (20%) of **17e** as an oil (Found: C, 40.15; H, 4.48; N, 5.20. $C_{28}H_{36}I_2N_3O_9P$ requires C, 39.88; H, 4.30; I, 30.09; N, 4.98; P, 3.67%); IR(neat): ν/cm^{-1} 3300, 1698, 1502, 1237, 1036, 756; δ_H 0.96 (6 H, d, *J* 8), 1.57–1.73 (3 H, m), 2.11 (3 H, s), 2.24–2.36 (2 H, m), 3.73 (3 H, d, *J* 10), 3.74 (3 H, d, *J* 10), 4.09 (2 H, d, *J* 6), 4.37 (1 H, "t"), 5.07 (2 H, s), 5.68 (1 H, br s), 6.07 (1 H, m), 7.30 (5 H, s), 7.59 (1 H, br s), 8.17 (1 H, s), 8.24 (1 H, br s), 8.29 (s, 1 H); δ_C 20.84 (q), 21.75 (q), 23.00 (q), 24.66 (d), 30.91 (dt, J_{C-P} 138.82), 41.34 (t), 44.44 (t), 52.73 (2q), 53.53 (d), 67.22 (t), 73.47 (d), 90.69 (s), 91.12 (s), 120.15 (d), 127.99 (2d), 128.23 (d), 128.50 (2d), 135.87 (s), 138.83 (s), 143.55 (d, J_{C-P} 13.58), 147.94 (d), 156.36 (s), 164.48 (s), 169.37 (s), 173.66 (s); δ_P 27.69; *m*/*z* (%) 844 (100) [MH$^+$], 784 (30) [M$^+$ − OAc].

Dimethyl 2-acetoxy-2-{2,4-diiodo-5-[*N*-(benzyloxycarbonyl)-glycylalanylamino]phenyl}ethylphosphonate 17f

This compound was prepared analogously to **17c** from *N*-Cbz-glycylalanine (0.31 g, 1.11 mmol) and amine **6** (0.3 g, 0.55 mmol) to yield 0.15 g (17%) of **17f** as an oil (Found: C, 37.85; H, 3.98; N, 5.41. $C_{25}H_{30}I_2N_3O_9P$ requires C, 37.47; H, 3.77; I, 31.67; N, 5.24; P, 3.87%); IR(neat): ν/cm^{-1} 3400, 2360, 1702, 1500, 1245, 1047, 753; δ_H 1.46 (3 H, d, *J* 6), 2.12 (3 H, s), 2.24–2.36 (2 H, m), 3.73 (3 H, d, *J* 10), 3.75 (3 H, d, *J* 10), 3.96 (2 H, d, *J* 6), 4.66 (1 H, q, *J* 6), 5.12 (2 H, s), 5.70 (1 H, br s), 6.08 (1 H, m), 7.04 (1 H, br s), 7.33 (5 H, s), 8.19 (1 H, s), 8.21 (1 H, s), 8.29 (1 H, s); δ_C 17.32 (q), 20.96 (q), 31.04 (dt, J_{C-P} 137.82), 44.66 (t), 49.84 (d), 52.50–52.76 (2q), 67.37 (t), 73.56 (d), 90.58 (s), 91.04 (s), 119.87 (d), 128.13 (2d), 128.35 (d), 128.57 (2d), 135.91 (s), 138.92 (s), 143.76 (d, J_{C-P} 12.57), 147.94 (d), 156.70 (s), 169.43 (s), 169.61 (s), 170.18 (s); δ_P 27.63; *m*/*z* (%) 802 (100) [MH$^+$], 742 (30) [M$^+$ − OAc].

Dimethyl 2-acetoxy-2-{2,4-diiodo-5-[*N*-(benzyloxycarbonyl)-alanylvalylamino]phenyl}ethylphosphonate 17g

This compound was prepared analogously to **17c** from *N*-Cbzalanylvaline (0.89 g, 2.78 mmol) and amine **6** (0.5 g, 0.92 mmol) to yield 0.78 g (50%) of **17g** as an oil (Found: C, 39.79; H, 4.55; N, 4.81. $C_{28}H_{36}I_2N_3O_9P$ requires C, 39.88; H, 4.30; I, 30.09; N, 4.98; P, 3.67%); IR(neat): *ν*/cm^{-1} 3290, 2952, 1702, 1500, 1236, 1030, 752; δ_H 0.92–1.02 (6 H, m), 1.39–1.45 (3 H, m), 2.12 (3 H, s), 2.17–2.36 (2 H, m), 3.74 (3 H, d, *J* 10), 3.75 (3 H, d, *J* 10), 4.33–4.47 (2 H, m), 5.10 (2 H, d, *J* 6), 5.60–5.70 (1 H, m), 6.02–6.14 (1 H, m), 7.14 (1 H, br d, *J* 6), 7.31 (5 H, s), 8.14–8.24 (3 H, m); δ_C 17.68 (q), 18.72 (q), 19.36 (q), 20.89 (q), 30.23 (d), 30.99 (dt, J_{C-P} 140.33), 50.50 (d), 52.42–52.69 (2q), 59.54 (d), 67.15 (t), 73.46 (d), 90.42 (s), 90.95 (s), 119.69 (d), 128.04 (2d), 128.23 (d), 128.48 (2d), 135.87 (s), 138.75 (s), 143.83 (d, J_{C-P} 14.08), 147.83 (d), 156.16 (d, *J* 13.07), 169.36 (s), 172.90 (s), 173.10 (s); δ_P 27.69; *m*/*z* (%) 844 (100) [MH$^+$], 784 (25) [M$^+$ − OAc].

Dimethyl 2-acetoxy-2-{2,6-diiodo-3,5-bis[*N*-(benzyloxycarbonyl)glycylamino]phenyl}ethylphosphonate 18

A solution of isobutyl chloroformate (0.35 ml, 2.70 mmol) and *N*-methylmorpholine (0.29 ml, 2.70 mmol) in dry THF (25 ml) cooled to −20 °C (CO_2–CCl_4 bath) and stirred at this temperature for 20 min. A solution of **13** (0.15 g, 0.27 mmol) in dry THF (5 ml) was then introduced dropwise over 20 min, and the reaction mixture was further stirred for another 1–1.5 h at −20 °C, followed by additional 12 h at room temperature. The reaction mixture was then filtered, and the solvent was evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2, washed in 0.2 M HCl solution, then with 5% $NaHCO_3$ solution and then with brine. The organic phase was dried using anhydrous $MgSO_4$, filtered, and the solvent was evaporated under reduced pressure. The residue was purified by chromatography (alumina) using a 10% solution of methanol in ethyl acetate as the eluent, to give 0.26 g (35%) of **18** as a yellow oil (Found: C, 41.36; H, 4.11; I, 26.83; N, 6.12. $C_{32}H_{35}I_2N_4O_{11}P$ requires C, 41.04; H, 3.77; I, 27.10; N, 5.98; P, 3.31%); IR(neat): *ν*/cm^{-1} 3350, 1698, 1509, 1420, 1239, 1037, 760; δ_H 2.04 (3 H, s), 2.13–2.45 (1 H, m), 2.66–2.87 (1 H, m), 3.69 (3 H, d, *J* 10), 3.70 (3 H, d, *J* 12), 4.00 (4 H, d, *J* 6), 5.14 (4 H, s), 6.16 (2 H, br s), 6.63 (1 H, m), 7.33 (10 H, s), 8.57 (2 H, br s), 9.06 (1 H, s); δ_C 20.58 (q), 27.98 (dt, J_{C-P} 139.83), 45.68 (2t), 52.38–52.73 (2q), 67.28 (2t), 67.95 (d), 114.89 (d), 128.08 (4d), 128.19 (2d), 128.47 (4d), 133.68 (s), 136.01 (2s), 156.86 (2s), 167.93 (2s), 169.85 (s); δ_P 27.93; *m*/*z* (%) 772 (100) [M$^+$ − $CH_2NHCO_2CH_2Ph$].

Dimethyl 2-acetoxy-2-{2,4,6-triiodo-5-amino-3-[*N*-(benzyloxycarbonyl)glycylamino]phenyl}ethylphosphonate 19

This compound was prepared analogously to **18** from *N*-Cbz-glycine (0.27 g, 1.32 mmol) and compound **12** (0.20 g, 0.29 mmol) to yield 0.01 g (3%) of **19** as an oil (Found: C, 30.01; H, 3.12; I, 44.03; N, 4.80. $C_{22}H_{25}I_3N_3O_8P$ requires C, 30.33; H, 2.89; I, 43.70; N, 4.82; P, 3.56%); δ_H 2.03 (3 H, s), 2.17–2.50 (1 H, m), 2.75–2.96 (1 H, m), 3.71 (3 H, d, *J* 10), 3.72 (3 H, d, *J* 10), 3.96 (2 H, d, *J* 6), 4.31 (-NH_2, br s), 5.14 (2H, s), 5.76 (-NH, br s), 6.64 (1 H, m), 7.32 (5 H, 2), 8.45 (Ar-NH, br s); δ_C 20.66 (q), 28.20 (dt, J_{C-P} 140.33), 46.00 (t), 52.55 (2q), 67.61 (t), 68.02 (d), 87.24 (s), 107.48 (2s), 128.23 (2d), 128.42 (d), 128.59 (2d), 143.04 (s), 150.47 (s), 155.68 (s), 169 (s), 178.61 (s); δ_P 28.47; *m*/*z* (%) 871 (10) [M$^+$], 855 (5) [M$^+$ − NH_2], 664 (15) [M$^+$ − $NHCOCH_2NHCO_2CH_2Ph$], 662 (17), 621 (20) [664 − Ac], 605 (25) [664 − OAc], 598 (25), 583 (80) [MH$^+$ − $NHCO_2CH_2Ph$ − $CH_2PO_3Me_2$ − 16], 581 (100) [MH$^+$ − $CH_2NHCO_2CH_2Ph$ − 127], 579 (75), 562 (43).

Dimethyl 2-acetoxy-2-{2,4,6-triiodo-3,5-bis[*N*-*tert*-butoxycarbonyl)alanylamino]phenyl}ethylphosphonate 20

This compound was prepared analogously to **18** from t-Boc-alanine (0.41 g, 2.20 mmol) and compound **12** (0.15 g, 0.22 mmol). The residue obtained after work-up was purified by chromatography (alumina) using a 5% solution of methanol in ethyl acetate as the eluent to give 0.03 g (4.5%) of **20** as an oil (Found: C, 33.14; H, 3.83; I, 36.91; N, 5.40; P, 3.03. $C_{28}H_{42}I_3N_4O_{11}P$ requires C, 32.90; H, 4.14; I, 37.24; N, 5.48; P, 3.03%); δ_H 1.43–1.46 (24 H, 2s), 2.03 (3 H, s), 2.18–2.52 (1 H, m), 2.73–2.94 (1 H, m), 3.67–3.77 (6 H, 2d), 4.34 (2 H, m), 5.12 (2H = 2(NH), br d, *J* 6), 6.68 (1 H, m), 8.80 (2H = 2(Ar-NH), br d, *J* 8); δ_C 17.52 (2q), 20.55 (q), 28.27 (6q), 32.36 (dt, J_{C-P} 139.33), 51.01 (2d), 52.63 (2q), 67.97 (d), 80.64 (2s), 107.50 (s), 114.79 (2s), 128.06 (s), 128.51 (s), 134.39 (s), 155.77 (2s), 169.51 (s), 170.80 (2s); δ_P 28.57; *m*/*z* (%) 900 (10) [MH$^+$ − $CH_2PO_3Me_2$], 835 (10) [M$^+$ − $NHCOCH(Me)NHCO_2CMe_3$], 735 (28) [835 − CMe_3 − Ac], 734 (32), 732 (50), 648 (30) [M$^+$ − $2NHCOCH(Me)NHCO_2CMe$], 566 (40), 559 (85) [MH$^+$ − (2 × 187) − OAc − OMe].

Dimethyl 2-acetoxy-2-(2,6-diiodo-3,5-diacetamidophenyl)ethylphosphonate 21

Acetic anhydride (0.038 ml, 0.40 mmol) was added to a stirred solution of compound **13** (0.05 g, 0.09 mmol) in dry pyridine. The reaction mixture was stirred for 48 h at room temperature. The solvent was evaporated under reduced pressure. The residue was dissolved in chloroform, washed twice with cold solution of 2 M HCl, dried with anhydrous $MgSO_4$, filtered and the solvent was evaporated under reduced pressure to give 0.09 g (90%) of **21** as a yellow oil (Found: C, 30.53; H, 3.17; I, 40.54; N, 4.96. $C_{16}H_{21}I_2N_2O_7P$ requires C, 30.12; H, 3.32; I, 39.77; N, 4.39; P, 4.85%); IR(neat): *ν*/cm^{-1} 3350, 2925, 1744, 1610, 1437, 1371, 1239, 1033; δ_H 2.07 (3 H, s), 2.23 (6 H, s), 2.34–2.51 (1 H, m), 2.74–2.96 (1 H, m), 3.71 (3 H, d, *J* 10), 3.73 (3 H, d, *J* 10), 6.72 (1 H, m), 7.73 (2 H, br s), 9.08 (1 H, s); δ_C 20.55 (q), 24.57 (2q), 28.11 (dt, J_{C-P} 140.84), 52.57 (2q), 67.93 (d), 116.23 (d), 133.75 (d, J_{C-P} 11.06), 134.22 (2s), 168.20 (2s), 169.38 (s); δ_P 28.06; *m*/*z* (%) 456 (5) [M$^+$ − OAc − $CH_2PO_3Me_2$], 419 (62), 377 (13), 359 (40), 317 (38) [MH$^+$ − 127 − 109 − 2 × Ac], 109 (39) [PO_3Me_2], 43 (100) [Ac].

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