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# Syntheses of Phosphonic Esters of Alendronate, Pamidronate and Neridronate

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**Keywords:** Phosphonic ester / Alendronate / Pamidronate / Neridronate / Arbusov reaction

Several synthetic pathways for obtaining phosphonic esters of the amino bisphosphonic acids (NBPs) pamidronate, alendronate and neridronate were investigated. The general guideline was to react *N*-protected amino acids activated as phthalimide esters or as acyl chlorides. Succinimide esters were found less reactive and quickly abandoned. γ-Lactam formation arises when starting from Boc- or Cbz-protected amino acids. The phthalimide *N*-protecting group allowed access to alkyl or aryl mono-, di- (symmetric or not) and triesters of these three NBPs in high yields.


## Introduction

(Hydroxymethylene)bis(phosphonic acids) (HMBPs) (Figure 1) are an important class of phosphorus compounds with diverse and important pharmacological uses. They are isosteres of pyrophosphate, where a P–O–P bridge is replaced by P–C–P, and are stable to enzymatic hydrolysis. HMBPs also exhibit a powerful binding affinity for bones, and are routinely used for treatment in bone resorption and other bone disorders, such as Paget's disease, osteoporosis, or tumor-induced osteolysis.[1,2] More recently, HMBPs have been shown to have new pharmacological effects in inhibition of growth, attachment, and invasion of cancer cells in culture, and to promote their apoptosis.[3,4] They are also intensively studied for their potential uses in various parasital diseases like inhibition of *Trypanozoma cruzi* or Leishmania diseases.[5,6]

Among HMBPs, authors usually describe two classes of compounds: those in which the lateral chain (R) contains an amino group, and those that do not. HMBPs containing no N have been proven to act via formation of ATP cytotoxic species,[7] whereas N-containing HMBPs (NBPs), although still able to induce such species,[8] are also inhibitors of the mevalonate pathway through inhibition of the FPPase.[9,10] Several NBP structures have been described; the first and simplest ones are pamidronate, alendronate and neridronate, where R is a simple aminoalkyl chain varying in length (Figure 1). Although not the best compounds used so far, these NBPs remain widely used in medicine.

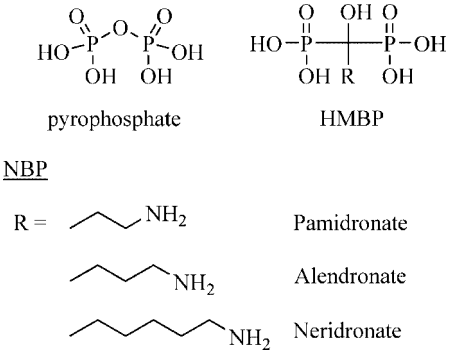


Figure 1. Structure of (hydroxymethylene)bis(phosphonic acids) (HMBPs).

One of the major drawbacks of these compounds remains their low bioavaibility (less than 1% of oral dose)[11] due to poor lipophilicity and the presence of negative charge(s) at physiological pH. Moreover, their strong affinity for bones may be a serious side effect in other applications such as antitumoral uses. Some further developments were made by increasing lipophilicity of HMBPs.[12] Recently Vachal and coworkers[13] described (in six steps) the first alendronate prodrug. Their approach consisted in forming a myristoyl amide with the terminal amine group. Though in vivo conversion to the parent drug seems effective, because the nitrogen atom is known to play an important role in the active site of its target enzyme,[14] a loss of activity could be feared. Moreover, for other applications targeting soft tissue, bone affinities of the bisphosphonic moiety still remains problematic. Another interesting route would be the ester functionalisation of their phosphonic acid functions. This strategy is already well described in the

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phosphate, phosphonate and phosphinate series that were investigated as prodrugs.[15] The problems addressed by adding ester functions to pamidronate, alendronate or neridronate arise from the strongly acidic conditions and high temperatures usually employed in their syntheses.[16] Moreover, Vachal demonstrated that the use of indirect methodologies to prepare tetraesters of alendronate was impossible due to isomerisation. To the best of our knowledge, no general approach exists to obtain, in few steps, esters of pamidronate, alendronate or neridronate prodrugs.

Recently, we described a mild one-pot synthesis of HMBPs[17,18] which can be used for preparing mono-, di- and triesters.[19–21] These esterified HMBPs are obtained from acyl chlorides and mixed alkyl (or aryl) trimethylsilyl phosphite. The aim of this paper is to describe a new approach using conditions close to those used in activated *N*-protected amino acid syntheses (Figure 2).

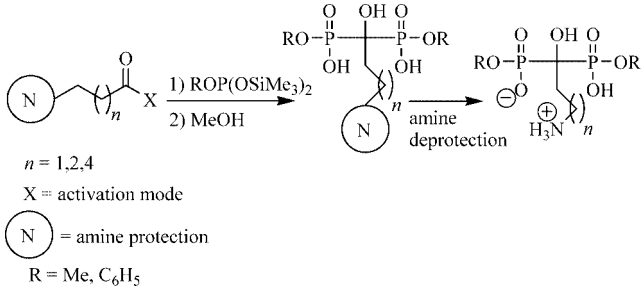


Figure 2. Strategy of synthesis of amino (hydroxymethylene)-bis(phosphonic) partial esters.

## Results and Discussion

Esterification of alendronate was first attempted starting from *N*-Boc-butyric acid activated as its NHS ester (**1**), a strategy that was patented by Gibson et al.[22] during the synthesis of radiolabelled HMBPs. They used *N*-protected or resin-attached amino acids activated as NHS esters and reacted them with $^{32}$P-radiolabelled tris(trimethymethylsilyl) phosphite. In our case, previous work in our laboratory demonstrated that general reactions of alkyl, aryl, or substituted aryl NHS esters with tris(trimethylsilyl) phosphite were quite efficient (data not shown). However, compared to reactions with acyl chlorides,[17] reaction times were longer (minimum 48 h rather than 2 h), and completions of reactions were only obtained by heating at 50 °C for most of the substrates. As a test reaction, we reacted compound **1** with tris(trimethylsilyl) phosphite for 3 d. After methanolysis of the trimethylsilyl esters, alendronate was obtained (Figure 3). No further Boc deprotection reaction was necessary, because methanolysis led to formation of phosphonic acids, which were sufficient for Boc removal. However, this approach was much less efficient when conducted with methyl or phenyl bis(trimethylsilyl) phosphite. In both cases, the prolonged heating led to dealkylation of the resulting diesterified bisphosphonate. This was easily confirmed by $^{31}$P NMR because the diesterified compound gave a single signal for the two identical phosphorus atoms, whereas in the monoesterified compound, the two phosphorus atoms became different and two signals were observed (two doublets−the two phosphorus atoms were coupled together). Using the less reactive phenyl bis(trimethylsilyl) phosphite, the diesterified alendronate was never obtained as phenyl esters. These esters are even more fragile than methyl esters.[21] With methyl bis(trimethylsilyl) phosphite, though less prone to dealkylation, the dimethyl ester of alendronate was only obtained in 20% yield after methanolysis and purification.

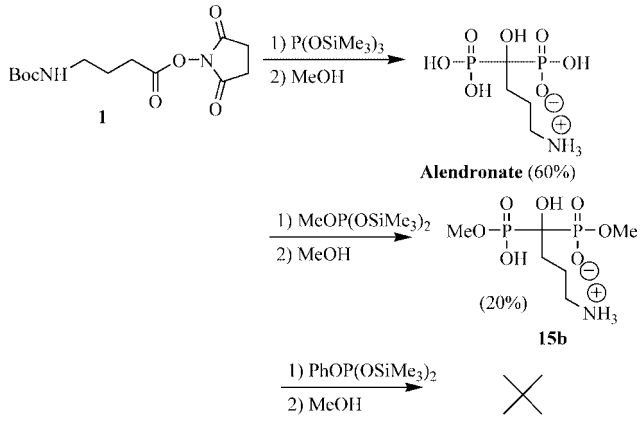


Figure 3. Synthesis of alendronate and dimethyl alendronate **15b** from NHS ester **1**.

Because the major problem of this reaction was the prolonged heating, the use of acyl chlorides rather than NHS esters was preferred with silylated phosphites. The reaction efficiency at room temperature was already shown with various alkyl or aryl substrates. We first chose to start from β-alanine and amino butyric acid *N*-protected by a Cbz group. *N*-Cbz-protected aminopropyl chloride **3** was obtained from treatment of the corresponding acid **2** with oxalyl chloride. The reaction of **3** with tris(trimethylsilyl) phosphite led to the *N*-Cbz-protected pamidronate **4**, which was hydrogenolysed to pamidronate (Figure 4).

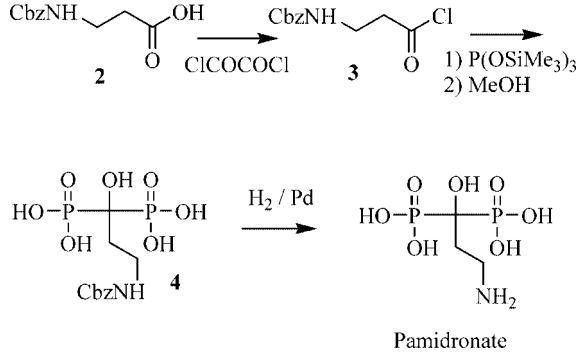


Figure 4. Synthesis of pamidronate from *N*-Cbz-β-alanine **2**.

Unexpectedly, when reacting *N*-Cbz-protected aminobutyric acid **5** with oxalyl chloride, whatever the conditions in use, the corresponding acyl chloride was never obtained (Figure 5). The only product isolated so far exhibited $^{1}$H

  

NMR signals upfield from what was expected for both methylene protons near the nitrogen atom and the carbonyl. Moreover, the methylene protons near the nitrogen appeared as a triplet rather than a multiplet, indicating no coupling with a proton bound to the nitrogen. Also, no signal corresponding to the N–H was found in the spectra. In the IR spectrum, no carbonyl vibration around 1800 $cm^{-1}$ was observed, indicating the absence of an acid chloride, and the carbonyl vibration of the acid disappeared to give new vibrations at 1786, 1752 and 1717 $cm^{-1}$. In addition, no N–H vibration could be found in the IR spectrum. Based on these data, the Cbz-protected γ-lactam structure **6** was proposed for this product. NMR, MS, and IR results were in accordance with literature data.[23] To prove this γ-lactam structure, we opened it in basic media with dimethylamine, leading to the corresponding amide, **7**. We furthermore deprotected compound **6**, and the NMR and IR spectra were once again in accordance with the proposed γ-lactam structure **6a**. Unfortunately, compound **6** was totally unreactive toward tris(trimethylsilyl) phosphite and even after a week of reflux in dry THF, the starting materials were totally recovered. The use of another protecting group such as Boc did not change these results. The *N*-Boc-protected aminobutyric acid **8** led to the formation of the Boc-protected γ-lactam structure, **9**, which did not further react with tris(trimethylsilyl) phosphite (Figure 5).

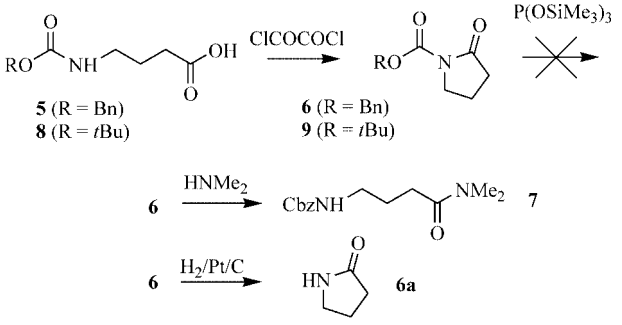


Figure 5. Attempted alendronate synthesis from *N*-Cbz-aminobutyric acid (**5**).

Following these observations, we decided to protect the side chain amine group using a method which would avoid the formation of a γ-lactam. Phthalimide seemed a convenient protecting group, as long as the deprotection could be carried out under mild conditions. Such *N*-phthalimide-protected bisphosphonates have already been studied by El Manouni et al.,[24] but the use of alkyl phosphites to form tetraalkyl bisphosphonates gave rise to phosphate-phosphonate isomerisation problems. Griffiths[25] proposed the same methodology in the course of a tetramethylester bisphosphonate preparation, but deprotection of the phthalimides in refluxing HBr also cleaved all the phosphonic esters. Nevertheless, Gali et al.[26] showed that on diethyl alkylphthalimide phosphonates, the use of excess hydrazine can selectively deprotect the amine function without any ester cleavage.

Phthalimide-protected amino acids **10a**–**c** were easily obtained from the parent amino acids and phthalic anhydride. Further treatment with oxalyl chloride gave the corresponding acyl chlorides **11a**–**c** (Figure 6). The acyl chlorides reacted with tris(trimethylsilyl) phosphite, methyl bis(trimethylsilyl) phosphite or phenyl bis(trimethylsilyl) phosphite at room temperature without any solvent in two hours to yield fully trimethylsilylated bisphosphonates (not isolated). With phenyl bis(trimethylsilyl) phosphite, the reaction time was longer (6 h) because of a weaker reactivity compared to the other phosphites. Reactions were usually followed by $^{31}P\{^{1}H\}$ NMR, and the formation of the fully silylated bisphosphonates could be assessed by the disappearance of the phosphite signal around 116 ppm and the appearance of the signal around 0 ppm for the fully trimethylsilylated bisphosphonates. After evaporation of volatile fractions, methanolyses and purifications, compounds **12a**–**c**, **13a**–**c** and **14a**–**c** were obtained (Figure 6). One must note that in the case of phenyl bis(trimethylsilyl) phosphite, addition of the phosphite was done at 0 °C to avoid local heating which may induce partial dealkylation. Most of the bisphosphonates were easily purified by precipitation from diethyl ether to remove unreacted materials (i.e., hydrolysed phosphite). For the diphenyl esters, extraction or even silica gel chromatography using organic solvent (chloroform, methanol) could be done to purify the bisphosphonates. All products were readily soluble in organic solvent (methanol, chloroform, dichloromethane, tetrahydrofuran), and some of them were also soluble in water.

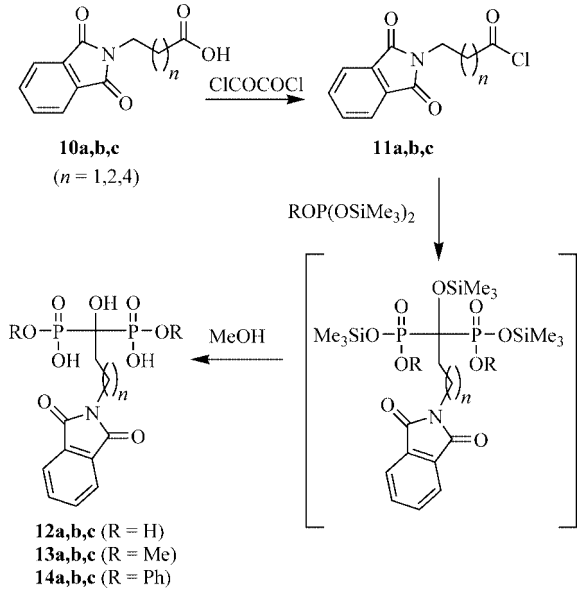


Figure 6. Synthesis of *N*-phthalimide-protected NBP.

Deprotection of the amine function was performed using an excess of hydrazine in water, a better solvent than organics for this reaction.[27] The reaction was monitored by $^{31}P\{^{1}H\}$ NMR, and completion usually occurred in 30 min. Under these conditions no dealkylation was observed, nor phosphate–phosphonate isomerisation, which could have been feared in basic media.[28] However, in the case of

  

phenyl esters, when the reaction was prolonged over one hour, a dealkylation reaction was observed. The reaction was usually stopped by quenching the hydrazine in acidic media (HCl, 0.1 M). One must note that for compound **16c**, after addition of hydrazine, the phthalimide bisphosphonate remained weakly soluble in water. Methanol (10 mL) was then added to dissolve the product. The final workup was the same, and quenching was also performed using HCl. Pamidronate, alendronate, neridronate and their diesters **15a**–**c** and **16a**–**c** (Figure 7) were purified either as acids by precipitation in water or by dialysis with Spectrapor 100 dialysis membranes. For compound **15c**, purification was successfully tested using low pressure reverse phase chromatography (C-18). Detection was carried out using a UV detector at 215 nm. Because bisphosphonates usually have an absorption maximum at 200 nm, this technique could be a reliable way to purify all of them. In all cases, the removal of the phthalimide protection was verified by the absence of a C=O vibration in the IR spectra and by $^{1}H$ and $^{13}C$ NMR spectroscopy. Overall yields for the syntheses starting from phthalimide alkyl acids were evaluated to be 60% in the worst cases and 80% in the best cases.

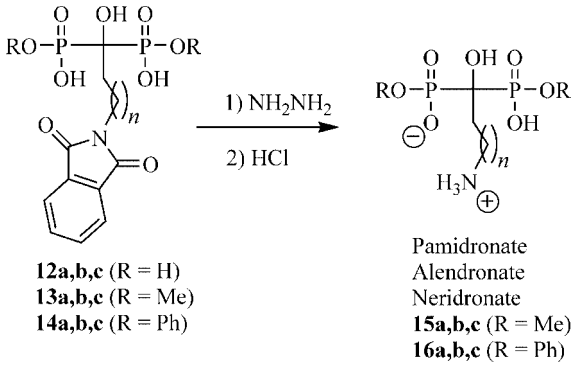


Figure 7. Phthalimide deprotection. Preparation of pamidronate, alendronate, neridronate and their diesterified analogs.

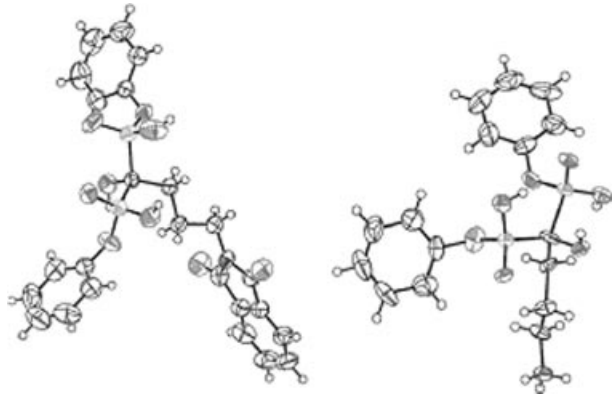

Figure 8. ORTEP views of protected **14b** (left), and naked **16b** (right), structures. Ellipsoids at the 50% probability level, hydrogens are represented as circles of arbitrary radii.

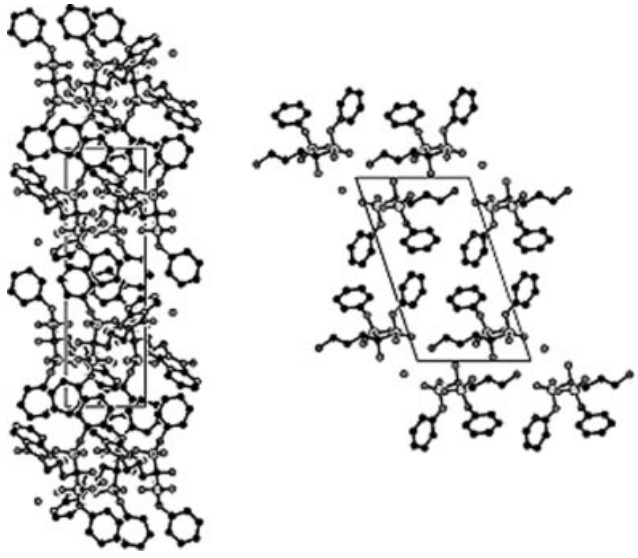

Figure 9. Packing arrangements for **14b** (left), and **16b** (right), viewed along the a* axis.

Both protected and unprotected compounds **14b** and **16b** gave monocrystals from slow evaporation of a water solution, and their structures are reported in Figures 8 and 9.

The X-ray analyses confirmed the general assumption that the two compounds remain strongly hydrophilic. Both structures form layers of hydrophobic and polar zones running along the b* axis in both cases (Figure 9). Lipophilic layers are built by the stacked phenyl groups (esters) while polar zones encompass the side chain amino group and all the polar oxygens of the phosphonates (plus the water molecules of hydration).

As already described, this synthetic method using mixed alkyl (or aryl) trimethylsilyl phosphites could also lead to the obtaining of mono-, bis(unsymmetric) and triesters of bisphosphonic acids.[20] The interest of the present synthetic pathway is demonstrated by obtaining the mono-, bis(unsymmetric) and trimethyl esters of alendronate. The reaction first went through the preparation of the dimethyl (1-oxopropyl)phosphonate **17** with the amine protected as a phthalimide,[24] which could then react with tris(trimethylsilyl) phosphite or methyl bis(trimethylsilyl) phosphite to give bis(unsymmetric) ester **18** or trimethyl ester **19** of alendronate protected by phthalimide (Figure 10). Monomethyl ester **20** was obtained by first silylating the dimethyl (1-oxopropyl)phosphonate and then adding methyl bis(trimethylsilyl) phosphite. We further enhanced this reaction by preparing monophenyl ester **21** with the corresponding alkylsilyl phosphite. Deprotection of the amine using the same methodology led to the various esters of alendronate, **23**–**26**. $^{31}P\{^{1}H\}$ NMR spectra of the unsymmetric bisphosphonate esters are slightly more complicated than those of the triesters because doublets are observed when the two phosphorus chemical shifts are different enough. Signals could be attributed to each of the phosphorus atoms, the bisphosphonic esters presenting signals at higher field than the bisphosphonic acids. For the unsymmetrical bisphosphonates, the signal of the methylene carbon in $^{13}C$ NMR should have theoretically appeared as a doublet of doublets. Exper-

  

imentally only a few products had different carbon–phosphorus coupling constant−most of them gave a triplet signal.

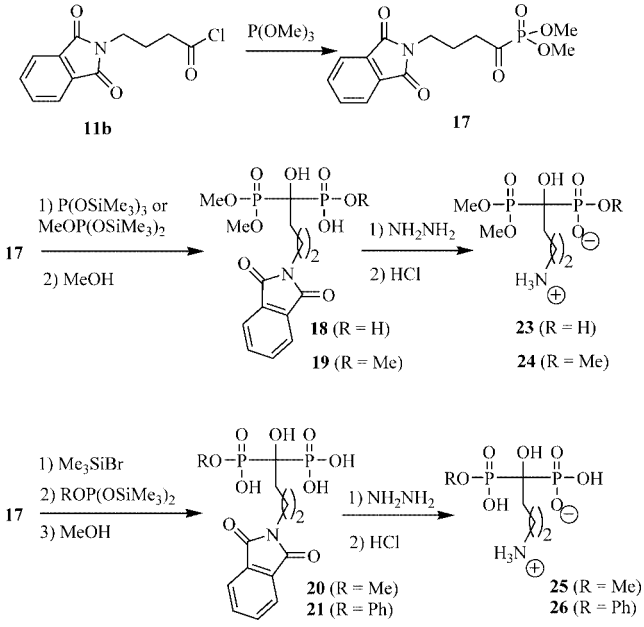


Figure 10. Synthesis of mono-, bis(asymmetric), and triesters of alendronate.

For the alendronate esters **23**–**26**, two enantiomers were formed because the central carbon was asymmetric, but the stereoisiomers were not separated.

Finally, it is interesting to note that all the obtained esters of pamidronate, alendronate and neridronate were soluble in water, even for mono- or diphenyl esters at physiological pH.

## Conclusions

Several synthetic pathways were investigated for obtaining phosphonic esters of amino bisphosphonic acids pamidronate, alendronate and neridronate. From Boc or Cbz-*N*-protected amino acids most of our assays were fruitless, but the use of phthalimide as an amino protecting group allowed us to synthesise mono-, di-, (symmetric or not), and triesters of these three NBP drugs with good yields and in a few steps. In addition, alkyl or aryl esters could be obtained opening new possibilities for further functionalisation. These new compounds, more lipophilic than the bisphosphonic acids but still soluble in water, open an interesting way to increase the bioavailability of NBPs; more biological studies in that direction are in progress.

## Experimental Section

**General Remarks:** Unless otherwise noted, materials were obtained from commercial suppliers. Oxalyl chloride was distilled prior to use. Triethylamine was distilled from KOH. THF was distilled from benzophenone and sodium. Dichloromethane and chloroform were distilled from calcium hydride. Diethyl ether was distilled from sodium. Methyl and phenyl bis(trimethylsilyl) phosphite were synthesised according to Monteil et al.[21] It proved difficult to obtain reliable elemental analytical data for the bisphosphonates because they were very hygroscopic. Nevertheless, we tried to prove the structure and purity of our products by coupling various NMR, FTIR and mass spectroscopic data (ESI-TOF). NMR Spectra were recorded with VARIAN Unity Inova 500 MHz ($^{13}$C: 125.9 MHz, $^{1}$H: 500.6 MHz, $^{31}$P: 200.7 MHz) or VARIAN Gemini 200 MHz ($^{13}$C: 50.3 MHz, $^{1}$H: 200 MHz, $^{31}$P: 80.9 MHz) spectrometers in $D_2O$, $CDCl_3$, $CD_3OD$ or [$D_6$]DMSO. Chemical shifts ($\delta$) are given in ppm. $^{31}$P and $^{13}$C NMR spectra were recorded using phosphoric acid or methanol as external references, respectively. $^{1}$H NMR spectra were recorded using HOD or tetramethylsilane as an internal standard in $D_2O$ or $CDCl_3$, respectively. Multiplicity is given as follows: s for singlet, d for doublet, t for triplet, q for quadruplet, qt for quintuplet, dt for doublet of triplets, and m for multiplet. Attribution of aromatic carbons and protons is given in the text by adding *o* for *ortho*, *m* for *meta* and *p* for *para*. MS was carried out on an ESI/TOF Mariner spectrometer. Analytical LC-MS separations were carried out on Waters HPLC 2525 with a $C_{18}$ column (Xterra, 5 μm, 4.6 × 50 mm) eluting with $H_2O$/$CH_3CN$/HCOOH (gradient from 95:05:0.1 to 0:100:0.1) at a 1.0 mL min$^{-1}$ flow rate; detection was carried out by UV detector (254 nm) and DEDL PL-ELS 1000 (Polymer laboratories); mass spectra were taken on Waters Micromass ZQ by positive electrospray method (ES+). IR spectra were recorded with a Nicolet FT-IR model 380 spectrophotometer in the 4000–500 cm$^{-1}$ spectral domain. Spectral resolution was 0.8 cm$^{-1}$ and 30 scans were usually accumulated. Samples were studied as KBr discs or directly as a film on KBr plates for oils. X-ray diffraction experiments were performed using a Nonius Kappa-CCD diffractometer operating the Mo-$K_a$ radiation (λ = 0.7107 Å). Diffraction data were processed using the DENZO/HKL software[29] and the structures were solved and refined with the SHELXS/SHELXL programs.[30] CCDC-620098 (for **14a**) and -620099 (for **16a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.

**Preparation and Activation of Boc and Cbz-Protected Amino Acids:** 4-[(*tert*-Butoxycarbonyl)amino]butyric acid (**8**), 4-[(benzyloxycarbonyl)amino]butyric acid (**5**) and 3-[(benzyloxycarbonyl)amino]-propionic acid (**2**) were obtained from 4-aminobutyric acid and 3-aminopropionic acid using standard protection methods.[31] 2,5-dioxopyrrolidin-1-yl 4-[(*tert*-butoxycarbonyl)amino]butyrate (**1**) was synthesized by standard procedures using *N*-hydroxysuccinimide and dicyclohexylcarbodiimide.[31]

**4-[(*tert*-Butoxycarbonyl)amino]butyric Acid (8):** Yield 70%. M.p. 60 °C. IR (KBr): ṽ = 3346, 2978, 2935, 2500–3200, 1712, 1526, 1479, 1452, 1410, 1394, 1275, 1253, 1170 cm$^{-1}$. $^{1}$H NMR ($CDCl_3$, 200 MHz, 298 K): $\delta$ = 1.43 [s, 9 H, C($CH_3$)$_3$], 1.81 [qt, $^{3}J_{H,H}$ = 7.0 Hz, 2 H, NHCH$_2$C$H_2$CH$_2$COOH], 2.38 (t, $^{3}J_{H,H}$ = 7.0 Hz, 2 H, NHCH$_2$CH$_2$C$H_2$COOH), 3.27–3.09 (m, 2 H, NHC$H_2$CH$_2$CH$_2$COOH), 4.80–4.62 (m, 1 H, N*H*) ppm. $^{13}$C{$^{1}$H} NMR ($CDCl_3$, 50.3 MHz, 298 K): $\delta$ = 25.2 (s, NHCH$_2$*C*H$_2$CH$_2$COOH), 28.5 [s, C(*C*H$_3$)$_3$], 31.5 (s, NHCH$_2$CH$_2$*C*H$_2$COOH), 39.9 (s, NH*C*H$_2$CH$_2$CH$_2$COOH), 79.5 [s, *C*(CH$_3$)$_3$], 156.3 [s, O*C*(O)NH], 178.1 (s, *C*OOH) ppm.

**4-[(Benzyloxycarbonyl)amino]butyric Acid (5):** Yield 92%. M.p. 70 °C. IR (KBr): ṽ = 3333, 3063, 3034, 2971, 2923, 2500–3200, 1688, 1550, 1451, 1429, 1414, 1314, 1299, 1274, 1259, 1208, 1142, 1104, 1016, 914, 778, 746, 725, 693 cm$^{-1}$. $^{1}$H NMR ($CDCl_3$, 200 MHz, 298 K): $\delta$ = 1.84 (qt, $^{3}J_{H,H}$ = 7.0 Hz, 2 H,

  

$NHCH_2CH_2CH_2COOH$), 2.40 (t, $^3J_{H,H}$ = 7.0 Hz, 2 H, $NHCH_2CH_2CH_2COOH$), 3.20–3.30 (dt, $^3J_{H,H}$ = 7.0 Hz, 2 H $NHCH_2CH_2CH_2COOH$), 4.82–5.00 (d, $^3J_{H,H}$ = 7.0 Hz, 1 H, N*H*), 5.10 [s, 2 H, $CH_2OC(O)$], 7.32–7.38 (m, 5 H, $C_6H_5$) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 50.3 MHz, 298 K): $\delta$ = 25.1 (s, $NHCH_2CH_2CH_2COOH$), 31.3 (s, $NHCH_2CH_2CH_2COOH$), 40.4 (s, $NHCH_2CH_2CH_2COOH$), 67.0 [s, $CH_2OC(O)$], 128.3 (s, *o,p*-$C_6H_5$), 128.7 (s, *m*-$C_6H_5$), 136.6 (s, $CH_2C_6H_5$), 156.7 [s, $OC(O)NH$], 178.2 (s, *C*OOH) ppm.

**3-[(Benzyloxycarbonyl)amino]propionic Acid (2):** Yield 90%. M.p. 110 °C. IR (KBr): $\tilde{\nu}$ = 3334, 3060, 3029, 2977, 2953, 2909, 2500–3200, 1685, 1536, 1439, 1422, 1322, 1295, 1263, 1248, 1219, 1140, 1095, 1027, 937, 752, 729, 697 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 200 MHz, 298 K): $\delta$ = 2.62 (t, $^3J_{H,H}$ = 7.0 Hz, 2 H, $NHCH_2CH_2COOH$), 3.39–3.56 (m, 2 H, $NHCH_2CH_2COOH$), 5.10 [s, 2 H, $CH_2OC(O)$], 5.19–5.37 (m, 1 H, N*H*), 7.25–7.46 (m, 5 H, $C_6H_5$) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 50.3 MHz, 298 K): $\delta$ = 36.8 (s, $NHCH_2CH_2COOH$), 40.0 (s, $NHCH_2CH_2COOH$), 67.2 [s, $CH_2OC(O)$], 128.4 (s, *o,p*-$C_6H_5$), 128.9 (s, *m*-$C_6H_5$), 138.1 (s, $CH_2C_6H_5$), 158.3 [s, $OC(O)NH$], 178.3 (s, *C*OOH) ppm.

**2,5-Dioxopyrrolidin-1-yl 4-[(*tert*-Butoxycarbonyl)amino]butyrate (1):** Yield 65%. M.p. 110 °C. IR (KBr): $\tilde{\nu}$ = 3327, 3035, 2928, 2850, 1627, 1574, 1534, 1448, 1436, 1311, 1271, 1244, 1230, 1186, 1088, 1069, 1046, 892, 641 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 200 MHz, 298 K): $\delta$ = 1.39 [s, 9 H, $C(CH_3)_3$], 1.88 (qt, $^3J_{H,H}$ = 7.0 Hz, 2 H, $NHCH_2CH_2CH_2COON$), 2.61 (t, $^3J_{H,H}$ = 7.0 Hz, 2 H, $NHCH_2CH_2CH_2COON$), 2.79 [s, 4 H, $C(O)(CH_2)_2C(O)$], 3.25–3.07 (m, 2 H, $NHCH_2CH_2CH_2COON$), 4.92–4.75 (m, 1 H, N*H*) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 50.3 MHz, 298 K): $\delta$ = 25.2 (s, $NHCH_2CH_2CH_2COON$), 25.7 [s, $C(O)(CH_2)_2C(O)$], 28.5 [s, $C(CH_3)_3$], 35.0 (s, $NHCH_2CH_2CH_2COON$), 39.4 (s, $NHCH_2CH_2CH_2COON$), 79.4 [s, $C(CH_3)_3$], 156.0 [s, $OC(O)NH$], 168.3 [s, $C(O)(CH_2)_2C(O)$], 169.2 (s, *C*OOH) ppm.

**Synthesis of Alendronate and Esterified Alendronate:** In a 50 mL round-bottom three-neck flask equipped with a thermometer and a condenser, butyrate **1** (300 mg, 1 mmol) in THF (5 mL) was added under $N_2$ to tris(trimethylsilyl) phosphite or methyl (or phenyl) bis(trimethylsilyl) phosphite (2 mmol). The reaction was heated at 50 °C for 72 h. The evolution of the reaction was monitored by $^{31}P\{^1H\}$ NMR spectroscopy. The volatile fractions were evaporated under reduced pressure (0.1 Torr) before being hydrolysed with methanol. After evaporation, the crude products were washed with diethyl ether and precipitated in tetrahydrofuran/dichloromethane, 95:5 to give alendronate; yield 150 mg (61%). See IR and NMR spectroscopic data below. Monomethyl [4-amino-1-hydroxy-1-(hydroxymethoxyphosphoryl)butyl]phosphonate (**15b**) Yield 55 mg (20%). See IR and NMR spectroscopic data below.

**Synthesis of Pamidronate:** In a 50 mL round-bottom flask oxalyl chloride (0.75 mL, 5 mmol) was added under $N_2$ to a solution of 3-[(benzyloxycarbonyl)amino]propionic acid (**2**) (237 mg, 1 mmol) in dichloromethane (5 mL). The reaction was stirred at room temperature for 6 h. The mixture was then evaporated under vacuum (0.1 Torr) to yield a yellow powder of carbamate **3**, which was not isolated; its structure was confirmed by $^1H$ NMR spectroscopy.

**Benzyl *N*-(3-Chloro-3-oxopropyl)carbamate (3):** Yield 1.18 g (98%). $^1H$ NMR ($CDCl_3$, 200 MHz, 298 K): $\delta$ = 3.16 (t, $^3J_{H,H}$ = 5.7 Hz, 2 H, $NHCH_2CH_2COCl$), 3.37–3.54 (m, 2 H, $NHCH_2CH_2COCl$), 5.10 [s, 2 H, $CH_2OC(O)$], 5.07–5.24 (m, 1 H, N*H*), 7.25–7.46 (m, 5 H, $C_6H_5$) ppm. In a 50 mL round-bottom three-neck flask equipped with a thermometer, tris(trimethylsilyl) phosphite (0.42 mL, 2 mmol) was added at 0 °C, under $N_2$ to **3**. When the addition was completed, the reaction mixture was allowed to stand at room temperature for 2 h. The evolution of the reaction was monitored by $^{31}P\{^1H\}$ NMR spectroscopy. The volatile fractions were evaporated under reduced pressure (0.1 Torr) before being hydrolyzed with methanol. After evaporation, the crude product was precipitated successively in diethyl ether and chloroform to give **4** as a white powder.

**[3-(Benzyloxycarbonylamino)-1-hydroxy-1-phosphonopropyl]phosphonic Acid (4):** Yield 362 mg (98%). M.p. 75 °C. IR (KBr): $\tilde{\nu}$ = 3368, 3247, 2961, 2929, 1693, 1645, 1537, 1455, 1146, 1001, 931, 751, 696, 512 $cm^{-1}$. $^1H$ NMR ($CD_3OD$, 200 MHz, 298 K): $\delta$ = 2.12–2.41 (m, 2 H, $NHCH_2CH_2COH$), 3.16 (t, $^3J_{H,H}$ = 6.9 Hz, 2 H, $NHCH_2CH_2COH$), 5.07 [s, 2 H, $CH_2OC(O)$], 7.25–7.39 (m, 5 H, $C_6H_5$) ppm. $^{13}C\{^1H\}$ NMR ($D_2O$, 125.7 MHz, 298 K): $\delta$ = 34.4 (s, $NHCH_2CH_2COH$), 37.1 (s, $NHCH_2CH_2COH$), 67.9 [s, $CH_2OC(O)$], 73.1 (t, $J_{C,P}$ = 147.3 Hz, $NHCH_2CH_2COH$), 128.7 (s, *o*-$C_6H_5$), 129.5 (s, *m*-$C_6H_5$), 129.7 (s, *p*-$C_6H_5$), 137.3 (s, $CH_2C_6H_5$), 159.1 [s, $OC(O)NH$] ppm. $^{31}P\{^1H\}$ NMR ($D_2O$, 202.4 MHz, 298 K): $\delta$ = 19.6 (s) ppm. In a 50 mL round-bottom flask connected to a hydrogenation apparatus, 270 mg of palladium (10 wt.-%) on activated carbon was added to a methanol solution (20 mL) of **4** (1 mmol). The flask was purged several times with hydrogen, and the reaction was stirred for 24 h. The palladium on activated carbon was filtered, the solvent was evaporated under reduced pressure (0.1 Torr), and pamidronate was precipitated in diethyl ether.

**(3-Amino-1-hydroxy-1-phosphonopropyl)phosphonic Acid (Pamidronate):** Yield 90%. See IR and NMR spectroscopic data below.

**Protected γ-Lactam Formation of 6, 9:** In a 50 mL round-bottom flask oxalyl chloride (3 mL, 20 mmol) was added under $N_2$ to a solution of protected aminobutyric acid **8** or **5** (4 mmol) in dichloromethane (20 mL). For the synthesis of compound **9**, freshly distilled pyridine (4 mmol) was added prior to the addition of oxalyl chloride. The reaction was stirred at room temperature for 4 h. The mixture was then evaporated under vacuum (0.1 Torr) to yield a yellow powder. For compound **9**, the pyridinium chloride precipitate was filtered off before evaporation.

**Benzyl 2-Oxopyrrolidine-1-carboxylate (6):** Yield 836 mg (95%). IR (film): $\tilde{\nu}$ = 3064, 3033, 2961, 2902, 1786, 1751, 1717, 1498, 1456, 1383, 1298, 1241, 1176, 1040, 1027, 773, 753, 699 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 200 MHz, 298 K): $\delta$ = 1.95 (qt, $^3J_{H,H}$ = 7.5 Hz, 2 H, $NCH_2CH_2CH_2CO$), 2.45 (t, $^3J_{H,H}$ = 7.5 Hz, 2 H, $NCH_2CH_2CH_2CO$), 3.45 (t, $^3J_{H,H}$ = 7.5 Hz, 2 H, $NCH_2CH_2CH_2CO$), 5.20 [s, 2 H, $CH_2OC(O)N$], 7.24–7.38 (m, 5 H, $C_6H_5$) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 50.3 MHz, 298 K): $\delta$ = 17.5 (s, $NCH_2CH_2CH_2CO$), 32.7 (s, $NCH_2CH_2CH_2CO$), 46.4 (s, $NCH_2CH_2CH_2CO$), 67.9 [s, $CH_2OC(O)N$], 128.1 (s, *o,p*-$C_6H_5$), 128.5 (s, *m*-$C_6H_5$), 135.3 (s, $CH_2C_6H_5$), 151.4 [s, $CH_2OC(O)N$], 173.9 (s, *C*ON) ppm. MS (ES+): *m*/*z* = 220.1 [$M^+$ + H].

***tert*-Butyl 2-Oxopyrrolidine-1-carboxylate (9):** Yield 718 mg (97%). $^1H$ NMR ($CDCl_3$, 200 MHz, 298 K): $\delta$ = 1.52 [s, 9 H, $C(CH_3)_3$], 1.99 [qt, $^3J_{H,H}$ = 7.5 Hz, 2 H, $NCH_2CH_2CH_2CO$], 2.51 [t, $^3J_{H,H}$ = 7.5 Hz, 2 H, $NCH_2CH_2CH_2CO$], 3.75 [t, $^3J_{H,H}$ = 7.5 Hz, 2 H, $NCH_2CH_2CH_2CO$] ppm. $^{13}C\{^1H\}$ NMR [$CDCl_3$, 50.3 MHz, 298 K]: $\delta$ = 17.5 [s, $NCH_2CH_2CH_2CO$], 28.2 [s, $C(CH_3)_3$], 33.0 [s, $NCH_2CH_2CH_2CO$], 46.5 [s, $NCH_2CH_2CH_2CO$], 82.1 [s, $C(CH_3)_3$], 164.4 [s, $OC(O)N$], 174.2 (s, *C*ON) ppm.

**Ring Opening of Benzyl 2-Oxopyrrolidine-1-carboxylate:** In a 50 mL round-bottom flask a tetrahydrofuran dimethylamine solution (4 mL, 4 mmol) was added to the Z-protected γ-lactam (**6**) (2 mmol). The reaction was stirred 30 min. and then evaporated under vacuum (0.1 Torr). The resulting oil was dissolved in dichloromethane (20 mL) and washed 2 times with 10 mL of dilute

  

NaOH (0.1 M). The organic layer were then dried on magnesium sulfate, filtered and the solvents evaporated.

**Benzyl *N*-(3-Dimethylcarbamoylpropyl)carbamate (7):** Yield 422 mg (80%). IR (film): $\tilde{\nu}$ = 3315, 3064, 3032, 2954, 2930, 1717, 1634, 1532, 1499, 1455, 1401, 1294, 1259, 1138, 1041, 1025, 753, 698, 666 cm$^{-1}$. $^1$H NMR ($CDCl_3$, 200 MHz, 298 K): $\delta$ = 1.84 (qt, $^3J_{H,H}$ = 6.9 Hz, 2 H, NHCH$_2$C*H*$_2$CH$_2$CON), 2.34 (t, $^3J_{H,H}$ = 6.9 Hz, 2 H, NHCH$_2$CH$_2$C*H*$_2$CON), 2.90 (s, 3 H, NC*H*$_3$), 2.94 (s, 3 H, NC*H*$_3$), 3.23 (dt, $^3J_{H,H}$ = 6.9 Hz, 2 H, NHC*H*$_2$CH$_2$CH$_2$CON), 5.07 [s, 2 H, C*H*$_2$OC(O)NH], 5.21–5.35 (m, 1 H, N*H*), 7.20–7.45 (m, 5 H, C$_6$*H*$_5$) ppm.

**Deprotection of Benzyl 2-Oxopyrrolidine-1-carboxylate:** In a 50 mL round-bottom flask connected to a hydrogenation apparatus, palladium (10 wt.-%) on activated carbon (1 g) was added to a solution of **6** (4 mmol) in methanol (50 mL). The flask was purged several times with hydrogen, and the reaction was stirred for 24 h. The palladium on activated carbon was filtered, and the solvent was evaporated under reduced pressure (0.1 Torr). After washes with diethyl ether (3 × 10 mL), compound **6a** was obtained quantitatively as a yellow oil. **Pyrrolidin-2-one (6a):** IR (KBr): $\tilde{\nu}$ = 3219, 2987, 1669, 1498, 1456, 1421, 1292, 1208, 1138, 996 cm$^{-1}$. $^1$H NMR ($CD_3OD$, 200 MHz, 298 K): $\delta$ = 2.21–2.25 (m, 2 H, NHCH$_2$C*H*$_2$CH$_2$CO), 2.58–2.62 (m, 2 H, NHCH$_2$CH$_2$C*H*$_2$CO), 3.50–3.77 (m, 2 H, NHC*H*$_2$CH$_2$CH$_2$CO), 8.29–8.31 (m, 1 H, N*H*CH$_2$CH$_2$CH$_2$CO) ppm. $^{13}$C{$^1$H} NMR ($CD_3OD$, 125.7 MHz, 298 K): $\delta$ = 21.7 (s, NHCH$_2$*C*H$_2$CH$_2$CO), 31.9 (s, NHCH$_2$CH$_2$-*C*H$_2$CO), 45.4 (s, NH*C*H$_2$CH$_2$CH$_2$CO), 174.8 (s, O*C*NH) ppm.

**Synthesis of 10a–c:** Phthalic anhydride (5.92 g, 40 mmol) and amino acid (40 mmol) were heated at 170 °C for 6 h in a 100 mL round-bottomed flask equipped with a condenser. The reaction mixture was cooled, the resulting solid was dissolved in dichloromethane (50 mL) and washed with HCl solution (0.1 M, 3 × 20 mL). The organic layer was dried, and the solvents were evaporated under vacuum to yield quantitatively a white solid.

**3-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)propionic Acid (10a):** M.p. 152 °C. IR (KBr): $\tilde{\nu}$ = 2981, 2969, 1770, 1700, 1466, 1440, 1408, 1378, 1296, 1284, 1254, 1212, 1103, 1088, 1072, 1031, 1001, 910, 873, 824, 730, 615 cm$^{-1}$. $^1$H NMR ($CDCl_3$, 200 MHz, 298 K): $\delta$ = 2.80 (t, $^3J_{H,H}$ = 7.0 Hz, 2 H, NCH$_2$C*H*$_2$COOH), 4.00 (t, $^3J_{H,H}$ = 7.0 Hz, 2 H, NC*H*$_2$CH$_2$COOH), 7.65–7.76 (m, 2 H, C$_6$*H*$_4$), 7.80–7.89 (m, 2 H, C$_6$*H*$_4$) ppm. $^{13}$C{$^1$H} NMR ($CDCl_3$, 125.7 MHz, 298 K): $\delta$ = 33.8 (s, NCH$_2$*C*H$_2$COOH), 33.6 (s, N*C*H$_2$CH$_2$COOH), 123.6 (s, *C*$_6$H$_4$), 132.1 (s, *C*$_6$H$_4$), 134.3 (s, *C*$_6$H$_4$), 168.2 [s, N*C*(O)], 176.7 (s, *C*OOH) ppm.

**4-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)butyric Acid (10b):** M.p. 117 °C. IR (KBr): $\tilde{\nu}$ = 2958, 2940, 1767, 1705, 1469, 1437, 1396, 1358, 1338, 1314, 1285, 1249, 1195, 1121, 1033, 1020, 945, 894, 781, 720 cm$^{-1}$. $^1$H NMR ($CDCl_3$, 200 MHz, 298 K): $\delta$ = 2.02 (qt, $^3J_{H,H}$ = 7.0 Hz, 2 H, NCH$_2$C*H*$_2$CH$_2$COOH), 2.44 (t, $^3J_{H,H}$ = 7.0 Hz, 2 H, NCH$_2$CH$_2$C*H*$_2$COOH), 3.75 (t, $^3J_{H,H}$ = 7.0 Hz, 2 H, NC*H*$_2$CH$_2$CH$_2$COOH), 7.65–7.80 (m, 2 H, C$_6$*H*$_4$), 7.81–7.86 (m, 2 H, C$_6$*H*$_4$) ppm. $^{13}$C{$^1$H} NMR ($CDCl_3$, 50.3 MHz, 298 K): $\delta$ = 23.7 (s, NCH$_2$*C*H$_2$CH$_2$COOH), 31.4 (s, NCH$_2$CH$_2$*C*H$_2$COOH), 37.2 (s, N*C*H$_2$CH$_2$CH$_2$COOH), 123.3 (s, *C*$_6$H$_4$), 134.0 (s, *C*$_6$H$_4$), 168.4 [s, N*C*(O)], 178.4 (s, *C*OOH) ppm.

**6-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)hexanoic Acid (10c):** M.p. 109 °C. IR (KBr): $\tilde{\nu}$ = 2932, 2864, 1773, 1725, 1465, 1438, 1395, 1363, 1336, 1313, 1255, 1206, 1188, 1111, 1050, 952, 875, 721, 712 cm$^{-1}$. $^1$H NMR ($CDCl_3$, 500 MHz, 298 K): $\delta$ = 1.30–1.42 (m, 2 H, NCH$_2$CH$_2$C*H*$_2$CH$_2$CH$_2$COOH), 1.61–1.72 (m, 4 H, NCH$_2$C*H*$_2$CH$_2$C*H*$_2$CH$_2$COOH), 2.32 (t, $^3J_{H,H}$ = 7.3 Hz, 2 H, NCH$_2$CH$_2$CH$_2$CH$_2$C*H*$_2$COOH), 3.66 (t, $^3J_{H,H}$ = 7.3 Hz, 2 H, NC*H*$_2$CH$_2$CH$_2$CH$_2$CH$_2$COOH), 7.67–7.82 (m, 4 H, C$_6$*H*$_4$) ppm. $^{13}$C{$^1$H} NMR ($CDCl_3$, 125.7 MHz, 298 K): $\delta$ = 24.3 (s, NCH$_2$CH$_2$*C*H$_2$CH$_2$CH$_2$COOH), 26.4 (s, NCH$_2$CH$_2$CH$_2$*C*H$_2$-CH$_2$COOH), 28.4 (s, NCH$_2$*C*H$_2$CH$_2$CH$_2$CH$_2$COOH), 33.9 (s, NCH$_2$CH$_2$CH$_2$CH$_2$*C*H$_2$COOH), 37.9 (s, N*C*H$_2$CH$_2$CH$_2$CH$_2$-CH$_2$COOH), 123.4, 132.3, 134.1 (s, *C*$_6$H$_4$), 168.6 [s, N*C*(O)], 179.3 (s, *C*OOH) ppm.

**Synthesis of 11a–c:** In a 50 mL round-bottom flask, oxalyl chloride (3.75 mL, 25 mmol) was added under $N_2$ to a solution of **10a–c** (10 mmol) in dichloromethane (25 mL). The solution was refluxed for 6 h. The reaction mixture was then evaporated under vacuum (0.1 Torr) to yield quantitatively a pale yellow powder of **11a–c**.

**3-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)propionyl Chloride (11a):** M.p. 97 °C. IR (film): $\tilde{\nu}$ = 2956, 2934, 1802, 1710, 1466, 1437, 1398, 1368, 1289, 1246, 1171, 1109, 1090, 1053, 1053, 993, 965, 868, 753, 718, 656 cm$^{-1}$. $^1$H NMR ($CDCl_3$, 200 MHz, 298 K): $\delta$ = 3.33 (t, $^3J_{H,H}$ = 7.0 Hz, 2 H, NCH$_2$C*H*$_2$COCl), 4.03 (t, $^3J_{H,H}$ = 7.0 Hz, 2 H, NC*H*$_2$CH$_2$COCl), 7.67–7.73 (m, 2 H, C$_6$*H*$_4$), 7.78–7.84 (m, 2 H, C$_6$*H*$_4$) ppm. $^{13}$C{$^1$H} NMR ($CDCl_3$, 125.7 MHz, 298 K): $\delta$ = 33.3 (s, N*C*H$_2$CH$_2$COCl), 45.0 (s, NCH$_2$*C*H$_2$COCl), 123.6, 131.9, 134.3 (s, *C*$_6$H$_4$), 167.8 [s, N*C*(O)], 171.5 (s, *C*OCl) ppm.

**4-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)butyryl Chloride (11b):** M.p. 69 °C. IR (film): $\tilde{\nu}$ = 2940, 1805, 1708, 1468, 1438, 1398, 1360, 1338, 1314, 1286, 12487, 1192, 1117, 1087, 1065, 1033, 950, 894, 720 cm$^{-1}$. $^1$H NMR ($CDCl_3$, 200 MHz, 298 K): $\delta$ = 2.08 (qt, $^3J_{H,H}$ = 7.0 Hz, 2 H, NCH$_2$C*H*$_2$CH$_2$COCl), 2.99 (t, $^3J_{H,H}$ = 7.0 Hz, 2 H, NCH$_2$CH$_2$C*H*$_2$COCl), 3.77 (t, $^3J_{H,H}$ = 7.0 Hz, 2 H, NC*H*$_2$CH$_2$CH$_2$COCl), 7.70–7.74 (m, 2 H, C$_6$*H*$_4$), 7.83–7.87(m, 2 H, C$_6$*H*$_4$) ppm. $^{13}$C{$^1$H} NMR ($CDCl_3$, 50.3 MHz, 298 K): $\delta$ = 24.3 (s, NCH$_2$*C*H$_2$CH$_2$COCl), 36.5 (s, N*C*H$_2$CH$_2$CH$_2$COCl), 44.5 (s, NCH$_2$CH$_2$*C*H$_2$COCl), 123.4, 132.1, 134.2 (s, *C*$_6$H$_4$), 168.4 [s, N*C*(O)], 173.3 (s, *C*OCl) ppm.

**6-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)hexanoyl Chloride (11c):** M.p. 58 °C. IR (film): $\tilde{\nu}$ = 2936, 2867, 1798, 1709, 1465, 1437, 1397, 1369, 1333, 1286, 1208, 1186, 1051, 1018, 943, 872, 719 cm$^{-1}$. $^1$H NMR ($CDCl_3$, 500 MHz, 298 K): $\delta$ = 1.31–1.42 (m, 2 H, NCH$_2$CH$_2$C*H*$_2$CH$_2$CH$_2$COCl), 1.60–1.75 (m, 4 H, NCH$_2$C*H*$_2$CH$_2$C*H*$_2$CH$_2$COCl), 2.85 (t, $^3J_{H,H}$ = 7.3 Hz, 2 H, NCH$_2$CH$_2$CH$_2$CH$_2$C*H*$_2$COCl), 3.64 (t, $^3J_{H,H}$ = 7.3 Hz, 2 H NC*H*$_2$CH$_2$CH$_2$CH$_2$CH$_2$COCl), 7.66–7.81 (m, 4 H, C$_6$*H*$_4$) ppm. $^{13}$C{$^1$H} NMR ($CDCl_3$, 125.7 MHz, 298 K): $\delta$ = 24.7 (s, NCH$_2$CH$_2$*C*H$_2$CH$_2$CH$_2$COCl), 25.8 (s, NCH$_2$CH$_2$CH$_2$*C*H$_2$-CH$_2$COCl), 28.3 (s, NCH$_2$*C*H$_2$CH$_2$CH$_2$CH$_2$COCl), 37.7 (s, N*C*H$_2$CH$_2$CH$_2$CH$_2$CH$_2$COCl), 47.0 (s, NCH$_2$CH$_2$CH$_2$CH$_2$-*C*H$_2$COCl), 123.4, 132.2, 134.1 (s, *C*$_6$H$_4$), 168.6 [s, N*C*(O)], 173.8 (s, *C*OCl) ppm.

**Synthesis of 12a–c, 13a–c, 14a–c:** In a 50 mL round-bottom three-neck flask equipped with a thermometer, acid chloride **11a–c** (2.5 mmol) was added dropwise, under Ar, at –5 °C, to silylated phosphite (5 mmol). When the addition was completed, reaction mixture was allowed to stand at room temperature for 4 h [6 h for the reaction with phenyl bis(trimethylsilyl) phosphite]. The evolution of the reaction was monitored by $^{31}$P{$^1$H} NMR. The volatile fractions were evaporated under reduced pressure (0.1 Torr) before being hydrolyzed with methanol. After evaporation, the crude products were purified as follows.

**[3-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)-1-hydroxy-1-phosphonopropyl]phosphonic Acid (12a):** After solvent removal in vacuo, the residue was precipitated from methanol/diethyl ether (60:40). The white powder was then lyophilised. Yield 545 mg (60%). M.p.

  

201 °C. IR (KBr): $\tilde{\nu}$ = 3446, 3244, 3140, 3032, 1766, 1690, 1616, 1496, 1441, 1410, 1375, 1174, 1140, 1098, 1082, 1032, 962, 731, 668, 533 $cm^{-1}$. $^1H$ NMR ($D_2O$, 200 MHz, 298 K): $\delta$ = 2.09–2.20 (m, 2 H, $NCH_2CH_2COH$), 3.85 (m, 2 H, $NCH_2CH_2COH$), 7.63–7.68 (m, 2 H, $C_6H_4$), 7.69–7.73 (m, 2 H, $C_6H_4$) ppm. $^{13}C\{^1H\}$ NMR ($D_2O$, 125.7 MHz, 298 K): $\delta$ = 31.1 (s, $HOCCH_2CH_2N$), 34.6 (s, $HOCCH_2CH_2N$), 72.1 (t, $J_{C,P}$ = 143.6 Hz, $HOCCH_2CH_2NH_2$), 123.1, 130.9, 135.0 (s, $C_6H_4$), 170.2 [s, $NC(O)$] ppm. $^{31}P\{^1H\}$ NMR ($D_2O$, 202.4 MHz, 298 K): $\delta$ = 18.8 (s) ppm.

**[4-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)-1-hydroxy-1-phosphonobutyl]phosphonic Acid (12b):** After solvent removal in vacuo, the residue was washed with diethyl ether (3 × 10 mL) to remove traces of $H_3PO_3$, giving a white powder. Yield 853 mg (90%). M.p. 193 °C. IR (KBr): $\tilde{\nu}$ = 3427, 2925, 1774, 1697, 1467, 1444, 1406, 1384, 1171, 1130, 1042, 996, 948, 723, 650 $cm^{-1}$. $^1H$ NMR ($CD_3OD$, 200 MHz, 298 K): $\delta$ = 1.89–2.14 (m, 4 H, $NCH_2CH_2CH_2COH$), 3.57–3.74 (m, 2 H, $NCH_2CH_2CH_2COH$), 7.70–7.86 (m, 4 H, $C_6H_4$) ppm. $^{13}C\{^1H\}$ NMR ($CD_3OD$, 50.3 MHz, 298 K): $\delta$ = 22.7 (s, $NCH_2CH_2CH_2COH$), 31.0 (s, $NCH_2CH_2CH_2COH$), 38.1 (s, $NCH_2CH_2CH_2COH$), 73.0 (t, $J_{C,P}$ = 145.8 Hz, $NCH_2CH_2CH_2COH$), 123.2, 131.1, 134.7 (s, $C_6H_4$), 170.4 [s, $NC(O)$] ppm. $^{31}P\{^1H\}$ NMR ($CD_3OD$, 80.9 MHz, 298 K): $\delta$ = 18.6 (s) ppm.

**[6-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)-1-hydroxy-1-phosphonohexyl]phosphonic Acid (12c):** After solvent removal in vacuo, the residue was washed with diethyl ether (3 × 10 mL) to remove traces of $H_3PO_3$, giving a white powder. Yield 916 mg (90%). M.p. 136 °C. IR (KBr): $\tilde{\nu}$ = 3419, 2951, 1770, 1705, 1466, 1441, 1406, 1373, 1187, 1058, 992, 726, 668 $cm^{-1}$. $^1H$ NMR ($CD_3OD$, 500 MHz, 298 K): $\delta$ = 1.36 (qt, $^3J_{H,H}$ = 7.6 Hz, 2 H, $NCH_2CH_2CH_2CH_2CH_2COH$), 1.65–1.78 (m, 4 H, $NCH_2CH_2CH_2CH_2CH_2COH$), 1.95–2.08 (m, 2 H, $NCH_2CH_2CH_2CH_2CH_2COH$), 3.66 (t, 2 H, $^3J_{H,H}$ = 7.3 Hz, $NCH_2CH_2CH_2CH_2CH_2COH$), 7.59–7.67 (m, 4 H, $C_6H_4$) ppm. $^{13}C\{^1H\}$ NMR ($CD_3OD$, 125.7 MHz, 298 K): $\delta$ = 24.4 (s, $NCH_2CH_2CH_2CH_2CH_2COH$), 29.0 (s, $NCH_2CH_2CH_2CH_2CH_2COH$), 29.7 (s, $NCH_2CH_2CH_2CH_2CH_2COH$), 35.2 (s, $NCH_2CH_2CH_2CH_2CH_2COH$), 39.1 (s, $NCH_2CH_2CH_2CH_2CH_2COH$), 74.5 (t, $J_{C,P}$ = 147.4 Hz, $NCH_2CH_2CH_2COH$), 124.2, 133.5, 135.5 (s, $C_6H_4$), 170.0 [s, $NC(O)$] ppm. $^{31}P\{^1H\}$ NMR ($CD_3OD$, 202.4 MHz, 298 K): $\delta$ = 22.9 (s) ppm.

**Monomethyl [3-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)-1-hydroxy-1-(hydroxy-methoxy-phosphoryl)propyl]phosphonate (13a):** After solvent removal in vacuo, the residue was washed with diethyl ether (3 × 10 mL) to remove traces of $H_3PO_3$, giving a white powder. Yield 836 mg (85%). M.p. 178 °C. $^1H$ NMR ($D_2O$, 200 MHz, 298 K): $\delta$ = 2.24–2.34 (m, 2 H, $NCH_2CH_2COH$), 3.75–3.77 (m, 6 H, $OCH_3$), 3.95–3.98 (m, 2 H, $NCH_2CH_2COH$), 7.78–7.84 (m, 4 H, $C_6H_4$) ppm. $^{13}C\{^1H\}$ NMR ($D_2O$, 50.3 MHz, 298 K): $\delta$ = 30.3 (s, $NCH_2CH_2COH$), 31.5 (s, $NCH_2CH_2COH$), 51.7 (s, $OCH_3$), 71.1 (t, $J_{C,P}$ = 148.9 Hz, $NCH_2CH_2COH$), 121.4, 129.3, 132.9 (s, $C_6H_4$), 168.1 [s, $NC(O)$] ppm. $^{31}P\{^1H\}$ NMR ($D_2O$, 202.4 MHz, 298 K): $\delta$ = 20.5 (s) ppm.

**Monomethyl [4-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)-1-hydroxy-1-(hydroxy-methoxy-phosphoryl)-butyl]phosphonate (13b):** After solvent removal in vacuo, the residue was washed with of diethyl ether (3 × 10 mL) to remove traces of $CH_3OP(OH)_2$, giving a white powder. Yield 916 mg (90%). M.p. 106 °C. IR (KBr): $\tilde{\nu}$ = 3467, 2952, 2858, 1770, 1707, 1468, 1437, 1400, 1363, 1211, 1052, 983, 918, 899, 877, 802, 716 $cm^{-1}$. $^1H$ NMR ($CD_3OD$, 500 MHz, 298 K): $\delta$ = 1.85–2.04 (m, 4 H, $NCH_2CH_2CH_2COH$), 3.47 (t, $^3J_{H,H}$ = 6.5 Hz, 2 H, $NCH_2CH_2CH_2COH$), 3.69–3.73 (m, 6 H, $OCH_3$), 7.46–7.50 (m, 2 H, $C_6H_4$), 7.56–7.61 (m, 2 H, $C_6H_4$) ppm. $^{13}C\{^1H\}$ NMR ($CD_3OD$, 50.3 MHz, 298 K): $\delta$ = 20.7 (t, $^4J_{P,H}$ = 0.2 Hz, $NCH_2CH_2CH_2COH$), 29.4 (s, $NCH_2CH_2CH_2COH$), 36.1 (s, $NCH_2CH_2CH_2CH_2COH$), 51.5 (s, $OCH_3$), 71.9 (t, $J_{C,P}$ = 150.4 Hz, $NCH_2CH_2CH_2COH$), 121.2, 128.8, 132.7 (s, $C_6H_4$), 167.9 [s, $NC(O)$] ppm. $^{31}P\{^1H\}$ NMR ($CD_3OD$, 202.4 MHz, 298 K): $\delta$ = 21.2 (s) ppm.

**Monomethyl [6-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)-1-hydroxy-1-(hydroxy-methoxy-phosphoryl)hexyl]phosphonate (13c):** After solvent removal in vacuo, the residue was washed with of diethyl ether (3 × 10 mL) to remove traces of $CH_3OP(OH)_2$, giving a white powder. Yield 979 mg (90%). $^1H$ NMR ($D_2O$, 500 MHz, 298 K): $\delta$ = 1.30–1.38 (m, 2 H, $NCH_2CH_2CH_2CH_2CH_2COH$), 1.58–1.64 (m, 4 H, $NCH_2CH_2CH_2CH_2CH_2COH$), 1.88–2.00 (m, 2 H, $NCH_2CH_2CH_2CH_2CH_2COH$), 3.56–3.59 (m, 2 H, $NCH_2CH_2CH_2CH_2CH_2COH$), 3.70–3.73 (m, 6 H, $OCH_3$), 7.71–7.74 (m, 4 H, $C_6H_4$) ppm. $^{13}C\{^1H\}$ NMR ($D_2O$, 125.7 MHz, 298 K): $\delta$ = 23.4 (s, $NCH_2CH_2CH_2CH_2CH_2COH$), 27.4 (s, $NCH_2CH_2CH_2CH_2CH_2COH$), 28.0 (s, $NCH_2CH_2CH_2CH_2CH_2COH$), 34.5 (s, $NCH_2CH_2CH_2CH_2CH_2COH$), 38.4 (s, $NCH_2CH_2CH_2CH_2CH_2COH$), 53.6 (s, $OCH_3$), 74.8 (t, $J_{C,P}$ = 148.3 Hz, $NCH_2CH_2CH_2CH_2CH_2COH$), 123.7, 131.7, 135.1 (s, $C_6H_4$), 171.3 [s, $NC(O)$] ppm. $^{31}P\{^1H\}$ NMR ($D_2O$, 202.4 MHz, 298 K): $\delta$ = 21.8 (s) ppm.

**Monophenyl [3-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)-1-hydroxy-1-(hydroxy-phenoxy-phosphoryl)propyl]phosphonate (14a):** After solvent removal in vacuo, the residue was disolved in dichloromethane (50 mL) and washed with water (50 mL). The resulting emulsion was filtered through celite and the organic layer was separated and evaporated, giving a yellow powder. Yield 647 mg (50%). $^1H$ NMR ([D$_6$]DMSO, 500 MHz, 298 K): $\delta$ = 2.15–2.45 (m, 2 H, $NCH_2CH_2COH$), 3.89–4.11 (m, 2 H, $NCH_2CH_2COH$), 6.79–7.28 (m, 10 H, $C_6H_5$), 7.75–7.85 (m, 4 H, $C_6H_4$) ppm. $^{13}C\{^1H\}$ NMR ([D$_6$]DMSO, 125.7 MHz, 298 K): $\delta$ = 33.5 (s, $NCH_2CH_2COH$), 38.6 (s, $NCH_2CH_2COH$), 72.3 (t, $J_{C,P}$ = 146.7 Hz, $NCH_2CH_2COH$), 120.8 (s, $o$-$C_6H_5$), 122.9 (s, $C_6H_4$), 129.2 (s, $p$-$C_6H_5$), 129.4 (s, $C_6H_4$), 131.4 (s, $m$-$C_6H_5$), 134.4 (s, $C_6H_4$), 156.8 (s, $OC_6H_5$), 168.1 [s, $NC(O)$] ppm. $^{31}P\{^1H\}$ NMR ([D$_6$]DMSO, 202.4 MHz, 298 K): $\delta$ = 20.0 (s) ppm.

**Monophenyl [4-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)-1-hydroxy-1-(hydroxy-phenoxy-phosphoryl)butyl]phosphonate (14b):** After solvent removal in vacuo, the residue was dissolved in dichloromethane (50 mL) and washed with water (50 mL). The resulting emulsion was filtered through celite, and the organic layer was separated and evaporated, giving a white powder. Yield 797 mg (60%).Crystals were obtained as white needles by slow evaporation of a water solution of **14b** (0.1 mg/mL). M.p. 130 °C. IR (KBr): $\tilde{\nu}$ = 3464, 3062, 2959, 1773, 1711, 1592, 1491, 1467, 1443, 1404, 1383, 1198, 1108, 1051, 1025, 959, 918, 902, 765, 723, 714, 692 $cm^{-1}$. $^1H$ NMR ([D$_6$]DMSO, 500 MHz, 298 K): $\delta$ = 2.01–2.18 (m, 4 H, $NCH_2CH_2CH_2COH$), 3.56–3.70 (m, 2 H, $NCH_2CH_2CH_2COH$), 7.07 (t, $^3J_{H,H}$ = 7.0 Hz, 2 H, $p$-$C_6H_5$), 7.16 (d, $^3J_{H,H}$ = 7.9 Hz, 4 H, $o$-$C_6H_5$), 7.27 (dd, $^3J_{H,H}$ = 7.9, 7.0 Hz, 4 H, $m$-$C_6H_5$), 7.83–7.91 (m, 4 H, $C_6H_4$) ppm. $^{13}C\{^1H\}$ NMR ([D$_6$]DMSO, 125.7 MHz, 298 K): $\delta$ = 22.9 (s, $NCH_2CH_2CH_2COH$), 31.5 (s, $NCH_2CH_2CH_2COH$), 37.9 (s, $NCH_2CH_2CH_2CH_2COH$), 73.2 (t, $J_{C,P}$ = 146.5 Hz, $NCH_2CH_2CH_2COH$), 120.6 (s, $o$-$C_6H_5$), 123.0 (s, $C_6H_4$), 123.5 (s, $p$-$C_6H_5$), 129.0 (s, $C_6H_4$), 131.6 (s, $m$-$C_6H_5$), 134.3 (s, $C_6H_4$), 151.6 (s, $OC_6H_5$), 167.8 [s, $NC(O)$] ppm. $^{31}P\{^1H\}$ NMR ([D$_6$]DMSO, 202.4 MHz, 298 K): $\delta$ = 21.2 (s) ppm. X-ray structure: Dihydrate, monoclinic, space group $P2_1/c$, cell parameters: $a$ = 18.452(1); $b$ = 6.5837(5); $c$ = 22.400(1) Å; $\beta$ = 107.537(3)°; $Z$ = 4

  

and $V$ = 2 594.8(3) Å$^3$. 13129 measured reflections, reduced to 4142 independent reflections of which 2667 were considered as observed - criterion $I \geq 4\sigma(I)$. Final $R$ = 5.98% (observed reflections); $R$ = 8.4% (all data).

**Monophenyl [6-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)-1-hydroxy-1-(hydroxy-phenoxy-phosphoryl)hexyl]phosphonate (14c):** After solvent removal in vacuo, the residue was dissolved in methanol (2 mL) and precipitated by adding $H_2O$ (20 mL). The resulting powder was then purified by silica gel chromatography using methanol/chloroform (90:10) as the eluent. $R_f$ = 0.4. Yield 840 mg (60%). M.p. 182 °C. IR (KBr): $\tilde{\nu}$ = 3400, 3067, 2939, 2861, 1771, 1708, 1593, 1490, 1467, 1438, 1397, 1360, 1202, 1070, 1056, 1025, 1010, 981, 934, 766, 718, 689 cm$^{-1}$. $^1$H NMR ($CDCl_3$, 200 MHz, 298 K): $\delta$ = 1.20–1.42 (m, 2 H, $NCH_2CH_2CH_2CH_2CH_2COH$), 1.48–1.91 (m, 4 H, $NCH_2CH_2CH_2CH_2CH_2COH$), 2.12–2.38 (m, 2 H, $NCH_2CH_2CH_2CH_2CH_2COH$), 3.54–3.71 (m, 2 H, $NCH_2CH_2CH_2CH_2CH_2COH$), 6.79–7.28 (m, 10 H, $C_6H_5$), 7.66–7.80 (m, 4 H, $C_6H_4$) ppm. $^{13}$C{$^1$H} NMR ($CDCl_3$, 125.7 MHz, 298 K): $\delta$ = 23.2 (s, $NCH_2CH_2CH_2CH_2CH_2COH$), 27.6 (s, $NCH_2CH_2CH_2CH_2CH_2COH$), 28.5 (s, $NCH_2CH_2CH_2CH_2CH_2COCl$), 33.6 (s, $NCH_2CH_2CH_2CH_2CH_2COH$), 38.1 (s, $NCH_2CH_2CH_2CH_2CH_2COH$), 74.8 (t, $J_{C,P}$ = 152.8 Hz, $NCH_2CH_2CH_2CH_2CH_2COH$), 120.9 (s, $o$-$C_6H_5$), 123.4 (s, $C_6H_4$), 125.3 (s, $p$-$C_6H_5$), 129.8 (s, $C_6H_4$), 132.5 (s, $m$-$C_6H_5$), 134.0 (s, $C_6H_4$), 150.2 (s, $OC_6H_5$), 168.7 [s, $NC(O)$] ppm. $^{31}$P{$^1$H} NMR ($CDCl_3$, 202.4 MHz, 298 K): $\delta$ = 16.0 (s) ppm.

**Synthesis of Dimethyl [4-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)butyryl]phosphonate (17):** In a 50 mL round-bottom three-neck flask equipped with a thermometer, 4-(1,3-dioxo-1,3-dihydroisoindol-2-yl)butyryl chloride (**11b**, 1.25 g, 5 mmol) was added dropwise at –10 °C under Ar to trimethyl phosphite (0.6 mL, 5 mmol). The reaction mixture was then stirred at room temperature for 2 h. The end of the reaction was ascertained by $^{31}$P{$^1$H} NMR spectroscopy. Evaporation of volatile fractions under reduced pressure (0.1 Torr) yielded quantitatively the corresponding α-keto dimethyl phosphonate **17** as a white powder. M.p. 51 °C. IR (KBr): $\tilde{\nu}$ = 2964, 2941, 1772, 1713, 1469, 1444, 1397, 1360, 1263, 1088, 1123, 1034, 832, 800, 765, 724 cm$^{-1}$. $^1$H NMR ($CDCl_3$, 500 MHz, 298 K): $\delta$ = 1.98 (qt, $^3J_{H,H}$ = 7.3 Hz, 2 H, $NCH_2CH_2CH_2COPO$), 2.88 (t, $^3J_{H,H}$ = 7.3 Hz, 2 H, $NCH_2CH_2CH_2COPO$), 3.69 (t, $^3J_{H,H}$ = 7.3 Hz, 2 H, $NCH_2CH_2CH_2COPO$), 3.82 (d, $^3J_{H,P}$ = 10.2 Hz, 6 H, $OCH_3$), 7.65–7.70 (m, 2 H, $C_6H_4$), 7.77–7.82 (m, 2 H, $C_6H_4$) ppm. $^{13}$C{$^1$H} NMR ($CDCl_3$, 50.3 MHz, 298 K): $\delta$ = 21.5 (s, $NCH_2CH_2CH_2COPO$), 37.0 (s, $NCH_2CH_2CH_2COPO$), 40.9 (d, $^2J_{P,C}$ = 55.6 Hz, $NCH_2CH_2CH_2COPO$), 54.1 (d, $^2J_{P,C}$ = 6.1 Hz, $OCH_3$), 123.4, 132.1, 134.1 (s, $C_6H_4$), 168.4 [s, $NC(O)$], 209.3 (d, $^1J_{P,C}$ = 169.2 Hz, $COPO$) ppm. $^{31}$P{$^1$H} NMR ($CDCl_3$, 202.4 MHz, 298 K): $\delta$ = –0.6 (s) ppm.

**General Procedure for Reaction of α-Keto Dimethyl Phosphonate 17 with Methyl Bis(trimethylsilyl) Phosphite and Tris(trimethylsilyl) Phosphite:** In a 50 mL round-bottom three-neck flask equipped with a thermometer, dimethyl [4-(1,3-dioxo-1,3-dihydroisoindol-2-yl)butyryl]phosphonate (**17**, 1.30 g, 5 mmol) was added dropwise at 0 °C under Ar to silylated phosphite (5 mmol). The reaction mixture was then stirred at room temperature for 4 h. The evolution of the reaction was monitored by $^{31}$P{$^1$H} NMR spectroscopy. The volatile fractions were evaporated at 40 °C under reduced pressure (0.1 Torr) before being hydrolyzed with methanol. After evaporation, crude products were purified as follows.

**[1-(Dimethoxyphosphoryl)-4-(1,3-dioxo-1,3-dihydroisoindol-2-yl)-1-hydroxybutyl]phosphonic Acid (18):** After solvent removal in vacuo, the residue was washed with diethyl ether (3 × 10 mL) to remove traces of $H_3PO_2$, giving a white powder. Yield 1.8 g (90%). M.p. 87 °C. IR (KBr): $\tilde{\nu}$ = 3456, 2959, 2857, 1771, 1704, 1617, 1465, 1437, 1401, 1364, 1223, 1187, 1142, 1035, 944, 891, 834, 780, 717, 530 cm$^{-1}$. $^1$H NMR ($D_2O$, 500 MHz, 298 K): $\delta$ = 1.91–2.09 (m, 4 H, $NCH_2CH_2CH_2COH$), 3.68–3.73 (m, 2 H, $NCH_2CH_2CH_2COH$), 3.76 (d, $^3J_{P,H}$ = 10.4 Hz, 3 H, $OCH_3$), 3.77 (d, $^3J_{P,H}$ = 10.4 Hz 3 H,, $OCH_3$), 7.80–7.84 (m, 2 H, $C_6H_4$), 7.84–7.89 (m, 2 H, $C_6H_4$) ppm. $^{13}$C{$^1$H} NMR ([D$_6$]DMSO, 120.7 MHz, 298 K): $\delta$ = 23.9 (s, $NCH_2CH_2CH_2COH$), 32.7 (s, $NCH_2CH_2CH_2COH$), 39.4 (s, $NCH_2CH_2CH_2COH$), 55.8 (s, $OCH_3$), 73.6 (dd, $J_{C,P}$ = 155.0 Hz, 147.9 Hz, $NCH_2CH_2CH_2COH$), 123.8, 131.7, 135.3 (s, $C_6H_4$), 170.9 [s, $NC(O)$] ppm. $^{31}$P{$^1$H} NMR ($CD_3OD$, 202.4 MHz, 298 K): $\delta$ = 15.0 [$J_{P,P}$ = 32.8 Hz, $P(O)(OCH_3)_2$], 27.7 [d, $J_{P,P}$ = 32.8 Hz, $P(O)(OH)_2$] ppm.

**Monomethyl [1-(Dimethoxyphosphoryl)-4-(1,3-dioxo-1,3-dihydroisoindol-2-yl)-1-hydroxybutyl]phosphonate (19):** After solvent removal in vacuo, the residue was precipitated from dichloromethane/diethyl ether (10:90) and washed with diethyl ether (3 × 10 mL), giving a white powder. Yield 1.37 g (65%). M.p. 155 °C. IR (KBr): $\tilde{\nu}$ = 3461, 3275, 2962, 2854, 1770, 1710, 1616, 1466, 1435, 1396, 1361, 1249, 1187, 1034, 991, 723, 668, 530 cm$^{-1}$. $^1$H NMR ($CDCl_3$, 200 MHz, 298 K): $\delta$ = 1.84–2.06 (m, 4 H, $NCH_2CH_2CH_2COH$), 3.56–3.68 (m, 2 H, $NCH_2CH_2CH_2COH$), 3.68–3.90 (m, 9 H, $OCH_3$), 7.60–7.71 (m, 2 H, $C_6H_4$), 7.73–7.91 (m, 2 H, $C_6H_4$) ppm. $^{13}$C{$^1$H} NMR ($CDCl_3$, 120.7 MHz, 298 K): $\delta$ = 22.9 (s, $NCH_2CH_2CH_2COH$), 32.3 (s, $NCH_2CH_2CH_2COH$), 38.5 (s, $NCH_2CH_2CH_2COH$), 53.5 (d, $^2J_{C,P}$ = 7.0 Hz, $OCH_3$), 54.3 (d, $^2J_{C,P}$ = 7.0 Hz, $OCH_3$), 55.1 (d, $^2J_{C,P}$ = 7.0 Hz, $OCH_3$), 74.5 (dd, $J_{C,P}$ = 145.8 Hz, 141.5 Hz, $NCH_2CH_2CH_2COH$), 123.3, 132.3, 134.0 (s, $C_6H_4$), 168.5 [s, $NC(O)$] ppm. $^{31}$P{$^1$H} NMR ($CDCl_3$, 80.9 MHz, 298 K): $\delta$ = 15.8 [d, $J_{P,P}$ = 29.4 Hz, $P(O)(OCH_3)_2$], 26.6 [d, $J_{P,P}$ = 29.4 Hz, $P(O)(OH)(OCH_3)$] ppm.

**General Procedure for Reaction of Phosphonate 17 with Bromotrimethylsilane Followed by Alkyl or Aryl Bis(trimethylsilyl) Phosphite:** In a 50 mL round-bottom three-neck flask equipped with a thermometer, dimethyl [4-(1,3-dioxo-1,3-dihydroisoindol-2-yl)butyryl] phosphonate (**17**, 1.30 g, 5 mmol) was dissolved in dry dichloromethane. Freshly distilled bromotrimethylsilane (1.39 mL, 10.5 mmol) was added dropwise at 0 °C under Ar. The reaction mixture was then stirred at room temperature for 6 h. The end of the silylation reaction was ascertained by obtaining of a single signal at –18.2 ppm in the $^{31}$P{$^1$H} NMR spectrum. The solvent was evaporated at 40 °C under reduced pressure (0.1 Torr). Methyl or phenyl bis(trimethylsilyl) phosphite was then added to the silylated α-keto phosphonate at 0 °C under Ar. When the addition was finished, the reaction was stirred at room temperature for 4 h [methyl bis(trimethylsilyl) phosphite] or overnight [phenyl bis(trimethylsilyl) phosphite]. The reaction mixture was evaporated under reduced pressure (0.1 Torr) and hydrolyzed with methanol. After evaporation, the crude products were purified as follows.

**[4-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)-1-hydroxy-1-(hydroxy-methoxy-phosphoryl)butyl]phosphonic Acid (20):** After solvent removal in vacuo, the residue was washed with diethyl ether (3 × 10 mL) to remove traces of $CH_3OP(OH)_2$, giving a white powder. Yield 1.77 g (90%). M.p. 67 °C. IR (KBr): $\tilde{\nu}$ = 3446, 2960, 2857, 1771, 1708, 1467, 1440, 1402, 1363, 1188, 1043, 796, 721 cm$^{-1}$. $^1$H NMR ($D_2O$, 500 MHz, 298 K): $\delta$ = 1.90–2.04 (m, 4 H, $NCH_2CH_2CH_2COH$), 3.73–3.68 (t, $^3J_{H,H}$ = 6.4 Hz, 2 H, $NCH_2CH_2CH_2COH$), 3.66 (d, $^3J_{P,H}$ = 10.4 Hz, 3 H, $OCH_3$), 7.72 (s, 4 H, $C_6H_4$) ppm. $^{13}$C-{$^1$H} NMR ($D_2O$, 120.7 MHz, 298 K): $\delta$ = 23.2 (s, $NCH_2CH_2CH_2COH$), 31.6 (s, $NCH_2CH_2CH_2COH$), 38.6 (s, $NCH_2CH_2CH_2COH$), 53.7 (d, $^2J_{C,P}$ = 6.4 Hz, $OCH_3$), 73.9 (dd,

  

$J_{C,P}$ = 147.4 Hz, $J_{C,P}$ = 146.5 Hz, $NCH_2CH_2CH_2COH$), 123.8, 131.7, 135.2 (s, $C_6H_4$), 171.0 [s, N*C*(O)] ppm. $^{31}P\{^1H\}$ NMR ($D_2O$, 202.4 MHz, 298 K): $\delta$ = 20.1 [m, $P(O)(OCH_3)OH$], 21.3 [m, $P(O)(OH)_2$] ppm.

**[4-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)-1-hydroxy-1-(hydroxy-phenoxy-phosphoryl)butyl]phosphonic Acid (21):** After solvent removal in vacuo, the residue was precipitated in dichloromethane/diethyl ether (10:90). The resulting powder was then purified by silica gel chromatography using a gradient from 2–15% methanol in dichloromethane. $R_f$ = 0.2. White powder. Yield 1.32 g (58%). M.p. 79 °C. IR (KBr): $\tilde{\nu}$ = 3428, 2939, 1770, 1711, 1651, 1592, 1490, 1468, 1440, 1399, 1361, 1210, 1024, 938, 766, 721, 692, 530 $cm^{-1}$. $^1H$ NMR ([$D_6$]DMSO, 500 MHz, 298 K): $\delta$ = 1.86–2.05 (m, 4 H, $NCH_2CH_2CH_2COH$), 3.48–3.58 (m, 2 H, $NCH_2CH_2CH_2COH$), 6.96–7.05 (m, 1 H, *p*-$C_6H_5$), 7.06–7.15 (m, 2 H, *o*-$C_6H_5$), 7.16–7.25 (m, 2 H, *m*-$C_6H_5$), 7.78–7.88 (m, 4 H, $C_6H_4$) ppm. $^{13}C\{^1H\}$ NMR ([$D_6$]DMSO, 125.7 MHz, 298 K): $\delta$ = 22.9 (s, $NCH_2CH_2CH_2COH$), 31.4 (s, $NCH_2CH_2CH_2COH$), 38.0 (s, $NCH_2CH_2CH_2COH$), 72.9 (t, $J_{C,P}$ = 143.6 Hz, $NCH_2CH_2CH_2COH$), 120.6 (s, *o*-$C_6H_5$), 123.0 (s, $C_6H_4$), 123.2 (s, *p*-$C_6H_5$), 129.0 (s, $C_6H_4$), 131.5 (s, *m*-$C_6H_5$), 134.3 (s, $C_6H_4$), 151.9 (s, $OC_6H_5$), 167.9 [s, N*C*(O)] ppm. $^{31}P\{^1H\}$ NMR ([$D_6$]DMSO, 202.4 MHz, 298 K): $\delta$ = 21.9 [d, $^2J_{P,P}$ = 44.7 Hz, $P(O)(OC_6H_5)OH$], 24.6 [d, $^2J_{P,P}$ = 44.7 Hz, $P(O)(OH)_2$] ppm.

**General Procedure for Amine Deprotection Using Hydrazine:** In a 50 mL round-bottom three-neck flask equipped with a thermometer, phthalimide bisphosphonate (5 mmol) was suspended in water (25 mL). Hydrazine monohydrate (2.50 g, 50 mmol) was added dropwise at 0 °C to the suspension. The phthalimide bisphosphonate quickly solubilised, and the solution was stirred for 30 min at room temperature. HCl (0.1 M) was then added dropwise until pH = 1. A precipitate formed and was filtered. The aqueous solution was then evaporated. After lyophilisation, the crude products were purified as follows.

**(3-Amino-1-hydroxy-1-phosphonopropyl)phosphonic Acid (Pamidronate):** Purification was carried out as described by Kieczykowski,[16] yielding a white powder. Yield 928 mg (67%). M.p. <300 °C. IR (KBr): $\tilde{\nu}$ = 3334, 2932, 2767, 2673, 2535, 1635, 1540, 1125, 1053, 976, 947, 896, 873, 650, 550, 524 $cm^{-1}$. $^1H$ NMR ($D_2O$, 200 MHz, 298 K): $\delta$ = 2.00–2.16 (m, 2 H, $H_2NCH_2CH_2COH$); 3.14 (t, $^3J_{H,H}$ = 6.6 Hz, 2 H, $H_2NCH_2CH_2COH$) ppm. $^{13}C\{^1H\}$ NMR ($D_2O$, 125.7 MHz, 298 K): $\delta$ = 31.2 (s, $H_2NCH_2CH_2COH$), 36.1 (s, $H_2NCH_2CH_2COH$), 72.3 (t, $J_{C,P}$ = 134.8 Hz, $H_2NCH_2CH_2COH$) ppm. $^{31}P\{^1H\}$ NMR ($D_2O$, 80.9 MHz, 298 K): $\delta$ = 16.8 (s) ppm.

**(4-Amino-1-hydroxy-1-phosphonobutyl)phosphonic Acid (Alendronate):** Purification was carried out as described by Kieczykowski,[16] yielding a white powder. Yield 1.1 g (82%). M.p. 119 °C. IR (KBr): $\tilde{\nu}$ = 3486, 3346, 3244, 2960, 2800, 2710, 2566, 1644.6, 1545, 1231, 1178, 1063, 1018, 953, 926, 866, 660, 576, 547, 472 $cm^{-1}$. $^1H$ NMR ($D_2O$, 500 MHz, 298 K): $\delta$ = 1.96–2.06 (m, 4 H, $H_2NCH_2CH_2CH_2COH$), 3.03–3.06 (t, $^3J_{H,H}$ = 6.5 Hz, 2 H, $H_2NCH_2CH_2CH_2COH$) ppm. $^{13}C\{^1H\}$ NMR ($D_2O$, 120.7 MHz, 298 K): $\delta$ = 23.4 (s, $H_2NCH_2CH_2CH_2COH$), 31.8 (s, $H_2NCH_2CH_2CH_2COH$), 41.2 (s, $H_2NCH_2CH_2CH_2COH$), 74.7 (t, $J_{C,P}$ = 134.6 Hz, $H_2NCH_2CH_2CH_2COH$) ppm. $^{31}P\{^1H\}$ NMR ($D_2O$, 202.4 MHz, 298 K): $\delta$ = 18.6 (s) ppm.

**(6-Amino-1-hydroxy-1-phosphonohexyl)phosphonic Acid (Neridronate):** Purification was carried out as described by Kieczykowski,[16] yielding a white powder.Yield 1.32 g (89%). M.p. 252 °C. IR (KBr): $\tilde{\nu}$ = 3608, 3463, 3217, 2940, 2754, 2677, 2642, 2565, 1638, 1536, 1221, 1149, 1092, 1070, 1050, 1070, 975, 907, 663, 586, 552 $cm^{-1}$. $^1H$ NMR ($D_2O$, 500 MHz, 298 K): $\delta$ = 1.39 (qt, $^3J_{H,H}$ = 7.2 Hz, 2 H, $H_2NCH_2CH_2CH_2CH_2CH_2COH$), 1.53–1.76 (m, 4 H, $H_2NCH_2CH_2CH_2CH_2CH_2COH$), 1.86–1.98 (m, 2 H, $H_2NCH_2CH_2CH_2CH_2CH_2COH$), 3.00 (t, $^3J_{H,H}$ = 7.0 Hz, 2 H, $H_2NCH_2CH_2CH_2CH_2CH_2COH$) ppm. $^{13}C\{^1H\}$ NMR ($D_2O$, 125.7 MHz, 298 K): $\delta$ = 24.1 (s, $H_2NCH_2CH_2CH_2CH_2CH_2COH$), 27.4 (s, $H_2NCH_2CH_2CH_2CH_2CH_2COH$), 27.6 (s, $H_2NCH_2CH_2CH_2CH_2CH_2COCl$), 34.6 (s, $H_2NCH_2CH_2CH_2CH_2CH_2COH$), 40.5 (s, $H_2NCH_2CH_2CH_2CH_2CH_2COH$), 75.4 (t, $J_{C,P}$ = 134.6 Hz, $H_2NCH_2CH_2$ $CH_2CH_2CH_2COH$) ppm. $^{31}P\{^1H\}$ NMR ($D_2O$, 202.4 MHz, 298 K): $\delta$ = 19.3 (s) ppm.

**Monomethyl [3-Amino-1-hydroxy-1-(hydroxy-methoxy-phosphoryl)-propyl]phosphonate (15a):** The crude product was dissolved in water and dialysed using a Spectrapor 100 membrane. Lyophilisation gave a white powder. Yield 705 mg (70%). M.p. 56 °C. IR: $\tilde{\nu}$ = 3421, 3302, 3046, 1616, 1506, 1497, 1405, 1190, 1085, 962, 780 $cm^{-1}$. $^1H$ NMR ($D_2O$, 200 MHz, 298 K): $\delta$ = 2.02 (tt, $^3J_{H,H}$ = 6.7 Hz, $^3J_{P,H}$ = 13.4 Hz, 2 H, $H_2NCH_2CH_2COH$), 3.09 (t, $^3J_{H,H}$ = 6.7 Hz, 2 H, $H_2NCH_2CH_2COH$), 3.40–3.44 (m, 6 H, $OCH_3$) ppm. $^{13}C\{^1H\}$ NMR ($D_2O$, 125.7 MHz, 298 K): $\delta$ = 32.3 (s, $H_2NCH_2CH_2COH$), 36.5 (s, $H_2NCH_2CH_2COH$), 53.2 (s, $OCH_3$), 74.4 (t, $J_{C,P}$ = 143.2 Hz, $H_2NCH_2CH_2COH$) ppm. $^{31}P\{^1H\}$ NMR ($D_2O$, 202.4 MHz, 298 K): $\delta$ = 19.2 (s) ppm. MS (ES+): *m*/*z* = 264.0 [$M^+$ + H].

**Monomethyl [4-Amino-1-hydroxy-1-(hydroxy-methoxy-phosphoryl)-butyl]phosphonate (15b):** The crude product was dissolved in water and dialysed using a Spectrapor 100 membrane. Lyophilisation gave a white powder. Yield 647 mg (60%). IR: $\tilde{\nu}$ = 3407, 3255, 2955, 2852, 1637, 1541, 1474, 1397, 1201, 1053, 914, 746, 669, 542 $cm^{-1}$. $^1H$ NMR ($D_2O$, 500 MHz, 298 K): $\delta$ = 1.95–1.99 (m, 4 H, $H_2NCH_2CH_2CH_2COH$), 2.97–3.04 (m, 2 H, $H_2NCH_2CH_2CH_2COH$), 3.63–3.66 (m, 6 H, $OCH_3$) ppm. $^{13}C\{^1H\}$ NMR ($D_2O$, 125.7 MHz, 298 K): $\delta$ = 25.3 (s, $H_2NCH_2CH_2CH_2COH$), 34.9 (s, $H_2NCH_2CH_2CH_2COH$), 43.2 (s, $H_2NCH_2CH_2CH_2COH$), 55.8 (s, $OCH_3$), 77.9 (t, $J_{C,P}$ = 143.7 Hz, $H_2NCH_2CH_2CH_2COH$) ppm. $^{31}P\{^1H\}$ NMR ($D_2O$, 202.4 MHz, 298 K): $\delta$ = 20.1 (s) ppm. MS (ES+): *m*/*z*= 300.0 [$M^+$ + H + Na]. MS (ES-): *m*/*z* = 275.7 [$M^-$ – H].

**Monomethyl [6-Amino-1-hydroxy-1-(hydroxy-methoxy-phosphoryl)-hexyl]phosphonate (15c):** The lyophilized powder was purified using low pressure C18 chromatography. A C18 silica gel column was coupled to a low pressure pump and a UV detector. An HCl (0.1 M) solution was used to elute; the flow rate was 15 mL $min^{-1}$ and detection was done at 215 nm. A white powder was obtained after lyophilisation. Yield 1.05 g (75%). M.p. 128 °C. IR (KBr): $\tilde{\nu}$ = 3423, 3290, 3042, 2962, 1607, 1498, 1403, 1186, 1086, 961, 493 $cm^{-1}$. $^1H$ NMR ($D_2O$, 500 MHz, 298 K): $\delta$ = 1.30–1.38 (m, 2 H, $H_2NCH_2CH_2CH_2CH_2CH_2COH$), 1.58–1.64 (m, 4 H, $H_2NCH_2CH_2CH_2CH_2CH_2COH$), 1.88–2.00 (m, 2 H, $H_2NCH_2CH_2CH_2CH_2CH_2COH$), 3.56–3.59 (m, 2 H, $H_2NCH_2CH_2CH_2CH_2CH_2COH$), 3.70–3.73 (m, 6 H, $OCH_3$), 7.71–7.74 (m, 4 H, $C_6H_4$) ppm. $^{13}C\{^1H\}$ NMR ($D_2O$, 125.7 MHz, 298 K): $\delta$ = 23.4 (s, $H_2NCH_2CH_2CH_2CH_2CH_2COH$), 27.4 (s, $H_2NCH_2CH_2CH_2CH_2CH_2COH$), 28.0 (s, $H_2NCH_2CH_2CH_2CH_2CH_2COH$), 34.5 (s, $H_2NCH_2CH_2CH_2CH_2CH_2COH$), 38.4 (s, $H_2NCH_2CH_2CH_2CH_2CH_2COH$), 53.6 (s, $OCH_3$), 74.6 (t, $J_{C,P}$ = 134.6 Hz, $H_2NCH_2CH_2CH_2CH_2CH_2COH$), 123.7, 131.7, 135.1 (s, $C_6H_4$), 171.3 [s, N*C*(O)] ppm. $^{31}P\{^1H\}$ NMR ($D_2O$, 202.4 MHz, 298 K): $\delta$ = 21.7 (s) ppm. MS (ES+): *m*/*z* = 306.1 [$M^+$ + H].

**Monophenyl [3-Amino-1-hydroxy-1-(hydroxy-phenoxy-phosphoryl)-propyl]phosphonate (16a):** The crude product was dissolved in water and dialysed using a Spectrapor 100 membrane. Lyophilisation gave a white powder. Yield 1.26 g (65%). M.p. 178 °C. IR (KBr):

  

$\tilde{\nu}$ = 3419, 3243, 3140, 3037, 2982, 1629, 1592, 1495, 1410, 1237, 1214, 1105, 1083, 965 $cm^{-1}$. $^1H$ NMR ($D_2O$, 200 MHz, 298 K): $\delta$ = 2.26–2.36 (tt, $^3J_{H,H}$ = 6.7 Hz, $^3J_{P,H}$ = 13.9 Hz, 2 H, $H_2NCH_2CH_2COH$), 3.27 (t, $^3J_{H,H}$ = 6.7 Hz, 2 H, $H_2NCH_2CH_2COH$), 6.99 (t, $^3J_{H,H}$ = 7.3 Hz, 2 H, *p*-$C_6H_5$), 7.05 (d, $^3J_{H,H}$ = 7.9 Hz, 4 H, *o*-$C_6H_5$), 7.18 (dd, $^3J_{H,H}$ = 7.9, 7.3 Hz, 4 H, *m*-$C_6H_5$) ppm. $^{13}C\{^1H\}$ NMR ($D_2O$, 50.4 MHz, 298 K): $\delta$ = 30.4 (s, $H_2NCH_2CH_2COH$), 35.1 (s, $H_2NCH_2CH_2COH$), 72.6 (t, $J_{C,P}$ = 144.2 Hz, $H_2NCH_2CH_2COH$), 119.8 (s, *o*-$C_6H_5$), 122.8 (s, *p*-$C_6H_5$), 128.4 (s, *m*-$C_6H_5$), 150.3 (s, $OC_6H_5$) ppm. $^{31}P\{^1H\}$ NMR ($D_2O$, 202.4 MHz, 298 K): $\delta$ = 20.5 (s) ppm. LC-MS (ES+): 6.26 min, *m*/*z* = 388.0 [$M^+$ + H].

**Monophenyl [4-Amino-1-hydroxy-1-(hydroxy-phenoxy-phosphoryl)-butyl]phosphonate (16b):** The crude product was dissolved in water and dialysed using a Spectrapor 100 membrane. Lyophilisation gave a white powder. Yield 1.22 g (61%). Crystals were obtained by slow evaporation of a dilute water solution. M.p. 112 °C. IR (KBr): $\tilde{\nu}$ = 3423, 3298, 3246, 3044, 1618, 1592, 1491, 1400, 1213, 1083, 963 $cm^{-1}$. $^1H$ NMR ($D_2O$, 500 MHz, 298 K): $\delta$ = 2.07–2.26 (m, 4 H, $H_2NCH_2CH_2CH_2COH$), 3.05 (t, 2 H, $^3J_{H,H}$ = 7.3 Hz, $H_2NCH_2CH_2CH_2COH$), 7.16 (t, 2 H, $^3J_{H,H}$ = 7.3 Hz, *p*-$C_6H_5$), 7.24 (d, $^3J_{H,H}$ = 8.5 Hz, 4 H, *o*-$C_6H_5$), 7.27 (dd, $^3J_{H,H}$ = 7.3, 8.5 Hz, 4 H, *m*-$C_6H_5$) ppm. $^{13}C\{^1H\}$ NMR ($D_2O$, 50.4 MHz, 298 K): $\delta$ = 21.1 (s, $H_2NCH_2CH_2CH_2COH$), 30.5 (s, $H_2NCH_2CH_2CH_2COH$), 38.9 (s, $H_2NCH_2CH_2CH_2COH$), 73.4 (t, $J_{C,P}$ = 146.6 Hz, $H_2NCH_2CH_2CH_2COH$), 119.9 (s, *o*-$C_6H_5$), 122.6 (s, *p*-$C_6H_5$), 128.3 (s, *m*-$C_6H_5$), 150.6 (s, $OC_6H_5$) ppm. $^{31}P\{^1H\}$ NMR ($D_2O$, 202.4 MHz, 298 K): $\delta$ = 16.4 (s) ppm. LC-MS (ES+): 6.33 min, *m*/*z* = 402.0 [$M^+$ + H]. X-ray structure of the monohydrate: triclinic, space group $P\bar{1}$, cell parameters: *a* = 6.8873(6); *b* = 9.8707(5); *c* = 16.085(1) Å; *α* = 107.68(2); *β* = 90.18(3); *γ* = 107.913(2)°, *Z* = 2 and *V* = 985.6(1) $Å^3$. 4153 measured reflections, reduced to 2769 independent reflections of which 1887 were considered as observed criterion $I \geq 4\sigma(I)$. Final *R* = 8.07% (observed reflections); *R* = 8.8% (all data).

**Monophenyl [6-Amino-1-hydroxy-1-(hydroxyphenoxyphosphoryl)-hexyl]phosphonate (16c):** After addition of hydrazine the phthalimide bisphosphonate remained hardly soluble in water. Methanol (10 mL) was added to solubilise the mixture. After 30 min, HCl (0.1 M) was added dropwise until pH = 1. More methanol was added (15 mL) and the precipitate formed was filtered. The crude product was then precipitated in water to yield a white powder. For NMR analysis the product was neutralised to pH = 7 using a potassium hydroxide solution (1 M). Yield 1.29 g (60%). M.p. 255 °C. IR (KBr): $\tilde{\nu}$ = 3405, 3038, 2927, 2860, 1629, 1591, 1489, 1454, 1374, 1216, 1094, 1025, 894, 764, 693 $cm^{-1}$. $^1H$ NMR ($CD_3OD$, 200 MHz, 298 K): $\delta$ = 1.33–1.39 (m, 2 H, $H_2NCH_2CH_2CH_2CH_2CH_2COH$), 1.60–1.66 and 1.76–1.79 (m, 4 H, $H_2NCH_2CH_2CH_2CH_2CH_2COH$), 2.16–2.22 (m, 2 H, $H_2NCH_2CH_2CH_2CH_2CH_2COH$), 2.82–2.86 (m, 2 H, $H_2NCH_2CH_2CH_2CH_2CH_2COH$), 7.08 (t, $^3J_{H,H}$ = 7.3 Hz, 2 H, *p*-$C_6H_5$), 7.19 (d, $^3J_{H,H}$ = 7.9 Hz, 4 H, *o*-$C_6H_5$), 7.25 (dd, $^3J_{H,H}$ = 7.3, 7.9 Hz, 4 H, *m*-$C_6H_5$) ppm. $^{13}C\{^1H\}$ NMR ($CD_3OD$, 125.7 MHz, 298 K): $\delta$ = 24.5 (s, $H_2NCH_2CH_2CH_2CH_2CH_2COH$), 28.2 (s, $H_2NCH_2CH_2CH_2CH_2CH_2COH$), 28.4 (s, $H_2NCH_2CH_2CH_2CH_2CH_2COH$), 35.6 (s, $H_2NCH_2CH_2CH_2CH_2CH_2COH$), 40.8 (s, $H_2NCH_2CH_2CH_2CH_2CH_2COH$), 75.6 (t, $J_{C,P}$ = 155.6 Hz, $H_2NCH_2CH_2CH_2CH_2CH_2COH$), 122.2 (s, *o*-$C_6H_5$), 125.9 (s, *p*-$C_6H_5$), 130.7 (s, *m*-$C_6H_5$), 152.5 (s, $OC_6H_5$) ppm. $^{31}P\{^1H\}$ NMR ($CD_3OD$, 202.4 MHz, 298 K): $\delta$ = 18.1 (s) ppm. LC-MS (ES+): 6.45 min, *m*/*z* = 430.1 [$M^+$ + H].

**[4-Amino-1-(dimethoxyphosphoryl)-1-hydroxybutyl]phosphonic Acid (23):** The crude product was dissolved in water and dialysed using a Spectrapor 100 membrane. Lyophilisation gave a white powder. Yield 900 mg (65%). M.p. 61 °C. IR (KBr): $\tilde{\nu}$ = 3419, 3301, 3053, 1616, 1559, 1540, 1506, 1458, 1182, 1084, 953, 688, 543 $cm^{-1}$. $^1H$ NMR ($D_2O$, 200 MHz, 298 K): $\delta$ = 1.72–1.93 (m, 4 H, $H_2NCH_2CH_2CH_2COH$), 2.86 (t, $^3J_{H,H}$ = 6.8 Hz, 2 H, $H_2NCH_2CH_2CH_2COH$), 3.68 (d, $^3J_{P,H}$ = 10.6 Hz, 6 H, $OCH_3$) ppm. $^{13}C\{^1H\}$ NMR ($D_2O$, 50.3 MHz, 298 K): $\delta$ = 22.3 (s, $H_2NCH_2CH_2CH_2COH$), 31.3 (s, $H_2NCH_2CH_2CH_2COH$), 40.3 (s, $H_2NCH_2CH_2CH_2COH$), 53.3 (s, $OCH_3$), 74.1 (dd, $J_{C,P}$ = 140.4, 140.5 Hz, $H_2NCH_2CH_2CH_2COH$) ppm. $^{31}P\{^1H\}$ NMR ($D_2O$, 80.9 MHz, 298 K): $\delta$ = 13.1 [$^2J_{P,P}$ = 28.6 Hz, $P(O)(OCH_3)_2$], 27.8 [d, $^2J_{P,P}$ = 28.6 Hz, $P(O)(OH)_2$] ppm.

**Monomethyl [4-Amino-1-(dimethoxyphosphoryl)-1-hydroxybutyl]-phosphonate (24):** The crude product was dissolved in water and dialysed using a Spectrapor 100 membrane. Lyophilisation gave a white powder. Yield 990 mg (68%). M.p. 138 °C. IR (KBr): $\tilde{\nu}$ = 3419, 3319, 3034, 3963, 1616, 1483, 1401, 1220, 1185, 1087, 962, 543, 451 $cm^{-1}$. $^1H$ NMR ($D_2O$, 500 MHz, 298 K): $\delta$ = 1.72–1.90 (m, 4 H, $H_2NCH_2CH_2CH_2COH$), 2.79–2.85 (m, 2 H, $H_2NCH_2CH_2CH_2COH$), 3.53 (d, $^3J_{P,H}$ = 10.4 Hz, 3 H, $OCH_3$), 3.64 (d, $^3J_{P,H}$ = 10.9 Hz, 6 H, $OCH_3$) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 120.7 MHz, 298 K): $\delta$ = 22.6 (s, $H_2NCH_2CH_2CH_2COH$), 31.9 (s, $H_2NCH_2CH_2CH_2COH$), 40.8 (s, $H_2NCH_2CH_2CH_2COH$), 54.6 (s, $OCH_3$), 55.7 (s, $2\times OCH_3$), 75.0 (t, $J_{C,P}$ = 152.9 Hz, $H_2NCH_2CH_2CH_2COH$) ppm. $^{31}P\{^1H\}$ NMR ($D_2O$, 202.4 MHz, 298 K): $\delta$ = 18.0 [$^2J_{P,P}$ = 31.7 Hz, $P(O)(OCH_3)_2$], 25.2 [d, $^2J_{P,P}$ = 31.7 Hz, $P(O)(OH)(OCH_3)$] ppm. MS (ES+): *m*/*z* = 292.0 [$M^+$ + H].

**[4-Amino-1-hydroxy-1-(hydroxy-methoxy-phosphoryl)butyl]phosphonic Acid (25):** The crude product was dissolved in water and dialysed using a Spectrapor 100 membrane. Lyophilisation gave a white powder. Yield 855 mg (65%). M.p. 88 °C. IR (KBr): $\tilde{\nu}$ = 3409, 3244, 3041, 2589, 1604, 1497, 1410, 1237, 1184, 1084, 1052, 947, 905, 766, 540, 494 $cm^{-1}$. $^1H$ NMR ($D_2O$, 200 MHz, 298 K): $\delta$ = 1.71–1.97 (m, 4 H, $H_2NCH_2CH_2CH_2COH$), 2.84–2.92 (m, 2 H, $H_2NCH_2CH_2CH_2COH$), 3.58 (d, $^3J_{P,H}$ = 9.8 Hz, , 3 H $OCH_3$) ppm. $^{13}C\{^1H\}$ NMR ($D_2O$, 50.3 MHz, 298 K): $\delta$ = 20.9 (t, $^4J_{P,C}$ = 6.8 Hz, $H_2NCH_2CH_2CH_2COH$), 29.9 (s, $H_2NCH_2CH_2CH_2COH$), 38.8 (s, $H_2NCH_2CH_2CH_2COH$), 51.4 (s, $OCH_3$), 73.0 (dd, $J_{C,P}$ = 139.4 Hz, $J_{C,P}$ = 139.4 Hz, $H_2NCH_2CH_2CH_2COH$) ppm. $^{31}P\{^1H\}$ NMR ($D_2O$, 80.96 MHz, 298 K): $\delta$ = 20.0 [s large, $P(O)(OCH_3)OH$ and $P(O)(OH)_2$] ppm. MS (ES-): *m*/*z* = 261.7 [$M^-$ – H].

**[4-Amino-1-hydroxy-1-(hydroxy-phenoxy-phosphoryl)butyl]phosphonic Acid (26):** The crude product was dissolved in water and dialysed using a Spectrapor 100 membrane. Lyophilisation gave a white powder. Yield 927 mg (57%). M.p. 86 °C. IR (KBr): $\tilde{\nu}$ = 3409, 3245, 3141, 3036, 2585, 1663, 1592, 1492, 1401, 1213, 1084, 1024, 992, 965, 922, 827, 770, 693, 503 $cm^{-1}$. $^1H$ NMR ($D_2O$, 500 MHz, 298 K): $\delta$ = 1.91–2.11 (m, 4 H, $H_2NCH_2CH_2CH_2COH$), 3.30–3.42 (m, 2 H, $H_2NCH_2CH_2CH_2COH$), 6.92–7.10 (m, 1 H, *p*-$C_6H_5$), 7.09–7.23 (m, 2 H, *o*-$C_6H_5$), 7.32–7.56 (m, 2 H, *m*-$C_6H_5$) ppm. $^{13}C\{^1H\}$ NMR ([$D_6$]DMSO, 125.7 MHz, 298 K): $\delta$ = 22.0 (s, $H_2NCH_2CH_2CH_2COH$), 30.5 (s, $H_2NCH_2CH_2CH_2COH$), 38.9 (s, $H_2NCH_2CH_2CH_2COH$), 73.0 (t, $J_{C,P}$ = 141.7 Hz, $H_2NCH_2CH_2CH_2COH$), 120.9 (s, *o*-$C_6H_5$), 125.2 (s, *p*-$C_6H_5$), 129.1 (s, *m*-$C_6H_5$), 152.3 (s, $OC_6H_5$) ppm. $^{31}P\{^1H\}$ NMR ($D_2O$, 202.4 MHz, 298 K): $\delta$ = 23.3–22.7 [m, $P(O)(OH)_2$], 21.9–21.3 [m, $P(O)(OC_6H_5)OH$] ppm. LC-MS (ES+): 6.51 min, *m*/*z* = 326.0 [$M^+$ + H].

**Supporting Information** (see also the footnote on the first page of this article): NMR spectra for most of the new products and mass

  

spectra (with HPLC traces when LC-MS was done) for the final esterified pamidronate, alendronate and neridronate derivatives.

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[1] J. R. Green, *J. Organomet. Chem.* **2005**, *690*, 2439 (16th International Conference on Phosphorus Chemistry).
[2] L. Widler, K. A. Jaeggi, M. Glatt, K. Muller, R. Bachmann, M. Bisping, A. R. Born, R. Cortesi, G. Guiglia, H. Jeker, R. Klein, U. Ramseier, J. Schmid, G. Schreiber, Y. Seltenmeyer, J. R. Green, *J. Med. Chem.* **2002**, *45*, 3721.
[3] D. Heymann, B. Ory, F. Gouin, J. R. Green, F. Redini, *Trends Mol. Med.* **2004**, *10*, 337.
[4] J. R. Green, *Cancer* **2003**, *97*, 840.
[5] M. B. Martin, J. S. Grimley, J. C. Lewis, H. T. Heath III, B. N. Bailey, H. Kendrick, V. Yardley, A. Caldera, R. Lira, J. A. Urbina, S. N. Moreno, R. Docampo, S. L. Croft, E. Oldfield, *J. Med. Chem.* **2001**, *44*, 909.
[6] J. M. Sanders, A. O. Gomez, J. Mao, G. A. Meints, E. M. Van Brussel, A. Burzynska, P. Kafarski, D. Gonzalez-Pacanowska, E. Oldfield, *J. Med. Chem.* **2003**, *46*, 5171.
[7] P. P. Lehenkari, M. Kellinsalmi, J. P. Napankangas, K. V. Ylitalo, J. Monkkonen, M. J. Rogers, A. Azhayev, H. K. Vaananen, I. E. Hassinen, *Mol. Pharmacol.* **2002**, *61*, 1255.
[8] H. Monkkonen, S. Auriola, P. Lehenkari, M. Kellinsalmi, I. E. Hassinen, J. Vepsalainen, J. Monkkonen, *Br. J. Pharmacol.* **2006**, *147*, 437.
[9] A. Montalvetti, B. N. Bailey, M. B. Martin, G. W. Severin, E. Oldfield, R. Docampo, *J. Biol. Chem.* **2001**, *276*, 33930.
[10] F. Yin, R. Cao, A. Goddard, Y. Zhang, E. Oldfield, *J. Am. Chem. Soc.* **2006**, *128*, 3524.
[11] A. Ezra, G. Golomb, *Adv. Drug Deliv. Rev.* **2000**, *42*, 175.
[12] P. A. Turhanen, M. J. Ahlgren, T. Jarvinen, J. J. Vepsalainen, *Synthesis* **2001**, *4*, 633.
[13] P. Vachal, J. J. Hale, Z. Lu, E. C. Streckfuss, S. G. Mills, M. MacCoss, D. H. Yin, K. Algayer, K. Manser, F. Kesioglou, S. Ghosh, L. L. Alani, *J. Med. Chem.* **2006**, *49*, 3060.
[14] D. J. Hosfield, Y. Zhang, D. R. Dougan, A. Broun, L. W. Tari, R. V. Swanson, J. Finn, *J. Biol. Chem.* **2004**, *279*, 8526.
[15] J. P. Krise, V. J. Stella, *Adv. Drug Deliv. Rev.* **1996**, *19*, 287.
[16] G. R. Kieczykowski, R. B. Jobson, D. G. Melillo, D. F. Reinhold, V. J. Grenda, I. Shinkai, *J. Org. Chem.* **1995**, *60*, 8310.
[17] M. Lecouvey, I. Mallard, T. Bailly, R. Burgada, Y. Leroux, *Tetrahedron Lett.* **2001**, *42*, 8475.
[18] M. Lecouvey, Y. Leroux, M. Kraemer, M. Crepin, D. el Manouni, M. Louriki, WO 03/008425, **2003**.
[19] E. Migianu, I. Mallard, N. Bouchemal, M. Lecouvey, *Tetrahedron Lett.* **2004**, *45*, 4511.
[20] E. Migianu, E. Guénin, M. Lecouvey, *Synlett* **2005**, *5*, 0425.
[21] M. Monteil, E. Guenin, E. Migianu, D. Lutomski, M. Lecouvey, *Tetrahedron* **2005**, *61*, 7528.
[22] A. M. Gibson, M. Mendizabal, S. P. Pullan, D. V. Griffiths, P. Duncanson, US 6,534,488 B1, **2003**.
[23] A. Giovannini, D. Savoia, A. Umani-Ronchi, *J. Org. Chem.* **1989**, *54*, 228.
[24] D. El Manouni, Y. Leroux, R. Burgada, *Phosphorus Sulfur Silicon* **1989**, *42*, 73.
[25] D. V. Griffiths, J. M. Hughes, J. W. Brown, J. C. Caesar, S. P. Swetnam, S. A. Cumming, J. D. Kelly, *Tetrahedron* **1997**, *53*, 17815.
[26] H. Gali, K. R. Prabhu, S. R. Karra, K. V. Katti, *J. Org. Chem.* **2000**, *65*, 676.
[27] M. Niyaz Khan, *J. Org. Chem.* **1996**, *61*, 8063.
[28] S. J. Fitch, K. Moedritzer, *J. Am. Chem. Soc.* **1962**, *84*, 1876.
[29] Z. Otwinowski, W. Minor, *Meth. Enzymol.* **1997**, 306.
[30] G. M. Sheldrick, *SHELXL, a program for crystal structure refinements*, University of Göttingen, Germany, **1997**.
[31] M. Bodanszky, A. Bodanszky, *The Practice of Peptide Synthesis*, Springer-Verlag, New York, **1984**.

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