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Introduction of chiral 2-(aminoalkyl) substituents into 5-amino-1,3-oxazol-4-ylphosphonic acid derivatives and their use in phosphonodipeptide synthesis

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Starting from phthalimidoalkanoylamines **1** (amino-protected derivatives of L-alanine, L-valine, and L-leucine), we have suggested a straightforward synthetic route to 5-amino-1,3-oxazol-4-ylphosphonic acid derivatives **5** containing a chiral aminoalkyl substituent on the 2-position of the oxazole ring. Compounds **5** have been further used to obtain phosphonodipeptides **8**, **9**, and **10** with the original optical purity retained.

Introduction

The past several decades have witnessed the vigorous development of 5-amino-1,3-oxazole chemistry since the compounds of this family are well recognized for their potent and diverse bioregulation activity. For instance, substituted 5-amino-1,3-oxazole-4-carboxylic acids exhibit a stimulating effect on the $GABA_B$ receptor,[1] inhibit enzymes (such as kinase cRaf1),[2, 3] and also have antibacterial properties.[4] Of particular interest are 1,3-oxazoles bearing optically active 2-substituents as they can be regarded as masked peptides; these derivatives are potent $\alpha_4\beta_1$ integrin antagonists[5] and also target arthritis-associated class II MHC A^q and DR4 proteins.

Substitution of the carboxyl group by a phosphoryl group in molecules of this kind appears promising, as the latter residue has significantly different properties: it is more bulky, tetrahedral-shaped in contrast to the planar carboxyl moiety, and more acidic. As a result of these features, phosphorylated analogues of carboxylic acids have been applied in the research of enzyme-substrate interactions[7-10] and new enzyme inhibitors can be found among such compounds.

As shown previously,[11] introduction of a phosphoryl group at position 4 of the 1,3-oxazole ring makes the heterocycle drastically more susceptible to acid cleavage leading to the formation of phosphonoglycine derivatives. It is notable that phosphorylated glycines have received much recent attention in bioorganic, biological, and medicinal chemistry, as evidenced by the plethora of publications including reviews[12, 13] on the synthesis and biological activity of aminophosphonic acids and mimetics of phosphonopeptides. However, peptidomimetics derived from phosphonoglycine appear to be the least studied. They have been employed in the synthesis of peptide natural products, e.g. azinomycins A and B,[14] (±) – tunichrome An-1,[15] tunichromes Mm-1 and Mm-2,[16] hexaacetylcelenamide A,[17,18] clionamide,[19] etc. Also, some compounds of this class are effective glutathione transferase inhibitors.[20, 21]

Among several available methods to synthesize such mimetics of phosphonopeptides, there is the reaction of α-metallated diethyl isocyanomethylphosphonates with allyl α-isocyanatocarboxylates at -70 °C.[22] Another approach is based on the reaction between glyoxylic acid derivatives and *N*-benzylurethane to give *N*-benzyloxycarbonyl-2-ethoxyglycine derivatives. On their successive treatment with phosphorus trichloride and triethyl phosphite, the corresponding *N*-benzyloxycarbonyl substituted phosphonoglycines are formed which, after reductive debenzylation with hydrogen on palladium, are used in peptide synthesis.[23] As an example, the cores of the natural macrocyclic peptides mucronine B and chlamydocin were constructed by this strategy.[25] A recently reported route to phosphonoglycine peptidomimetics involves the formation of 2-aminoalkyl-5-amino-1,3-oxazol-4-ylphosphonic acids followed by acid cleavage of the oxazole ring.[26, 27] The method is advantageous because of easily accessible and cheap starting materials as well as for high yields and facile isolation of products in each reaction step. However, it has not hitherto been attempted in the stereoselective synthesis of acylated phosphonoglycine derivatives starting from substrates with chiral 2-(aminoalkyl) substituents on the oxazole ring.

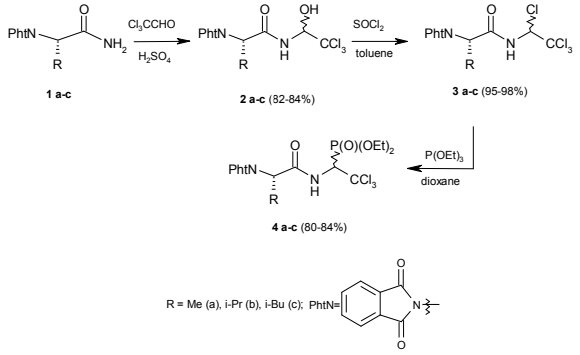
To find a pathway to 4-phosphorylated 5-amino-2-aminoalkyl-1,3-oxazoles with a chiral center in the aminoalkyl moiety, we have invoked the synthesis of 5-amino-1,3-oxazol-4-ylphosphonates developed in the seventies of the last century.[28, 29] It is based on the mild and smooth reaction of easily accessible dialkyl 1-acylamino-2,2,2-trichloroethylphosphonates with primary or secondary aliphatic amines. The thus obtained 2-unsubstituted 4-phosphorylated 5-amino-1,3-oxazoles were found to afford, in hydrochloric acid medium, phosphonoglycine amides or their *N*-formyl derivatives.[30] As recently reported,[27] this synthetic approach enables the introduction of phthalimidoalkyl groups (contained in amino-protected glycine, β-alanine, γ-amino butyric, δ-amino valeric, and

ε-amino capronic acids) at position 2 of the oxazole ring; subsequent phthaloyl deprotection provides 2-(aminoalkyl) substituted 4-phosphorylated oxazoles which have proved to be valuable building blocks in peptide synthesis.

The present work is aimed to extend the scope of the method to the amides of natural α-amino acids, L-alanine, L-valine, and L-leucine (containing the protective phthaloyl group), which have for the first time been reacted as described above to produce the corresponding phosphorylated oxazoles with chiral 2-(aminoalkyl) substituents and, finally, phosphonodipeptides.

Results and discussions

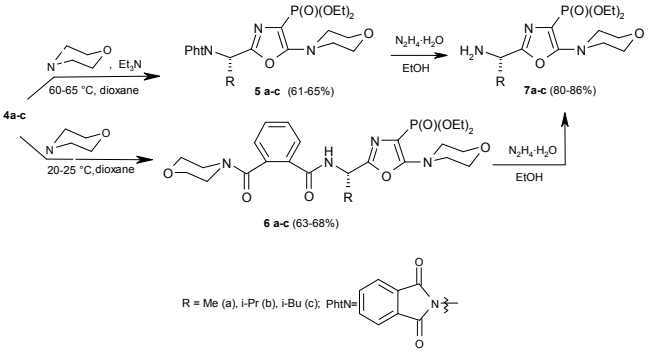
Heating phthalimido derivatives of α-amino acid amides **1a-c** with chloral in the presence of a catalytic amount of concentrated sulfuric acid leads to high yields of condensation products, corresponding chloralamides **2a-c** obtained in the form of colourless crystals (see Scheme 1). HPLC-MS/GC-MS demonstrate that due to the formation of a new asymmetric center, compounds **2a-c** are isolated as a 1:1 diastereomeric mixture. When treated with a small excess of thionyl chloride, they yield *N*-(1,2,2,2-tetrachloroethyl)amides **3a-c** appearing as thick viscous oils. Products **3a-c** react with triethyl phosphite by the Arbuzov reaction to give a 1:1 diastereomeric mixture of diethyl 1-acylamino-2,2,2-trichloroethylphosphonates **4a-c** (as determined by HPLC-MS and ^{31}P NMR spectroscopy).



Scheme 1

We have studied the reaction of compounds **4a-c** with morpholine in order to establish whether they can be cyclized to 1,3-oxazoles[26, 27] containing optically active aminoalkyl 2-substituents. Heating diethyl 1-acylamino-2,2,2-trichloroethylphosphonates **4a-c** with an equivalent quantity of morpholine in the presence of excess triethylamine affords the corresponding esters of 2-aminoalkyl-5-morpholino-1,3-oxazol-4-ylphosphonic acids **5a-c** (see Scheme 2).

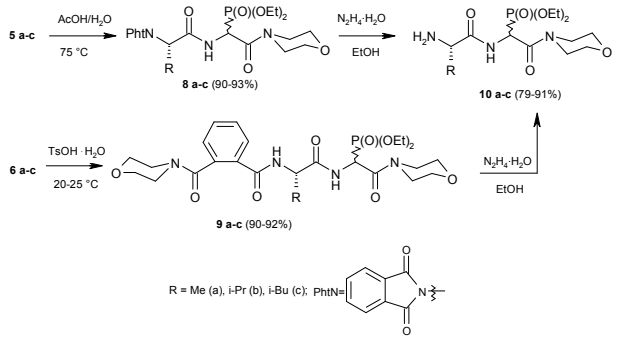
On treatment of compounds **4a-c** with excess morpholine at 20-25°C, oxazole cyclization is accompanied by the cleavage of the phthalimido moiety resulting in phthalic diamides **6a-c**. The amino group in compounds **5a-c** and **6a-c** is readily deprotected with hydrazine hydrate in ethanol to furnish phosphorylated 2-aminoalkyloxazoles **7a-c** in 80-86% yields (see Scheme 2).



Scheme 2

As already mentioned, 4-phosphorylated 1,3-oxazoles (e.g. 5-amino derivatives[26, 27]) are highly unstable in acidic medium to undergo ring opening. We have found that oxazoles **5a-c**, when heated to 70°C in 70% aqueous acetic acid, are cleaved to dipeptides **8a-c** in 90-93% yields, with the phthaloyl protection of amino groups retained. Contrastingly, the action of acetic acid on oxazoles **6a-c** leads to a mixture of unidentified products. To avoid this pathway, the oxazole ring cleavage in these compounds was performed under milder conditions, using *p*-toluenesulfonic acid in aqueous tetrahydrofuran at 20-25°C. The resulting mimetics of phosphornopeptides **9a-c** were isolated in 90-92% yields. Noteworthy, acidic cleavage of compounds **7** leads to a nonseparated mixture containing, among with **10**, products of interaction of a primary amino group with AcOH or TsOH, which was detected by LCMS.

Deprotection of products **8a-c** and **9a-c** with hydrazine hydrate in ethanol at 20-25°C provides phosphonodipeptides **10a-c** (see Scheme 3).



Scheme 3

Both the ^{1}H and ^{13}C NMR spectra of compounds **8a-c**, **9a-c**, and **10a-c** contain double sets of signals thus suggesting the presence of diastereomeric pairs. Likewise, two ^{31}P resonances of equal intensity emerge. These data indicate that acid-assisted oxazole ring cleavage to phosphonoglycine derivatives proceeds non-stereoselectively. To investigate the effect of the **1→2→3→4→5→7** and **5→8→10** conversions on the asymmetric center of the L-alanine, L-valine, and L-leucine residues, compounds **5a-c**, **7a**, **8a**, and **10a** were chromatographed on a HPLC chiral column. As found, oxazoles **5a-c** and **7a** are represented by one enantiomer, whereas phosphonodipeptides **8a** and **10a** are both formed as a diastereomeric pair. This is clear evidence that the asymmetric center of L-alanine, L-valine, and L-leucine remains intact when the amino acid residues are introduced into phosphonoglycine amides. For comparison, the approach developed was used with the same starting amino acids derivatives

(phthalimido amides **1**) in racemic form to give, finally, two diastereomeric pairs in each case.

Conclusions

Starting from L-alanine, L-valine, and L-leucine derivatives with phthaloyl-protected amino groups, we have presented a facile preparative route to 5-amino-1,3-oxazol-4-ylphosphonic acid derivatives **5** and **7** containing a chiral aminoalkyl substituent on the 2-position of the oxazole ring. It has been demonstrated that oxazoles **5** and **6** can be employed in peptide chain construction. As found, the chiral center of aminoalkyl moieties remains intact in the conversions studied, so that optical purity is retained for oxazoles **5** and **7** as well as for phosphonodipeptides **8** and **10**.

Experimental section

The NMR spectra were obtained on a Bruker Avance DRX-500 instrument [^{1}H (500 MHz), ^{31}P (202 MHz), ^{13}C (125 MHz)] in a solution of DMSO-d_6, relative to internal TMS or external 85% phosphoric acid. The IR spectra were recorded on a Vertex 70 spectrometer with an ATR adaptor from KBr pellets or dichloromethane solution. The melting points were determined on a Fisher-Johns instrument. Elemental analysis was carried out in the analytical laboratory of IBOPC NASU. The LC/MS spectra were recorded on an Agilent 1100 Series high-performance liquid chromatograph equipped with a diode matrix with an Agilent LC\MSD SL mass selective detector allowing fast switching between positive and negative ionization modes. The LC/MS parameters were set as follows: column, Zorbax SBC18 1.8 μm, 4.6x15 mm (PN 821975-932); solvents A, acetonitrile–water mixture (95:5), 0.1% trifluoroacetic acid, and B, 0.1% aqueous trifluoroacetic acid; eluent flow rate, 3 mL/min; injection volume, 1 μl; UV detection, 215, 254, 265 nm; ionization method, atmospheric-pressure chemical ionization (APCI); scanning range, *m/z* 80–1000. Optical purity was measured on the Agilent 1100 system with a diode array detector on a CHIRALPAK® IA column (5 μm, 4.6×250 mm); mobile phase, hexane:2-propanol. The reaction progress was TLC-monitored on Silica gel 60 F_{254} (Merck). Optical rotations were measured with an Anton Paar MCP 300 polarimeter.

Phthalimido amides

Commercially unavailable compounds **1a-c**[31] were obtained by known methods.

General procedure for the preparation of 2a-c. Condensation of amides 1a-e with chloral

A mixture of one of compounds **1a-c** (0.20 mol), anhydrous chloral (44.22 g, 0.30 mol), and conc. sulfuric acid (1 mL) was kept at a temperature of 95-100 °C for 8h and cooled by pouring into water (500 mL). The crystalline precipitate was filtered, washed on the filter with water to pH 7, and recrystallized from ethanol.

2-(1,3-Dioxo-2,3-dihydro-1H-isoindol-2-yl)-N-(2,2,2-trichloro-1-hydroxyethyl)propanamide (2a). Yield 60.35 g, 82% as a colourless solid; mp 149-151 °C; [Found: C, 42.65; H, 3.13; Cl, 29.11; N, 7.69. $C_{13}H_{11}Cl_3N_2O_4$ requires C, 42.71; H, 3.03; Cl, 29.09; N, 7.66%]; $[\alpha]_D^{20}$ -9.5 (*c* 0.7, CH_2Cl_2); ν_{max} (KBr) 3323, 1775, 1709, 1513 cm^{-1}; δ_H (DMSO-d_6) 8.98-8.92 (1H, m, NH), 7.88-7.85 (4H, m, aromatic), 7.76-7.75 (1H, m, OH), 5.76-5.74 (1H, m, CH), 4.90-4.83 (1H, m, CH), 1.67-1.65 (3H, m, CH_3); δ_C (DMSO-d_6) 169.27, 169.21 (C=O), 167.30, 167.14 (C=O), 134.05, 133.95, 131.38, 131.28, 122.55, 122.50 (aromatic), 101.95, 101.51 (CCl_3), 80.45, 80.28 (NCOH), 47.90, 47.88 (NCH), 14.10, 13.98 (CH_3).

2-(1,3-Dioxo-2,3-dihydro-1H-isoindol-2-yl)-3-methyl-N-(2,2,2-trichloro-1-hydroxyethyl)butanamide (2b). Yield 65.83 g, 84% as a colourless solid; mp 154-156°C; [Found: C, 45.63; H, 3.97; Cl, 27.21; N, 7.01. $C_{15}H_{15}Cl_3N_2O_4$ requires C, 45.79; H, 3.84; Cl, 27.02; N, 7.10%]; $[\alpha]_D^{20}$ +7.1 (*c* 1.3, CH_2Cl_2); ν_{max} (KBr) 3280, 1773, 1711, 1550 cm^{-1}; δ_H (DMSO-d_6) 8.81-8.79 (1H, m, NH), 7.93-7.87 (4H, m, aromatic), 7.72-7.71 (1H, m, OH), 5.74-5.71 (1H, m, CH), 4.51-4.48 (1H, m, CH), 2.91-2.84 (1H, m, CH), 1.06 (3H, d, *J* 6.2 Hz, CH_3), 0.82 (3H, d, *J* 6.2 Hz, CH_3); δ_C (DMSO-d_6) 168.22 (C=O), 167.51, 167.46 (C=O), 134.32, 134.09, 130.93, 130.62, 122.82, 122.65 (aromatic), 101.27, 94.34 (CCl_3), 79.91 (NCOH), 59.53, 57.50 (NCH), 26.10, 25.92 (CH), 19.86, 18.76, 18.30, 18.28 (CH_3).

2-(1,3-Dioxo-2,3-dihydro-1H-isoindol-2-yl)-4-methyl-N-(2,2,2-trichloro-1-hydroxyethyl)pentanamide (2c). Yield 67.46 g, 82% as a colourless solid; mp 135-137 °C; [Found: C, 47.07; H, 4.21; Cl, 26.14; N, 6.73. $C_{16}H_{17}Cl_3N_2O_4$ requires C, 47.14; H, 4.20; Cl, 26.09; N, 6.87%];$[\alpha]_D^{20}$ +4.7 (*c* 1.3, CH_2Cl_2); ν_{max} (KBr) 3351, 1774, 1715, 1526 cm^{-1}; δ_H (DMSO-d_6) 9.10-8.97 (1H, m, NH), 7.91-7.85 (4H, m, aromatic), 7.84-7.82 (1H, m, OH), 5.76-5.73 (1H, m, CH), 4.95-4.82 (1H, m, CH), 2.41-2.33 (1H, m, $CH_a\underline{H}_b$), 1.85-1.79 (1H, m, $C\underline{H}_aH_b$), 1.45-1.39 (1H, m, CH), 0.87-0.85 (6H, m, $2CH_3$); δ_C (DMSO-d_6) 168.05 (C=O), 166.65, 166.51 (C=O), 133.22, 133.15, 129.93, 129.91, 121.68, 121.65, (aromatic), 100.82, 100.47 (CCl_3), 79.39, 79.26 (NCOH), 50.37, 50.31 (NCH), 34.40, 34.33 (CH), 22.85, 22.83 (CH_2), 21.11, 21.05 (CH_3), 18.43, 18.31 (CH_3).

General procedure for the preparation of 3a-c. Tetrachloroethylamides

A mixture of one of compounds **2a-c** (0.16 mol), thionyl chloride (14 mL, 0.19 mol), and dry toluene (100 mL) was refluxed with stirring until no more gas was evolved and for another 30 min. The solvent was evaporated under reduced pressure to dryness to give the analytically pure product.

2-(1,3-Dioxo-2,3-dihydro-1H-isoindol-2-yl)-N-(1,2,2,2-tetrachloroethyl)propanamide (3a). Yield 58.49 g, 96% as a yellowish oil; [Found: C, 40.80; H, 2.55; Cl, 37.01; N, 7.39. $C_{13}H_{10}Cl_4N_2O_3$ requires C, 40.66; H, 2.62; Cl, 36.93; N, 7.29%]; $[\alpha]_D^{20}$ -22.1 (*c* 1.3, CH_2Cl_2); ν_{max} (ATR) 3317, 1779, 1702, 1508 cm^{-1}; δ_H ($CDCl_3$) 7.88 (2H, m, aromatic), 7.77 (2H, m, aromatic), 7.49 ($^1/_2$H, d, *J* 9.3 Hz, NH), 7.34 ($^1/_2$H, d, *J* 9.3 Hz, NH), 6.51-6.48 (1H, m, CHN), 5.05-5.01 (1H, m, CH), 1.77-1.74 (3H, m, CH_3); δ_C ($CDCl_3$) 167.80 (C=O), 168.71, 168.58 (C=O), 134.70, 134.62, 131.57, 131.54, 123.86, 123.82 (aromatic), 99.30 (CCl_3), 73.92, 73.76 (NCHCl), 50.02, 49.90 (NCH), 15.27, 15.10 (CH_3).

2-(1,3-Dioxo-2,3-dihydro-1H-isoindol-2-yl)-3-methyl-N-(1,2,2,2-tetrachloroethyl)butanamide (3b). Yield 64.63 g, 98% as a yellowish oil; [Found: C, 43.62; H, 3.50; Cl, 34.48; N, 6.65. $C_{15}H_{14}Cl_4N_2O_3$ requires C, 43.72; H, 3.42; Cl, 34.41; N, 6.80%]; $[\alpha]_D^{20}$ +9.4 (*c* 1.3, CH_2Cl_2); ν_{max} (ATR) 3281, 1779, 1706, 1512 cm^{-1}; δ_H ($CDCl_3$) 8.74 ($^1/_2$H, d, *J* 9.5 Hz, NH), 8.50 ($^1/_2$H, d, *J* 9.5 Hz, NH), 7.88 (2H, m, aromatic), 7.78 (2H, m, aromatic), 6.53-6.47 (1H, m, CH), 4.57-4.52 (1H, m, CH), 2.88-2.74 (1H, m, CH), 1.11-1.09 (3H, m, CH_3), 0.91-0.83 (3H, m, CH_3); δ_C ($CDCl_3$) 168.92, 168.78 (C=O), 168.22 (C=O), 135.26, 135.18, 131.79, 131.57, 123.81, 123.74, 102.90 (aromatic), 102.90, 102.52 (CCl_3),

81.43, 81.19 (NCHCl), 60.89, 60.20 (NCH), 27.61, 27.50 (CH), 20.55, 20.39, 20.17, 19.92 (CH_3)**.**

2-(1,3-Dioxo-2,3-dihydro-1H-isoindol-2-yl)-4-methyl-N-(1,2,2,2-tetrachloroethyl)pentanamide (3c*)*. Yield 64.54 g, 95% as a yellowish oil; [Found: C, 45.12; H, 3.87; Cl, 33.36; N, 6.49. $C_{16}H_{16}Cl_4N_2O_3$ requires C, 45.10; H, 3.78; Cl, 33.28; N, 6.57%]; $[\alpha]_D^{20}$ +24.25 (*c* 0.7, CH_2Cl_2); ν_{max} (ATR) 3315, 1776, 1704, 1512; δ_H ($CDCl_3$) 7.92-7.72 (5H, m, aromatic, NH), 6.50-6.47 (1H, m, CHN), 5.03-4.99 (1H, m, CH), 2.37-2.20 (1H, m, $C\underline{H_a}H_b$), 1.92-1.83 (1H, m, $CH_a\underline{H_b}$), 1.50-1.43 (1H, m, CH), 0.94-0.90 (6H, m, $2CH_3$); δ_C ($CDCl_3$) 169.92, 166,70 (C=O), 166.51, 166.44 (C=O), 132.81, 132.76, 126.35, 122.96, 121.90, 121.83 (aromatic), 97.17, 97.00 (CCl_3), 71.70, 71.44 (NCHCl), 51.60, 51.50 (NCH), 34.99, 34.90 (CH_2), 22.66, 22.55 (CH), 20.24, 20.15, 17.98, 17.66 (CH_3).

General procedure for the preparation of 4a-c. Arbuzov rearrangement

A mixture of one of compounds **3a-c** (0.14 mol), triethyl phosphite (30 mL, 0.17 mol), and dry dioxane (150 mL) was refluxed for 3 h and evaporated *in vacuo* to dryness. To isolate **4a** and **4c**, the residue was recrystallized from benzene; in the case of **4b**, the solvent was evaporated under reduced pressure to dryness to give the analytically pure product.

Diethyl {2,2,2-trichloro-1-[2-(1,3-dioxo-2,3-dihydro-1H-isoindol-2-yl)propanamido]ethyl}phosphonate (4a). Yield 58.44 g, 84% as a colourless solid; mp 142-144 °C; [Found: C, 42.13; H, 4.26; Cl, 21.81; N, 5.70; P, 6.43. $C_{17}H_{20}Cl_3N_2O_6P$ requires C, 42.04; H, 4.15; Cl, 21.90; N, 5.77; P, 6.38%]; $[\alpha]_D^{20}$ -15.8 (*c* 1.3, CH_2Cl_2); ν_{max} (KBr) 3248, 1778, 1716, 1540, 1260, 1023 cm^{-1}; δ_H (DMSO-d_6) 9.43 ($^1/_2$H, d, *J* 6.7 Hz, NH), 9.34 ($^1/_2$H, d, *J* 6.7 Hz, NH), 7.89 (4H, m, aromatic), 5.28-5.18 (1H, m, CHP), 5.04-4.98 (1H, m, CH), 4.15-4.05 (4H, m, $2O\underline{CH_2}CH_3$), 1.77-1.72 (3H, m, CH_3), 1.30-1.20 (6H, m, $2OCH_2\underline{CH_3}$); δ_C (DMSO-d_6) 170.71 (d, *J* 4.5 Hz, C=O), 170.57 (d, *J* 4.5 Hz, C=O), 168.05, 167.95 (C=O), 135.06, 135.00, 132.10, 132.01, 123.59, 123.57 (aromatic), 97.62, (d, *J* 14.5 Hz, CCl_3), 97.17 (d, *J* 14.5 Hz, CCl_3), 64.07 63.86 (d, *J* 6.5 Hz, $O\underline{C}H_2CH_3$), 62.10 (d, *J* 159.0 Hz, CP), 61.73 (d, *J* 159.0 Hz, CP), 49.73, 49.45 (CH), 16.74 (d, *J* 4.8 Hz, $OCH_2\underline{C}H_3$), 16.56 (d, *J* 4.8 Hz, $OCH_2\underline{C}H_3$), 15.85, 15.78 (CH_3); δ_P (DMSO-d_6) 14.6, 14.3; LCMS: found *m/z* 486.8 MH^+. $C_{17}H_{20}Cl_3N_2O_6P$ requires 485.7.

Diethyl {2,2,2-trichloro-1-[2-(1,3-dioxo-2,3-dihydro-1H-isoindol-2-yl)-3-methylbutanamido]ethyl}phosphonate (4b). Yield 58.84 g, 80% as a yellow oil; [Found: C, 44.55; H, 4.86; Cl, 20.82; N, 5.53; P, 6.19. $C_{19}H_{24}Cl_3N_2O_6P$ requires C, 44.42; H, 4.71; Cl, 20.70; N, 5.45; P, 6.03%]; $[\alpha]_D^{20}$ +5.5 (*c* 1.2, CH_2Cl_2); ν_{max} (ATR) 2974, 1779, 1712, 1519, 1259, 1014, 972 cm^{-1}; δ_H (DMSO-d_6) 9.32 ($^1/_2$H, d, *J* 9.3 Hz, NH), 9.22 ($^1/_2$H, d, *J* 9.3 Hz, NH), 7.92-7.88 (4H, m, aromatic), 5.29-5.21 (1H, m, CHP), 4.68-4.61 (1H, m, CH), 4.10-4.00 (4H, m, $2O\underline{CH_2}CH_3$), 2.97-2.90 (1H, m, CH), 1.22-1.15 (6H, m, $2OCH_2\underline{CH_3}$), 1.11-1.05 (3H, m, CH_3), 0.88-0.79 (3H, m, CH_3); δ_C (DMSO-d_6) 168.61 (d, *J* 4.5 Hz, C=O), 167.41 (d, *J* 4.5 Hz, C=O), 134.41, 134.36, 130.55, 130.53, 122.85, 122.80 (aromatic), 96.21 (d, *J* 14.5 Hz, CCl_3), 96.06 (d, *J* 14.5 Hz, CCl_3), 62.30 (d, *J* 6.5 Hz, $O\underline{C}H_2CH_3$), 62.07 (d, *J* 6.5 Hz, $O\underline{C}H_2CH_3$), 60.31 (d, *J* 158.8 Hz, CP), 60.26 (d, *J* 158.6 Hz, CP), 59.31, 59.22 (CH), 25.92, 25.84 (CH), 18.55, 18.50 (CH_3), 18.49, 18.36 (CH_3), 14.97 (d, *J* 6.0 Hz, $OCH_2\underline{C}H_3$), 14.86 (d, *J* 6.0 Hz, $OCH_2\underline{C}H_3$); δ_P (DMSO-d_6) 14.4. 14.2; LCMS: found *m/z* 515.0 MH^+. $C_{19}H_{24}Cl_3N_2O_6P$ requires 513.7.

Diethyl {2,2,2-trichloro-1-[2-(1,3-dioxo-2,3-dihydro-1H-isoindol-2-yl)-4-methylpentanamido]ethyl}phosphonate (4c). Yield 61.60 g, 82% as a colourless solid; mp 133-134 °C; [Found: C, 45.48; H, 4.84; Cl, 20.03; N, 5.41; P, 5.98. $C_{20}H_{26}Cl_3N_2O_6P$ requires C, 45.52; H, 4.97; Cl, 20.15; N, 5.31; P, 5.87%]; $[\alpha]_D^{20}$ +6.0 (*c* 1.1, CH_2Cl_2); ν_{max} (KBr) 3212, 1776, 1717, 1530, 1246, 1023, 980 cm^{-1}; δ_H (DMSO-d_6) 9.63 ($^1/_2$H, d, *J* 9.3 Hz, NH), 9.43 ($^1/_2$H, d, *J* 9.3 Hz, NH), 7.89 (m, 4H, aromatic), 5.27-5.17 (1H, m, CHP), 5.06-5.03 ($^1/_2$H, m, CH), 5.02-4.98 ($^1/_2$H, m, CH), 4.15-4.03 (4H, m, $2O\underline{CH_2}CH_3$), 2.45-2.36 (1H, m, $C\underline{H_a}H_b$), 1.95-1.86 (1H, m, $CH_a\underline{H_b}$), 1.51-1.44 (1H, m, CH), 1.31-1.19 (6H, m, $2OCH_2\underline{CH_3}$), 0.89 (6H, m, $2CH_3$); δ_C (DMSO-d_6)[a,c] 168.76 (d, *J* 4.5 Hz, C=O), 166.63 (C=O), 133.33, 129.75, 121.72 (aromatic), 95.32 (d, *J* 14.5 Hz, CCl_3) 61.72 (d, *J* 6.5 Hz, $O\underline{C}H_2CH_3$), 61.20 (d, *J* 6.5 Hz, $O\underline{C}H_2CH_3$), 59.28 (d, *J* 159.0 Hz, CP), 50.65 (CH), 34.21 (CH_2), 21.96, 21.11 (CH), 18.23 (CH_3), 14.03 (d, *J* 6.5 Hz, $OCH_2\underline{C}H_3$), 13.91 (d, *J* 4.5 Hz, $OCH_2\underline{C}H_3$); δ_P (DMSO-d_6) 14.6, 14.3; LCMS: found *m/z* 528.8 MH^+. $C_{20}H_{26}Cl_3N_2O_6P$ requires 527.8.

General procedure for the preparation of 5a-c. Oxazole cyclization

A mixture of one of compounds **4a-e** (30 mmol), morpholine (31.5 mmol), and triethylamine (25.05 mL, 180 mmol) in dry dioxane (125 mL) was refluxed for 24 h under TLC control, cooled, and evaporated *in vacuo* to dryness. If necessary, the reaction product can be purified by extraction with boiling petroleum ether (bp 80-110 °C), followed by evaporation of the combined extracts *in vacuo*.

Diethyl {2-[1-(1,3-dioxo-2,3-dihydro-1H-isoindol-2-yl)-ethyl]-5-(morpholin-4-yl)-1,3-oxazol-4-yl}phosphonate (5a). Yield 9.00 g, 65% as a colourless solid; mp 174-175°C; [Found: C, 54.56; H, 5.54; N, 9.16; P, 6.79. $C_{21}H_{26}N_3O_7P$ requires C, 54.43; H, 5.65; N, 9.07; P, 6.68%]; $[\alpha]_D^{20}$ +2.8 (*c* 0.6, CH_3OH); ν_{max} (KBr) 1777, 1715, 1612, 1573, 1263, 1025, 969 cm^{-1}; δ_H (DMSO-d_6) 7.93-7.85 (4H, m, aromatic), 5.45 (1H, q, *J* 6.8 Hz, CH), 4.02-3.91 (4H, m, $2O\underline{CH_2}CH_3$), 3.64 (4H, m, $2CH_2$), 3.42 (4H, m, $2CH_2$), 1.74 (3H, d, *J* 6.8 Hz, CH_3), 1.22-1.15 (6H, d, *J* 7.0 Hz, $2OCH_2\underline{CH_3}$); δ_C (DMSO-d_6)[a] 166.70 (C=O), 160.89 (d, *J* 38.0 Hz, O-$\underline{C}$=C-P), 151.07 (d, *J* 21.4 Hz, O-C=N), 134.34, 130.80, 122.83 (aromatic), 100.34 (d, *J* 251.3 Hz, CP), 64.55 (OCH_2, morpholine), 60.94-60.88 (m, $O\underline{C}H_2CH_3$), 46.88 (NCH_2, morpholine), 41.71 (CH), 15.76 (CH_3), 14.85-14.77 (m, $OCH_2\underline{C}H_3$); δ_P (DMSO-d_6) 12.4; LCMS: found *m/z* 464.5 MH^+. $C_{21}H_{26}N_3O_7P$ requires 463.4. Chiral HPLC: 1 peak; eluent, hexane/IPA (80:20, v:v); flow rate, 0.5 mL/min.

Diethyl {2-[1-(1,3-dioxo-2,3-dihydro-1H-isoindol-2-yl)-2-methylpropyl]-5-(morpholin-4-yl)-1,3-oxazol-4-yl}phosphonate (5b). Yield 10.22 g, 64% as a yellow oil; [Found: C, 56.32; H, 6.24; N, 8.53; P, 6.25. $C_{23}H_{30}N_3O_7P$ requires C, 56.21; H, 6.15; N, 8.55; P, 6.30%]; $[\alpha]_D^{20}$ +7.6 (*c* 0.7, CH_2Cl_2); ν_{max} (ATR) 1769, 1717, 1611, 1573, 1266, 1017, 961 cm^{-1}; δ_H (DMSO-d_6) 7.94-7.88 (4H, m, aromatic), 4.93 (1H, d, *J* 10.0 Hz, CH), 4.03-3.92 (4H, m, $2O\underline{CH_2}CH_3$), 3.66-3.63 (4H, m, $2CH_2$), 3.46-3.42 (4H, m, $2CH_2$), 2.93-2.86 (1H, m, CH), 1.23-1.16 (6H, m, $2OCH_2\underline{CH_3}$), 1.08 (3H, d, *J* 7.0 Hz, CH_3), 0.89 (3H, d, *J* 7.0 Hz, CH_3); δ_C (DMSO-d_6)[a,b] 165.91 (C=O), 159.70 (d, *J* 38.0 Hz, O-$\underline{C}$=C-P), 148.71 (d, *J* 21.4 Hz, O-C=N), 134.45, 129.40, 121.90 (aromatic), 98.71 (d, *J* 251.3 Hz, CP), 63.63, 63.49 (OCH_2, morpholine), 60.00-59.79 (m, $O\underline{C}H_2CH_3$), 46.00, 45.79 (NCH_2, morpholine), 36.63 (CH), 25.91 (CH), 17.94 (CH_3), 16.83 (CH_3), 13.95-13.78 (m, $OCH_2\underline{C}H_3$);δ_P (DMSO-d_6) 12.3; LCMS: found *m/z* 492.5 MH^+. $C_{23}H_{30}N_3O_7P$

requires 491.5. Chiral HPLC: 1 peak; eluent, hexane/IPA (90:10, v:v); flow rate, 0.6 mL/min.

Diethyl {2-[1-(1,3-dioxo-2,3-dihydro-1H-isoindol-2-yl)-3-methylbutyl]-5-(morpholin-4-yl)-1,3-oxazol-4-yl}phosphonate (5c). Yield 9.281 g, 61% as a yellow viscous oil; [Found: C, 57.15; H, 6.29; N, 8.29; P, 6.09. $C_{24}H_{32}N_3O_7P$ requires C, 57.02; H, 6.38; N, 8.31; P, 6.13%];$[\alpha]_D^{20}$ -12.2 (*c* 1.0, CH_2Cl_2); ν_{max} (ATR) 1771, 1714, 1611, 1572, 1265, 1019, 960 cm^{-1}; δ_H (DMSO-d_6) 7.92-7.84 (4H, m, aromatic), 5.38-5.34 (1H, m, CH), 3.99-3.87 (4H, m, $2OCH_2CH_3$), 3.64-3.61 (4H, m, $2CH_2$), 3.42-3.39 (4H, m, $2CH_2$), 2.32-2.23 (1H, m, CH_aH_b), 2.07-1.99 (1H, m, CH_aH_b), 1.59-1.49 (1H, m, CH), 1.19-1.12 (6H, m, $2OCH_2CH_3$), 0.92-0.88 (6H, m, $2CH_3$); δ_C (DMSO-d_6) 165.93 (C=O), 159.80 (d, *J* 36.9 Hz, O-C=C-P), 149.57 (d, *J* 21.4 Hz, O-C=N), 133.48, 125.51, 121.96 (aromatic), 99.8 (d, *J* 250.3 Hz, CP), 63.51 (OCH_2 morpholine), 59.94-59.88 (m, OCH_2CH_3), 45.81 (NCH_2, morpholine), 35.26 (CH), 22.26 (CH_2), 20.70 (CH), 19.09 (CH_3), 13.83-13.74 (m, OCH_2CH_3); δ_P (DMSO-d_6) 12.2; LCMS: found *m/z* 506.6 MH^+. $C_{24}H_{32}N_3O_7P$ requires 505.5. Chiral HPLC: 1 peak; eluent, hexane/IPA (80:20, v:v); flow rate, 0.5 mL/min.

General procedure for the preparation of 6a-c. Oxazole cyclization

A mixture of one of compounds **6a-c** (30 mmol) and morpholine (11.78 mL, 135 mmol) in dry THF (125 mL) was stirred at 20-25 °C for 48 h under TLC control. The precipitate was filtered and washed on the filter with dry dioxane, and the combined filtrates were evaporated *in vacuo* to dryness. If necessary, the reaction product can be purified by extraction with boiling water, followed by evaporation of the combined extracts *in vacuo*.

Diethyl [5-(morpholin-4-yl)-2-[1-({2-[(morpholin-4-yl)carbonyl]phenyl}formamido)ethyl]-1,3-oxazol-4-yl]phosphonate (6a). Yield 10.42 g, 63% as a yellow viscous oil; [Found: C, 54.69; H, 6.50; N, 10.20; P, 5.52. $C_{25}H_{35}N_4O_8P$ requires C, 54.54; H, 6.41; N, 10.18; P, 5.63%]; $[\alpha]_D^{20}$ +15.3 (*c* 1.1, CH_2Cl_2); ν_{max} (ATR) 3474, 1717, 1614, 1573, 1276, 1016, 960 cm-1; δ_H (DMSO-d_6) 8.95 (1H, d, *J* 8.0 Hz, NH), 7.68 (1H, d, *J* 7.3 Hz, aromatic), 7.55-7.52 (1H, m, aromatic), 7.49 (1H, t, *J* 7.3 Hz, aromatic), 7.30 (1H, d, *J* 7.3 Hz, aromatic), 5.14-5.08 (1H, m, CH), 4.03-3.99 (4H, m, $2OCH_2CH_3$), 3.68-3.63 (8H, m, $4CH_2$), 3.54-3.46 (8H, m, $4CH_2$), 1.48 (3H, d, *J* 7.0 Hz, CH_3), 1.26-1.21 (6H, m, $2OCH_2CH_3$); δ_C (DMSO-d_6) 167.58 (C=O), 165.01 (C=O), 159.60 (d, *J* 36.9 Hz, O-C=C-P), 152.89 (d, *J* 22.1 Hz, O-C=N), 135.08, 133.32, 131.89, 129.16, 126.94, 126.24, 125.12, 121.80 (aromatic), 104.79 (d, *J* 259.3 Hz, CP), 63.65 (OCH_2, morpholine), 59.85 (d, *J* 5.0 Hz, OCH_2CH_3), 45.99 (NCH_2, morpholine), 40.51 (CH), 15.89 (CH_3), 13.93 (d, *J* 6.5 Hz, OCH_2CH_3); δ_P (DMSO-d_6) 12.7; LCMS: found *m/z* 549.5 M-H$^-$. $C_{25}H_{35}N_4O_8$ requires 550.4.

Diethyl {2-[2-methyl-1-({2-[(morpholin-4-yl)carbonyl]-phenyl}formamido)propyl]-5-(morpholin-4-yl)-1,3-oxazol-4-yl}phosphonate (6b). Yield 10.93 g, 63% as a yellow viscous oil; [Found: C, 56.19; H, 6.63; N, 9.58; P, 5.27. $C_{27}H_{39}N_4O_8P$ requires C, 56.05; H, 6.79; N, 9.68; P, 5.35%]; $[\alpha]_D^{20}$ -26.7 (*c* 1.0, CH_2Cl_2); ν_{max} (ATR) 1719, 1613, 1572, 1262, 1016, 960 cm^{-1}; δ_H (DMSO-d_6) 8.84 (1H, d, *J* 8.3 Hz. NH), 7.67 (1H, d, *J* 6.0 Hz, aromatic), 7.54 (1H, t, *J* 6.0 Hz, aromatic), 7.48-7.52 (1H, m, aromatic), 7.31 (1H, d, *J* 6.0 Hz, aromatic), 4.81-4.78 (1H, m, CH), 4.04-3.95 (4H, m, $2OCH_2CH_3$), 3.74-3.59 (8H, m, $4CH_2$), 3.56-3.49 (8H, m, $4CH_2$), 2.26-2.23 (1H, m, CH), 1.24-1.20 (6H, m, $2OCH_2CH_3$), 1.00 (3H, d, *J* 5.2 Hz, CH_3), 0.91 (3H, d, *J* 5.2 Hz, CH_3); δ_C (DMSO-d_6) 169.21 (C=O), 167.36 (C=O), 161.03 (d, *J* 36.4 Hz, O-C=C-P), 153.58 (d, *J* 20.9 Hz, O-C=N), 136.70, 134.11, 131.01, 128.94, 128.48, 123.07 (aromatic), 101.84 (d, *J* 249.8 Hz, CP), 65.98 (OCH_2, morpholine), 62.27-62.19 (m, OCH_2CH_3), 48.46 (NCH_2, morpholine), 42.13 (CH), 31.3 (CH), 19.30 (CH_3), 19.28 (CH_3), 16.54 (d, *J* 6.5 Hz, OCH_2CH_3); δ_P (DMSO-d_6) 12.6; LCMS: found *m/z* 579.6 MH^+. $C_{27}H_{39}N_4O_8P$ requires 578.6.

Diethyl {2-[3-methyl-1-({2-[(morpholin-4-yl)carbonyl]-phenyl}formamido)butyl]-5-(morpholin-4-yl)-1,3-oxazol-4-yl}-phosphonate (6c). Yield 12.15 g, 68% as a yellow viscous oil; [Found: C, 56.69; H, 6.84; N, 9.39; P, 5.31. $C_{28}H_{41}N_4O_8P$ requires C, 56.75; H, 6.97; N, 9.45; P, 5.23%]; $[\alpha]_D^{20}$ -21.2 (*c* 0.9, CH_2Cl_2); ν_{max} (ATR) 3459, 1718, 1616, 1574, 1535, 1270, 1019, 963 cm^{-1}; δ_H (DMSO-d_6) 8.88 (1H, d, *J* 8.0 Hz, NH), 7.64 (1H, d, *J* 6.6 Hz, aromatic), 7.55-7.49 (2H, m, aromatic), 7.31 (1H, d, *J* 7.0 Hz, aromatic), 5.10-5.04 (1H, m, CH), 4.03-3.95 (4H, m, $2OCH_2CH_3$), 3.71-3.47 (16H, m, $8CH_2$), 2.43 (1H, m, CH_aH_b), 1.82-1.64 (2H, m, CH_aH_b, CH), 1.27-1.21 (6H, m, $2OCH_2CH_3$); 0.97-0.89 (6H, m, $2CH_3$); δ_C (DMSO-d_6) 169.65 (C=O), 167.49 (C=O), 159.53 (d, *J* 33.4 Hz, O-C=C-P), 152.64 (d, *J* 22.4 Hz, O-C=N), 134.98, 133.47, 129.52, 129.10, 126.95, 126.18, 125.09, 121.94 (aromatic), 99.17 (d, *J* 248.8 Hz, CP), 64.28 (OCH_2, morpholine), 59.86-59.78 (m, OCH_2CH_3), 45.97 (NCH_2, morpholine), 39.41 (CH), 26.66 (CH_2), 22.16 (CH), 20.61 (CH_3), 19.49 (CH_3), 13.92 (d, *J* 7.0 Hz, OCH_2CH_3); δ_P (DMSO-d_6) 12.7; LCMS: found *m/z* 563.6 MH^+. $C_{28}H_{41}N_4O_8P$ requires 592.6.

General procedure for the preparation of 7a-c. Removal of the phthaloyl protection by hydrazinolysis

A mixture of one of compounds **5a-c** or **6a-c** (4 mmol), hydrazine hydrate (0.4 mL, 8 mmol), and ethanol (50 mL) was kept at a temperature of 45-50 °C for 3h. The precipitate was filtered and washed on the filter with ethanol, and the combined filtrates were evaporated *in vacuo* to dryness. The residue was dissolved in dry dichloromethane (50 mL), followed by filtering the precipitate and washing it on the filter with dry dichloromethane. The combined filtrates were evaporated under reduced pressure to dryness to give the analytically pure product.

Diethyl [2-(1-aminoethyl)-5-(morpholin-4-yl)-1,3-oxazol-4-yl]phosphonate (7a). Yield 1.14 g, 86% as a yellow viscous oil; [Found: C, 46.75; H, 7.36; N, 12.55; P, 9.39. $C_{13}H_{24}N_3O_5P$ requires C, 46.84; H, 7.26; N, 12.61; P, 9.29%]; $[\alpha]_D^{20}$ +3.6 (*c* 7.6, CH_2Cl_2); ν_{max} (ATR) 2978, 1606, 1570, 1265, 1018, 959 cm^{-1}; δ_H (DMSO-d_6) 4.04-3.95 (4H, m, $2OCH_2CH_3$), 3.91-3.87 (1H, q, *J* 6.6 Hz,CH), 3.69-3.67 (4H, m, $2CH_2$), 3.48-3.46 (4H, m, $2CH_2$), 1.31-1.29 (3H, d, *J* 6.6 Hz, CH_3), 1.25-1.21 (6H, m, $2OCH_2CH_3$). δ_C (DMSO-d_6) 159.52 (d, *J* 37.4 Hz, O-C=C-P), 157.03 (d, *J* 20.4 Hz, O-C=N), 98.81 (d, *J* 51.8 Hz, CHP), 63.65 (OCH_2, morpholine), 59.74 (d, *J* 5.5 Hz, OCH_2CH_3), 46.05 (NCH_2-morpholine), 42.62 (CH), 19.16 (CH_3), 13.94 (d, *J* 6.0 Hz, OCH_2CH_3); δ_P (DMSO-d_6) 12.3; LCMS: found *m/z* 334.3 MH^+. $C_{13}H_{24}N_3O_5P$ requires 333.3. Chiral HPLC: 1 peak; eluent, hexane/IPA (80:20, v:v); flow rate, 0.5 mL/min.

Diethyl [2-(1-amino-2-methylpropyl)-5-(morpholin-4-yl)-1,3-oxazol-4-yl]phosphonate (7b*)*. Yield 1.198 g, 83% as a yellow viscous oil; Found: C, 49.75; H, 7.96; N, 11.61; P, 8.69. $C_{15}H_{28}N_3O_5P$ requires C, 49.86; H, 7.81; N, 11.63; P, 8.57%; $[\alpha]_D^{20}$-5.3 (*c* 1.2, CH_2Cl_2); ν_{max} (ATR) 1611, 1572, 1264, 1017, 962 cm^{-1}; δ_H (DMSO-d_6) 4.10-4.04 (1H, m, CH), 4.02-3.94 (4H, m, $2OCH_2CH_3$), 3.69-3.46 (10H, m, $4CH_2$, NH_2), 1.23-1.19 (6H, m,

2OCH$_2$CH$_3$), 0.89 (3H, d, *J* 6.3 Hz, CH$_3$), 0.81 (3H, d, *J* 6.32 Hz, CH$_3$); δ_C (DMSO-*d*$_6$) 159.46 (d, *J* 37.4 Hz, O-C=C-P), 155.73 (d, *J* 20.9 Hz, O-C=N), 98.63 (d, *J* 250.8 Hz, CHP), 63.63 (OCH$_2$, morpholine), 59.80 (d, *J* 5.0 Hz, OCH$_2$CH$_3$), 52.96 (NCH$_2$, morpholine), 46.11 (NCH), 30.80 (CH), 16.65 (CH$_3$), 16.06 (CH$_3$), 13.90 (d, *J* 6.0 Hz, OCH$_2$CH$_3$); δ_P (DMSO-*d*$_6$) 12.2; LCMS: found *m/z* 362.5 MH$^+$. $C_{15}H_{28}N_3O_5P$ requires 361.4.

Diethyl [2-(1-amino-3-methylbutyl)-5-(morpholin-4-yl)-1,3-oxazol-4-yl]phosphonate (7c). Yield 1.200 g, 80% as a yellow viscous oil; Found: C, 51.35; H, 8.06; N, 11.21; P, 8.19. $C_{16}H_{30}N_3O_5P$ requires C, 51.19; H, 8.05; N, 11.19; P, 8.25%]; $[\alpha]_D^{20}$-17.2 (*c* 1.3, CH_2Cl_2); ν_{max} (ATR) 1607, 1570, 1265, 1019, 959 cm^{-1}; δ_H (DMSO-*d*$_6$) 4.03-3.94 (4H, m, 2OCH$_2$CH$_3$), 3.78-3.74 (1H, t, *J* 7.4 Hz, CH), 3.68-3.66 (4H, m, 2CH$_2$), 3.48-3.45(4H, m, 2CH$_2$), 1.65-1.47 (3H, m, CHCH$_2$), 1.24-1.20 (6H, m, 2OCH$_2$CH$_3$), 0.86 (3H, d, *J* 6.3 Hz, CH$_3$), 0.83 (3H, d, *J* 6.3 Hz, CH$_3$); δ_C (DMSO-*d*$_6$) 159.40 (d, *J* 37.4 Hz, O-C=C-P), 156.70 (d, *J* 20.9 Hz, O-C=N), 98.76 (d, *J* 250.8 Hz, CHP), 63.66 (OCH$_2$, morpholine), 59.74 (d, *J* 5.5 Hz, OCH$_2$CH$_3$), 46.09 (NCH$_2$, morpholine), 42.47 (CH), 22.44 (CH$_2$), 20.20 (CH), 19.96 (CH$_3$), 13.88 (d, *J* 6.0 Hz, OCH$_2$CH$_3$). δ_P (DMSO-*d*$_6$) 12.2; LCMS: found *m/z* 376.5 MH$^+$. $C_{16}H_{30}N_3O_5P$ requires 375.4.

General procedure for the preparation of peptidomimetics 8a-c. Oxazole ring opening

The compounds were obtained as previously described.[27] One of oxazoles **5a-c** (6 mmol) was heated in a 5:1 (v:v) AcOH/H_2O mixture (20 mL) for 8 h at 75 °C, followed by evaporation of the solvents *in vacuo* to dryness. To remove AcOH completely, the residue was treated with a 5% Na_2CO_3 solution (20 mL) and extracted with dichloromethane (3×50 mL). The extract was dried over $MgSO_4$ and evaporated under reduced pressure to dryness. The resulting product was analyzed without further purification.

Diethyl {1-[2-(1,3-dioxo-2,3-dihydro-1H-isoindol-2-yl)propanamido]-2-(morpholin-4-yl)-2-oxoethyl}phosphonate (8a). Yield 2.773 g, 96% as a colourless solid; mp 114-115 °C; [Found: C, 52.23; H, 5.79; N, 8.61; P, 6.51. $C_{21}H_{28}N_3O_8P$ requires C, 52.39; H, 5.86; N, 8.73; P, 6.43%]; $[\alpha]_D^{20}$ -14.4 (*c* 0.6, CH_2Cl_2); ν_{max} (KBr) 3303, 1778, 1716, 1674, 1640, 1529, 1260, 1021, 971 cm^{-1}; δ_H (DMSO-*d*$_6$) 8.75 ($^1/_2$H, d, *J* 8.5 Hz, NH), 8.68 ($^1/_2$H, d, *J* 8.5 Hz, NH), 7.89-7.86 (4H, m, aromatic), 5.49-5.36 (1H, m, CHP), 4.99-4.87 (1H, m, CH), 4.12-3.98 (4H, m, 2OCH$_2$CH$_3$), 3.60-3.37 (8H, m, 4CH$_2$), 1.69-1.63 (3H, m, CH$_3$), 1.26-1.14 (6H, m, 2OCH$_2$CH$_3$); δ_C (DMSO-*d*$_6$)[a] 169.46 (d, *J* 5.0 Hz, C=O), 169.22 (d, *J* 5.0 Hz, C=O), 168.10, 167.98 (C=O), 164.44 (d, *J* 2.5 Hz, C=O), 164.37 (d, *J* 2.5 Hz, C=O), 135.01, 134.97, 132.11, 132.07, 123.54, 123.52 (aromatic), 66.42, 66.39 (OCH$_2$, morpholine), 63.55-63.46 (m, OCH$_2$CH$_3$), 63.21-63.11 (m, OCH$_2$CH$_3$), 49.43, 49.20 (NCH$_2$, morpholine), 48.46 (d, *J* 149.0 Hz, CHP), 48.25 (d, *J* 149.0 Hz, CHP), 46.81 (NCH$_2$, morpholine), 42.92, 42.84 (CH), 16.81-16.52 (m, OCH$_2$CH$_3$), 15.98, 15.74 (CH$_3$); δ_P (DMSO-*d*$_6$) 18.2; 17.9; LCMS: found *m/z* 482.4 MH$^+$. $C_{21}H_{28}N_3O_8P$ requires 481.4. Chiral HPLC: 1 peak; eluent, hexane/IPA (50:50, v:v); flow rate, 0.3 mL/min.

Diethyl {1-[2-(1,3-dioxo-2,3-dihydro-1H-isoindol-2-yl)-3-methylbutanamido]-2-(morpholin-4-yl)-2-oxoethyl}phosphonate (8b). Yield 2.923 g, 95% as a yellow viscous oil; [Found: C, 54.10; H, 6.38; N, 8.37; P, 6.19. $C_{23}H_{32}N_3O_8P$: C, 54.22; H, 6.33; N, 8.25; P, 6.08%]; $[\alpha]_D^{20}$ -19.2 (*c* 0.8, CH_2Cl_2); ν_{max} (ATR) 3320, 1769, 1712, 1644, 1514, 1250, 1014, 965 cm^{-1}; δ_H (DMSO-*d*$_6$) 8.60 ($^1/_2$H, d, *J* 8.5 Hz, NH), 8.39 ($^1/_2$H, d, *J* 8.5 Hz, NH), 7.94-7.86 (4H, m, aromatic), 5.47-5.38 (1H, m, CHP), 4.54 ($^1/_2$H, d, *J* 10.5 Hz, CH), 4.49 ($^1/_2$H, d, *J* 10.5 Hz, CH), 4.04-3.95 (4H, m, 2OCH$_2$CH$_3$), 3.60-3.43 (8H, m, 4CH$_2$), 2.88-2.80 (1H, m, CH), 1.24-1.10 (6H, m, 2OCH$_2$CH$_3$), 1.04-1.00 (3H, m, CH$_3$), 0.82-0.76 (3H, m, CH$_3$); δ_C (DMSO-*d*$_6$)[a,d] 166.49, 166.45 (C=O), 166.36, 166.33, 166.28 (C=O), 166.45 (d, *J* 2.0 Hz, C=O), 162.40 (d, *J* 2.0 Hz, C=O), 133.36, 129.55, 129.51, 121.81, 121.77 (aromatic), 64.04, 64.00 (OCH$_2$, morpholine), 61.13 (d, *J* 6.5 Hz, OCH$_2$CH$_3$), 60.96 (d, *J* 6.0 Hz, OCH$_2$CH$_3$), 60.76 (d, *J* 6.5 Hz, OCH$_2$CH$_3$), 60.64 (d, *J* 6.0 Hz, OCH$_2$CH$_3$), 58.58, 58.50 (NCH$_2$, morpholine), 45.66 (d, *J* 147.6 Hz, CHP), 45.54 (d, *J* 147.6 Hz, CHP), 44.42, 44.29 (NCH$_2$, morpholine), 40.48, 40.34 (CH), 24.92, 24.75 (CH), 17.60, 17.52, 17.26 (CH$_3$), 14.04-13.79 (m, OCH$_2$CH$_3$); δ_P (DMSO-*d*$_6$) 18.2, 17.9; LCMS: found *m/z* 510.5 MH$^+$. $C_{23}H_{32}N_3O_8P$ requires 509.5.

Diethyl {1-[2-(1,3-dioxo-2,3-dihydro-1H-isoindol-2-yl)-4-methylpentanamido]-2-(morpholin-4-yl)-2-oxoethyl}phosphonate (8c). Yield 3.078 g, 98% as a yellow viscous oil; [Found: C, 55.19; H, 7.09; N, 8.14; P, 5.81. $C_{24}H_{34}N_3O_8P$ requires C, 55.06; H, 6.55; N, 8.03; P, 5.93%]; $[\alpha]_D^{20}$ -7.4 (*c* 0.6, CH_2Cl_2); ν_{max} (ATR) 3318, 1765, 1714, 1645, 1516, 1251, 1016, 964 cm^{-1}; δ_H (DMSO-*d*$_6$) 8.90 ($^1/_2$H, d, *J* 8.5 Hz, NH), 8.87 ($^1/_2$H, d, *J* 8.5 Hz, NH), 7.91-7.86 (4H, m, aromatic), 5.46-5.38 (1H, m, CHP), 4.99-4.90 (1H, m, CH), 4.12-3.98 (4H, m, 2OCH$_2$CH$_3$), 3.61-3.36 (8H, m, 4CH$_2$), 2.45-2.27 (1H, m, CH$_a$H$_b$), 1.90-1.79 (1H, m, CH$_a$H$_b$), 1.43-1.37 (1H, m, CH), 1.25-1.14 (6H, m, 2OCH$_2$CH$_3$), 0.86-0.83 (6H, m, 2CH$_3$); δ_C (DMSO-*d*$_6$)[a,e] 167.54 (d, *J* 5.0 Hz, C=O), 167.24 (d, *J* 5.0 Hz, C=O), 166.67, 166.59 (C=O), 162.60-162.56 (m, C=O), 133.23, 129.82, 129.80, 121.67 (aromatic), 64.05, 64.03 (OCH$_2$, morpholine), 61.16-61.10 (d, *J* 6.0 Hz, OCH$_2$CH$_3$), 61.05-60.74 (d, *J* 6.0 Hz, OCH$_2$CH$_3$), 50.34, 50.20 (NCH$_2$, morpholine), 46.95 (d, *J* 147.6 Hz, CHP), 45.77 (d, *J* 147.6 Hz, CHP), 44.33 (NCH$_2$, morpholine) 40.41, 40.33 (CH), 34.55, 34.35 (CH$_2$), 22.95, 22.85 (CH), 18.35, 18.24 (CH$_3$), 14.15-13.84 (m, OCH$_2$CH$_3$); δ_P (DMSO-*d*$_6$) 18.0, 17.9; LCMS: found *m/z* 524.2 MH$^+$. $C_{24}H_{34}N_3O_8P$ requires 523.5.

General procedure for the preparation of peptidomimetics 9a-c. Oxazole ring opening

A mixture of one of compounds **6a-c** (6 mmol) and *p*-toluenesulfonic acid monohydrate (6 mmol, 0.64 g) in THF (50 mL) was stirred at 20-25 °C for 48 h under TLC control, followed by evaporation of the solvents *in vacuo* to dryness. To remove *p*-toluenesulfonic acid completely, the residue was treated with a 5% Na_2CO_3 solution (20 mL) and extracted with dichloromethane (3×50 mL). The extract was dried over $MgSO_4$ and evaporated under reduced pressure to dryness. The resulting product was analyzed without further purification.

Diethyl [2-(morpholin-4-yl)-1-[2-({2-[(morpholin-4-yl)carbonyl]phenyl}formamido)propanamido]-2-oxoethyl]phosphonate (9a). Yield 3.070 g, 90% as a yellow viscous oil; [Found: C, 52.69; H, 6.66; N, 9.73; P, 5.3:. $C_{25}H_{37}N_4O_9P$ requires C, 52.81; H, 6.56; N, 9.85; P, 5.45%]; $[\alpha]_D^{20}$ +20.5 (*c* 0.9, CH_2Cl_2); ν_{max} (ATR) 3290, 1716, 1635, 1526, 1251, 1013, 973 cm^{-1}; δ_H (DMSO-*d*$_6$) 8.76 ($^1/_2$H, d, *J* 8.7 Hz, NH), 8.69 ($^1/_2$H, d, *J* 8.7 Hz, NH), 8.54 ($^1/_2$H, d, *J* 7.4 Hz, NH), 8.37 ($^1/_2$H, d, *J* 7.4 Hz, NH), 7.76-7.72 (1H, m, aromatic), 7.56-7.46 (2H, m, aromatic), 7.30-7.27 (1H, m, aromatic), 5.49-5.38 (1H, m, CHP), 4.68-4.56 (1H, m, CH), 4.07-4.01 (4H, m, 2OCH$_2$CH$_3$), 3.68-3.31 (16H, m, 8CH$_2$), 1.31-1.29 (3H, d, *J* 6.3 Hz, CH$_3$), 1.25-1.15 (6H, m, 2OCH$_2$CH$_3$); δ_C (DMSO-*d*$_6$)[a,b] 170.67 (d, *J* 4.5 Hz, C=O), 170,59 (d, *J* 4.5 Hz, C=O), 167.63, 167.60 (C=O), 166.35, 166.22 (C=O), 162.69, 162.66 (C=O),

134.98, 134.90, 133.06, 133.03, 130.14, 130.09, 129.21, 129.17, 126.93, 126.88, 126.43 (aromatic), 64.07, 64.04 (OCH_2, morpholine), 61.26 (d, *J* 6.5 Hz, $O\underline{C}H_2CH_3$), 61.14 (d, *J* 6.5 Hz, $O\underline{C}H_2CH_3$), 60.94 (d, *J* 6.5 Hz, $O\underline{C}H_2CH_3$), 60.76 (d, *J* 6.5 Hz, $O\underline{C}H_2CH_3$), 50.47 (d, *J* 139.1 Hz, CP), 50.21 (d, *J* 139.1 Hz, CP), 47.74, 46.45, 45.05, 44.33 (NCH_2, morpholine), 40.45, 40.32 (CH), 15.85, 15.70 (CH_3), 14.15-13.96 ($OCH_2\underline{C}H_3$); δ_P (DMSO-d_6) 17.6, 17.5; LCMS: found *m/z* 541.5 MH $C_{25}H_{37}N_4O_9P$ requires 540.5.

Diethyl {1-[3-methyl-2-({2-[(morpholin-4-yl)carbonyl]-phenyl}formamido)butanamido]-2-(morpholin-4-yl)-2-oxoethyl}-phosphonate (9b). Yield 3.293 g, 92% as a yellow viscous oil; [Found: C, 54.23; H, 6.70; N, 9.71; P, 5.51. $C_{27}H_{41}N_4O_9P$ requires C, 54.36; H, 6.56; N, 9.85; P, 5.45%]; $[\alpha]_D^{20}$ -19.2 (*c* 0.9, CH_2Cl_2); ν_{max} (ATR) 3288, 1718, 1637, 1527, 1252, 1014, 965 cm^{-1}; δ_H (DMSO-d_6) 8.72-8.67 ($^1/_2$H, m, NH), 8.41-8.38 ($^1/_2$H, m, NH), 8.25-8.22 ($^1/_2$H, m, NH), 7.74-7.70 (1H, m, aromatic), 7.59-7.47 (2H, m, aromatic), 7.33-7.29 (1H, m, aromatic), 5.52-5.41 (1H, CHP), 4.59-4.52 ($^1/_2$H, m, CH), 4.45-4.42 ($^1/_2$H, m, CH), 4.11-3.97 (4H, m, $2O\underline{C}H_2CH_3$), 3.67-3.46 (16H, m, $8CH_2$), 2.10-2.07 (1H, m, CH), 1.27-1.20 (6H, m, $2OCH_2\underline{C}H_3$), 0.95-0.90 (6H, m, $2CH_3$); δ_C (DMSO-d_6)[a,b,d] 169.37, 169.30 (C=O), 167.57, 167.51 (C=O), 165.40, 165.26 (C=O), 162.76 (d, *J* 3.0 Hz, C=O), 162.68 (d, *J* 3.0 Hz, C=O), 134.60, 133.57, 132.07, 131.84, 129.11, 127.03, 126.94, 126.71, 126.51, 125.14, 125.05 (aromatic), 64.09, 63.98, 63.85, 63.77 (OCH_2, morpholine), 61.19 (d, *J* 6.0 Hz, $O\underline{C}H_2CH_3$), 61.07 (d, *J* 6.5 Hz, $O\underline{C}H_2CH_3$), 60.87 (d, *J* 6.0 Hz, $O\underline{C}H_2CH_3$), 60.56 (d, *J* 6.5 Hz, $O\underline{C}H_2CH_3$), 52.00 (d, *J* 128.6 Hz, CP), 51.90 (d, *J* 128.6 Hz, CP), 45.16-44.41 (m, NCH_2, morpholine), 40.32, 39.63 (CH), 28.48, 28.35 (CH), 17.07, 16.93 (CH_3), 16.26, 16.17 (CH_3), 14.12-13.93 (m, OCH_2CH_3); δ_P (DMSO-d_6) 17.7, 17.5; LCMS: found *m/z* 597.6 MH^+. $C_{27}H_{41}N_4O_9P$ requires 596.6.

Diethyl {1-[4-methyl-2-({2-[(morpholin-4-yl)carbonyl]-phenyl}formamido)pentanamido]-2-(morpholin-4-yl)-2-oxo-ethyl}phosphonate (9c). Yield 3.334 g, 91% as a yellow viscous oil; [Found: C, 55.23; H, 7.19; N, 9.31; P, 8.61. $C_{28}H_{43}N_3O_6P$ requires C, 55.07; H, 7.10; N, 9.18; P, 8.82%]; $[\alpha]_D^{20}$ -20.2 (*c* 1.1, CH_2Cl_2); ν_{max} (ATR) 3288, 1719, 1635, 1524, 1255, 1016, 964 cm^{-1}; δ_H (DMSO-d_6) 8.90 ($^1/_2$H, d, *J* 8.20 Hz, NH), 8.78 ($^1/_2$H, d, *J* 8.2 Hz, NH), 8.67 ($^1/_2$H, d, *J* 7.8 Hz, NH), 8.56 ($^1/_2$H, d, *J* 7.8 Hz, NH), 7.76-7.65 (1H, m, aromatic), 7.67-7.47 (2H, m, aromatic), 7.39-7.27 (1H, m, aromatic), 5.50-5.37 (1H, m, CHP), 5.00-4.90 ($^1/_2$H, m, CH), 4.71-4.55 ($^1/_2$H, m, CH), 4.11-4.00 (4H, m, $2O\underline{C}H_2CH_3$), 3.62-3.45 (16H, m, $8CH_2$), 2.42-2.28 (1H, m, $C\underline{H}_aCH_b$), 1.93-1.82 (1H, m, $CH_a\underline{C}H_b$), 1.54-1.38 (1H, m, CH), 1.26-1.14 (6H, m, $2OCH_2\underline{C}H_3$), 0.91-0.65 (6H, m, $2CH_3$); δ_C (DMSO-d_6) 169.45, 169.37, 167.63 (C=O), 165.60, 162.35 (C=O), 162.80 (d, *J* 4.0 Hz, C=O), 162.75 (d, *J* 4.0 Hz, C=O), 134.63, 133.60, 132.13, 131.90, 129.23, 127.10, 126.96, 126.78, 126.56, 125.24, 125.15 (aromatic), 64.05, 63.92, 63.81, 63.70 (OCH_2, morpholine), 61.15 (d, *J* 6.0 Hz, $O\underline{C}H_2CH_3$), 60.83 (d, *J* 6.0 Hz, $O\underline{C}H_2CH_3$), 51.97 (d, *J* 128.6 Hz, CP), 51.15 (d, *J* 128.6 Hz, CP), 45.20, 43.42 (NCH_2, morpholine), 40.31, 39.72 (CH), 33.48, 33.32 (CH_2), 22.03, 22.10 (CH), 18.42, 18.35 (CH_3), 14.10-13.83 (m, OCH_2CH_3); δ_P (DMSO-d_6) 17.1, 17.0; LCMS: found *m/z* 611.5 MH^+. $C_{28}H_{43}N_3O_6P$ requires 610.6.

General procedure for the preparation of peptidomimetics 10a-c. Removal of the phthaloyl protection by hydrazinolysis

The compounds were obtained starting from **8a-c** or **9a-c** by the same procedure as used for **7a-c**.

Diethyl [1-(2-aminopropanamido)-2-(morpholin-4-yl)-2-oxoethyl]phosphonate (10a). Yield 1.110 g, 79% as a yellow viscous oil; [Found: C, 44.31; H, 7.36; N, 11.91; P, 8.89. $C_{13}H_{26}N_3O_6P$ requires C, 44.44; H, 7.46; N, 11.96; P, 8.82%]; $[\alpha]_D^{20}$+3.6 (*c* 0.6, CH_3OH); ν_{max} (ATR) 3357, 1639, 1506, 1242, 1012, 974 cm^{-1}; δ_H ($CDCl_3$) 8.24 ($^1/_2$H, m, NH), 8.13 (1H, m, N_2), 5.48-5.41 (1H, m, CHP), 4.20-4.13 (4H, m, $2O\underline{C}H_2CH_3$), 3.85-3.46 (9H, m, $4CH_2$, CH), 2.15 (2H, br. s, NH_2), 1.36-1.29 (9H, m, $2OCH_2\underline{C}H_3$, CH_3); δ_C (DMSO-d_6)[a, b, d] 174.76-174.67 (m, C=O), 163.76-163.66 (m, C=O), 65.24, 65.21, 65.08 (OCH_2, morpholine), 62.26-62.16 (m, $O\underline{C}H_2CH_3$), 61.88 (d, *J* 6.0 Hz, $O\underline{C}H_2CH_3$), 49.12, 48.73 (NCH_2, morpholine), 45.84 (d, *J* 146.8 Hz, CHP), 45.90 (d, *J* 146.8 Hz, CHP), 45.36, 45.11 (NCH_2, morpholine), 41.40, 40.24 (CH), 20.15, 19.88 (CH_3), 15.13-14.92 (m, $OCH_2\underline{C}H_3$); δ_P ($CDCl_3$) 17.5, 17.3; LCMS: found *m/z* 352.4 MH^+. $C_{13}H_{26}N_3O_6P$ requires 351.4. Chiral HPLC: 2 peaks of equal intensity; eluent, EDA/IPA (70:30, v:v); flow rate, 0.4 mL/min.

Diethyl [1-(2-amino-3-methylbutanamido)-2-(morpholin-4-yl)-2-oxoethyl]phosphonate (10b). Yield 1.290 g, 85% as a viscous oil; Found: C, 47.55; H, 8.06; N, 11.21; P, 8.09. $C_{15}H_{30}N_3O_6P$ requires C, 47.49; H, 7.97; N, 11.08; P, 8.16%]; $[\alpha]_D^{20}$ -12.2 (*c* 1.0, CH_2Cl_2); ν_{max} (ATR) 3341, 1639, 1506, 1242, 1016, 963 cm^{-1}; δ_H (DMSO-d_6) 5.45-5.40 (1H, m, CHP), 4.08-4.02 (4H, m, $2O\underline{C}H_2CH_3$), 3.66-3.35 (9H, m, $4CH_2$, CH), 2.07-2.00 ($^1/_2$H, m, CH), 1.99-1.92 ($^1/_2$H, m, CH), 1.24-1.19 (6H, m, $2OCH_2\underline{C}H_3$), 1.06-1.03 (1H, m, CH), 0.93-0.85 (3H, m, CH_3), 0.78-0.72 (3H, m, CH_3); δ_C (DMSO-d_6)[b] 172.84 (d, *J* 5.0 Hz, C=O), 172.48 (d, *J* 5.0 Hz, C=O), 162.76 (d, *J* 2.0 Hz, C=O), 162.62 (d, *J* 2.0 Hz, C=O), 64.10, 64.06 (OCH_2, morpholine), 61.13 (d, *J* 6.5 Hz, $O\underline{C}H_2CH_3$), 60.79 (d, *J* 6.0 Hz, $O\underline{C}H_2CH_3$), 57.58, 57.17, 54.17, 54.11, 52.92 (NCH_2, morpholine), 44.74 (d, *J* 146.1 Hz, CHP), 45.54 (d, *J* 146.1 Hz, CHP), 44.40, 40.41 (CH), 29.20, 28.96 (CH), 17.18 (CH_3), 14.06-13.86 (m, $OCH_2\underline{C}H_3$); δ_P (DMSO-d_6) 17.3, 17.1; LCMS: found *m/z* 380.5 MH^+. $C_{15}H_{30}N_3O_6P$ requires 379.4.

Diethyl [1-(2-amino-4-methylpentanamido)-2-(morpholin-4-yl)-2-oxoethyl]phosphonate (10c). Yield 1.432 g, 91% as a yellow viscous oil; [Found: C, 48.71; H, 8.36; N, 10.50; P, 7.89. $C_{16}H_{32}N_3O_6P$ requires C, 48.85; H, 8.20; N, 10.68; P, 7.87%]; $[\alpha]_D^{20}$-9.8 (*c* 0.9, CH_2Cl_2); ν_{max} (ATR) 3345, 1639, 1507, 1242, 1015, 966 cm^{-1}; δ_H (DMSO-d_6) 5.43-5.37 (1H, m, CHP), 4.08-4.03 (4H, m, $2O\underline{C}H_2CH_3$), 3.73-3.67 (1H, m, CH), 3.64-3.55 (8H, m, $4CH_2$), 2.54-2.52 (1H, m, $C\underline{H}_aCH_b$), 1.78-1.69 (1H, m, $CH_a\underline{C}H_b$), 1.47-1.40 (1H, m, CH), 1.24-1.19 (6H, m, $2OCH_2\underline{C}H_3$), 0.89-0.83 (6H, m, $2CH_3$); δ_C (DMSO-d_6) 173.74 (d, *J* 5.5 Hz, C=O), 173.64 (d, *J* 5.5 Hz, C=O), 162.72 (d, *J* 2.5 Hz, C=O), 162.66 (d, *J* 2.5 Hz, C=O), 64.16, 64.06 (OCH_2, morpholine), 61.20 (d, *J* 6.5 Hz, $O\underline{C}H_2CH_3$), 61.12 (d, *J* 6.0 Hz, $O\underline{C}H_2CH_3$), 54.10, 50.90, 50.75, 50.44 (NCH_2, morpholine), 44.82 (d, *J* 145.4 Hz, CHP), 44.78 (d, *J* 145.4 Hz, CHP), 40.40, 40.37 (CH), 21.88 (CH_2), 21.20, 21.14 (CH), 19.47, 19.34 (CH_3), 14.14-13.93 (m, $OCH_2\underline{C}H_3$); δ_P (DMSO-d_6) 17.4, 17.3; LCMS: found *m/z* 394.4 MH^+. $C_{16}H_{32}N_3O_6P$ requires 393.4.

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Notes and references

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[a] - the diethoxyphosphoryl group signals appear as multiplets due to the nonequivalence of carbon atoms.
[b] - all carbon atoms in the morpholine residue are nonequivalent.
[c] - one of diastereomers.
[d] - the carbonyl group signals appear as broad peaks.
[e] - the carbon signals at 129.82-129.80 ppm appear as broad peaks

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