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Linear and Convergent Syntheses of Bifunctional Hydroxy-Bisphosphonic Compounds as Potential Bone-Targeting Prodrugs

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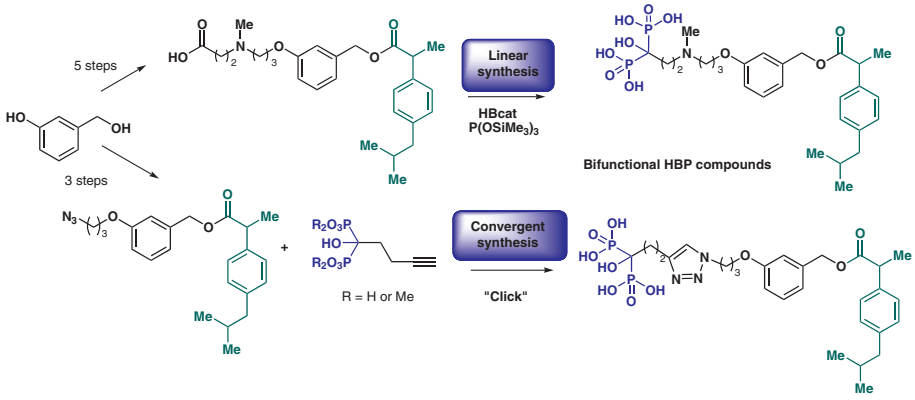
This article is dedicated to the memory of our colleague and friend Dr. Marc Padrines.



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Abstract The synthesis of two bifunctional compounds bearing a terminal hydroxy-bisphosphonic function (HBP) was achieved following a linear and a convergent strategy. In the linear approach, the free hydroxy-bisphosphonic function was introduced in the last step of the synthesis, under neutral conditions using an Arbuzov reaction with tris(trimethylsilyl) phosphite and a carboxylic acid precursor activated in situ with catecholborane. In the convergent approach, Huisgen type cycloaddition was studied starting from an HBP-functionalized alkyne partner to obtain the targeted bifunctional molecule. These complementary approaches allow for the preparation of complex bone-targeting molecules as potential prodrug candidates.

Key words bisphosphonate, Arbuzov reaction, click reaction, bifunctional derivatives, prodrug

The bone tissue differs from other tissues in that it mainly contains a mineral phase, the hydroxyapatite, an inorganic calcium phosphate compound.[1] Because a limited number of molecules exhibits a strong affinity to bone, osteotropic drug delivery systems (ODDS),[2] based upon the development of bioconjugates bearing bone-seeking functions such as the bisphosphonic acid (BP) or the hydroxybisphosphonic acid (HBP) function, have been proposed.[3] Since the 1990s various approaches to combine anticancer, antibacterial, anti-osteoporotic, and anti-inflammatory agents with BP moieties have been reported in the literature.[4] This is illustrated with the *gem*-bisphosphonic conjugate of methotrexate **A**[5] and diclofenac **B**[6] or with more complex delivery systems of antibacterial or anticancer agents such as the BP prodrug of gatifloxacin **C**[7] or the BP prodrug of doxorubicin **D**,[8] respectively (Figure 1). These *gem*-bisphosphonic acid bioconjugates or prodrugs were generally obtained by deprotection of the corresponding tetraalkylphosphonate esters in the last step of the synthesis. These tetraalkylphosphonate precursors were prepared by coupling a carboxylic or an aminophosphonate[9] fragment with the drug (Figure 1, compounds **A** to **C**), or involving the tetraethyl ethylidene-1,1′-bisphosphonate, which is a good Michael acceptor[10] (Figure 1, compound **D**). Similar strategies were also extensively developed for protein delivery to bone.[11]

Taking into account the better bone-seeking ability of the hydroxy-bisphosphonic function (HBP) compared to the bisphosphonic (BP) one, and the wide use of HBP compounds for the treatment of diseases such as osteoporosis,[12] hydroxy-bisphosphonic conjugates have also been proposed as drug or model drug delivery systems to bone.[13] Some non-cleavable HBP conjugates such as HBP-analogue of melphalan **E**,[14] or HBP-derived 5-fluorouracil **F**,[15] were prepared but did not show obvious activity (Figure 2). The HBP compounds could be prepared starting from a carboxylic acid precursor in harsh acidic conditions ($PCl_3/H_3PO_3/MeSO_3H$ at 65 °C)[16a] or from an acyl chloride precursor, to give the expected hydroxy-bisphosphonic tetraester in a two-step procedure. A first Michaelis–Arbuzov reaction with trialkyl phosphite afforded the α-ketophosphonate, which reacted in a second step with the dialkyl phosphite, to give the expected hydroxy-bisphosphonate tetraester. However, this hydroxy-bisphosphonate compound showed some tendency to rearrange to the corresponding phosphate-phosphonate, depending on the reaction conditions.[16c,d] Moreover, the acidic hydrolysis or the dealkylation by halogeno trimethylsilane of the phosphonate functions may be incompatible with sensitive functional groups in the molecule. In the last years, several laboratories have elaborated complex bioconjugated HBPs with the 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid (alendronate), a well-known anti-osteoporotic agent, introduced as the HBP fragment.[17] The terminal-free amino function of alendronate appeared suitable to introduce the HBP frag-

ment by simple nucleophilic substitution under mild conditions, and gave a chemically and biologically stable amide or carbamate linkage. This amino HBP fragment could be linked to a spacer bearing the drug, and which was also effective as a chemical-gate, as for example the biologically sensitive 4-alkoxyphenylacetate-linker in compound **G**,[18] or the acid sensitive hydrazone-linker present in compound **H**[19] (Figure 2). This strategy was also extended to HBP-biopolymers[20] and HBP nanoscale particles.[21]

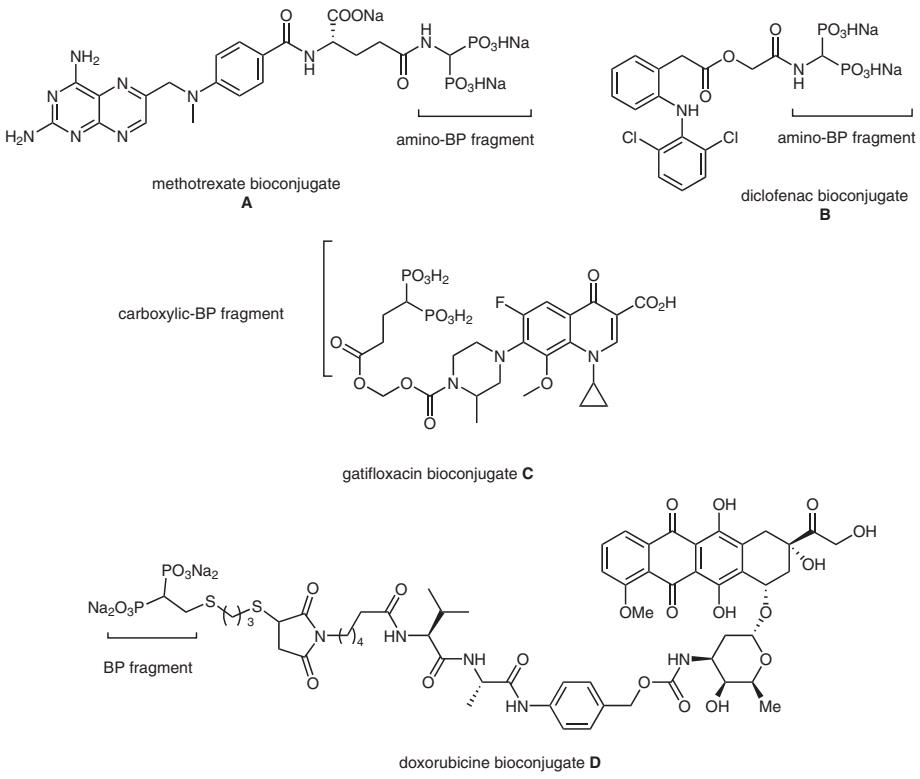


Figure 1 BP bioconjugates of known drugs (BP fragment involved in the synthesis)

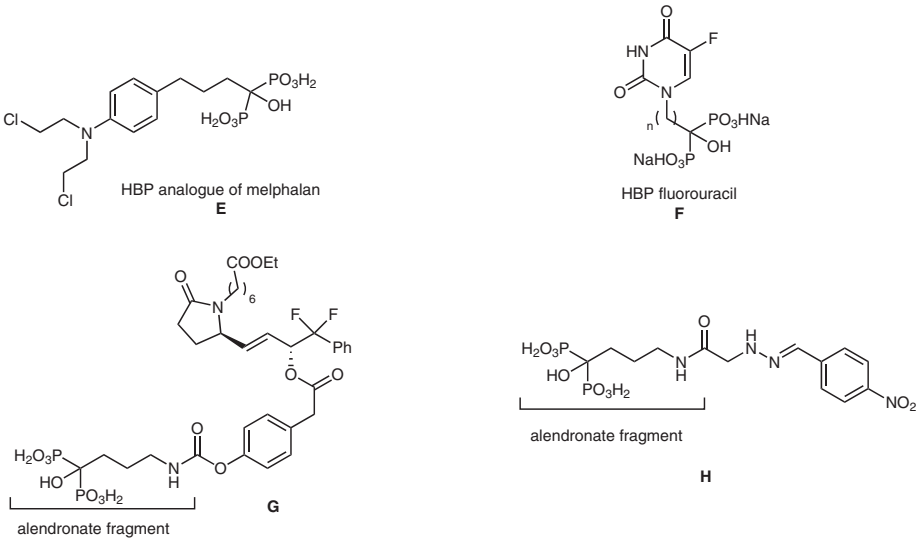


Figure 2 Some examples of HBP bioconjugates (HBP fragment involved in the synthesis)

In this study, we propose novel linear and convergent strategies to prepare nitrogen containing hydroxyl-bisphosphonate prodrugs with potential dual biological effects that include an antiresorptive activity. The synthetic challenge was to avoid the preparation of the hydroxy-bisphosphonate ester intermediates and to access the expected hydroxy-bisphosphonic compounds under mild conditions.

Owing to the fact that promising biological results were obtained with an anti-inflammatory prodrug such as BP conjugated diclofenac **B** (Figure 1),[6a] we first selected a non-steroidal anti-inflammatory agent such as ibuprofen, which could therefore be linked to our HBP-spacers with ester formation (Figure 3, compounds **1** to **3**). The HBP-linker was based on interesting structures reported earlier by Novartis as potent antiresorptive compounds.[22] Particularly the 1-hydroxy-(3-phenoxypropylamino)propylidene-1,1-bisphosphonate (Figure 3, compound **I**) revealed potency-enhancing effect compared to the dimethylamino analogue olpadronate **J**, probably due to the addition of a terminal phenyl group associated with the presence of the tertiary amine function. By combining ibuprofen with such (phenoxypropylamino)propylidene HBP fragment, as depicted in prodrug **2** (Figure 3), a dual anti-inflammatory–antiresorptive effect could therefore be expected. It is also to be noted that similar hydrosoluble prodrugs were recently claimed as effective bone-seekers with in vivo activity.[23]

To validate our linear strategy, we first prepared the ibuprofen HBP prodrug without nitrogen containing linker (Scheme 1). The commercially available 3-hydroxybenzaldehyde was first reduced with $NaBH_4$ to give quantitatively the corresponding benzylic alcohol **4**. All attempts to couple the ibuprofen with the benzylic alcohol **4** in the presence of coupling reagents such as dicyclohexylcarbodiimide (DCC) in the presence of *N*,*N*-dimethylaminopyridine (DMAP) systematically afforded a mixture of esters as the result of the acylation of the primary alcohol and the phenol functions. The phenol function was then blocked first by simple alkylation with the 5-bromo-1-pentene, under Williamson's conditions (K_2CO_3, DMF). A moderate yield (55%) of the expected ether **5** was obtained in DMF, but the yield could be increased up to 78% in a mixture of acetonitrile/water (5:1), at 75 °C. The terminal alkene in **5** appeared for us as a suitable masked function, to later introduce the carboxylic acid function required for the HBP formation. In this way, this O-protected compound **5** was esterified with ibuprofen using DCC and a catalytic amount of DMAP to afford compound **6** in good yield. The next steps consisted in an oxidative cleavage of the terminal alkene function with ozone to generate the aldehyde **7**, followed by an oxidation of the aldehyde under mild Pinnick conditions,[24] to give the carboxylic acid **8** in 66% yield over the two steps.

To access to the targeted molecule **1**, we tried Lecouvey's method,[25] which involved the activation of the carboxylic acid as the corresponding acyl chloride, followed by Arbuzov reaction with 2.5 equivalents of the nucleophilic tris(trimethylsilyl) phosphite [$P(OSiMe_3)_3$]. This sequence applied to compound **8** delivered after methanolysis, the expected hydroxy-bisphosphonic acid **1**, with some amount of the methyl ester of **8**, together with phosphorous acid by-products. Purification of **1** could then be achieved by precipitation in a mixture of Et_2O/petroleum ether, to give the expected HBP prodrug **1**, in 62% yield. Alternatively, the one-pot procedure developed in our laboratory[26] allowed us to obtain HBP compound **1**, in one-pot and 64% yield after reversed-phase chromatography purification, from the carboxylic acid **8** via the acyloxydioxaborolane intermediate.

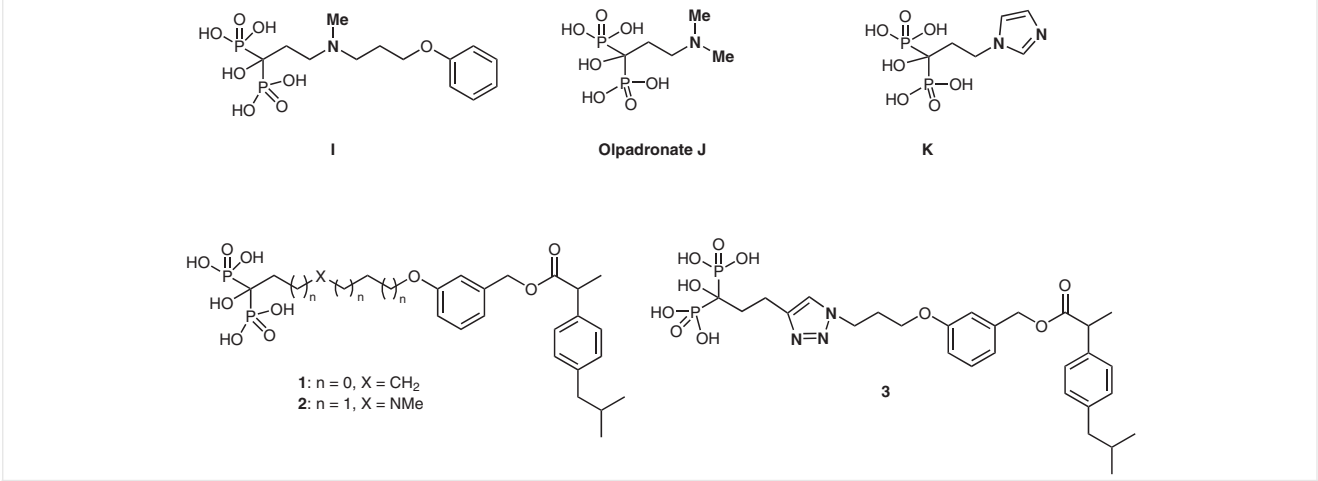
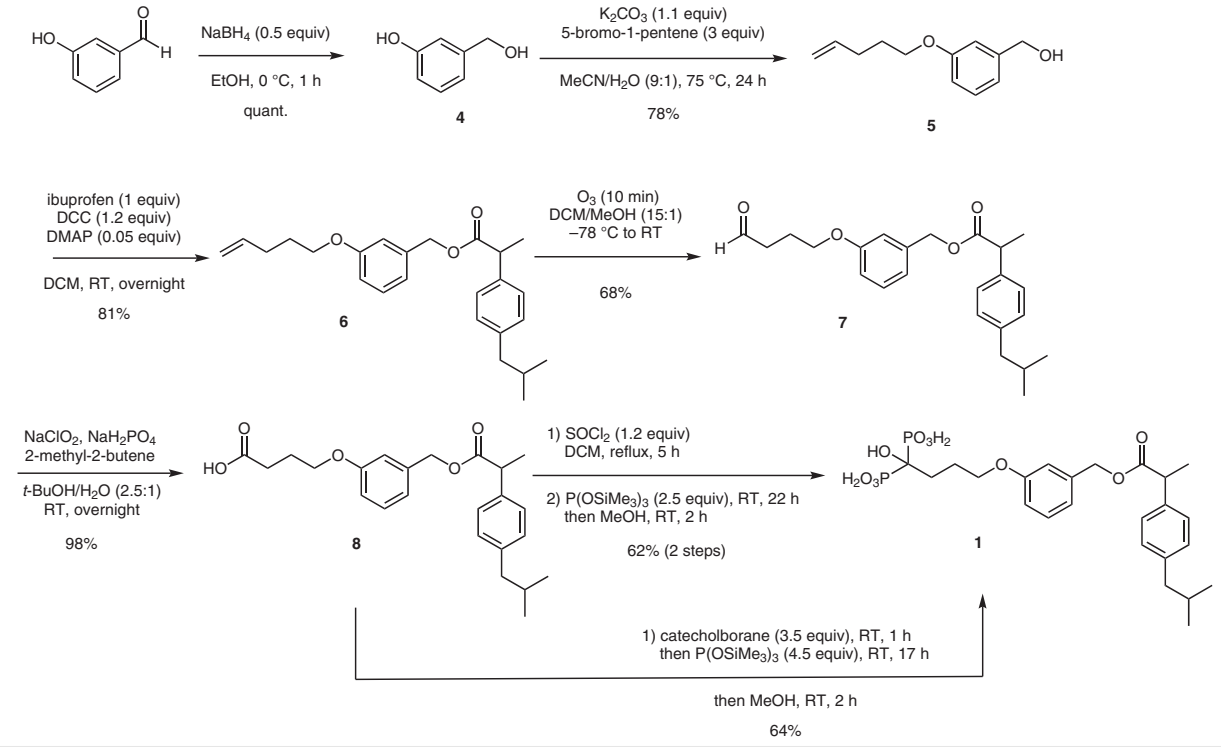


Figure 3 Potent antiresorptive compounds **I–K** [**I** : ED_{50} = 0.5 µg/kg; **J** (olpadronate) ED_{50} = 12 µg/kg, **K** : ED_{50} = 45 µg/kg][22] and the three targeted ibuprofen HBP prodrugs **1–3**



Scheme 1 Synthetic linear pathway to prepare the free HBP compound **1**

We then turned to the preparation of the ibuprofen HBP prodrug **2**, with a tertiary amine containing linker, according to a close linear strategy (Scheme 2).

Benzylic alcohol **4** was mono-alkylated with an excess of 1,3-dibromopropane to avoid dimer formation. Compound **9** thus obtained was engaged in the esterification reaction with ibuprofen to give **10**, followed by a nucleophilic substitution with methylamine to furnish the amino ester **11** in 45% yield over the two steps. We first tried to access the carboxylic acid **13** directly by simple Michael addition of the secondary amine **11** onto acrylic acid (2 equiv) in MeOH and in the presence of the Hünig base (2 equiv). We observed more than 80% conversion, however excess of acrylic acid always poisoned the expected compound **13** after purification. To circumvent this problem *tert*-butyl acrylate was chosen as the Michael acceptor. Diester **12** was then gently deprotected in anhydrous acidic conditions to give the carboxylic acid **13** in 68% yield (2 steps). As we did for the preparation of the HBP-ibuprofen prodrug **1**, we tried to prepare the HBP **2** from the corresponding amino acid **13**, using Lecouvey's method without success. Gratifyingly, with our one-pot procedure, HBP-prodrug **2** could be obtained with some residual phosphorous acid after simple purification by successive precipitations with selected solvents (37% yield), or in a pure form after reversed-phase chromatography purification (45% yield). During the reaction, the excess of catecholborane probably blocked the basic amine by complexation, as observed previously with simpler amino acid compounds,[26] thus avoiding side reactions (Scheme 2).

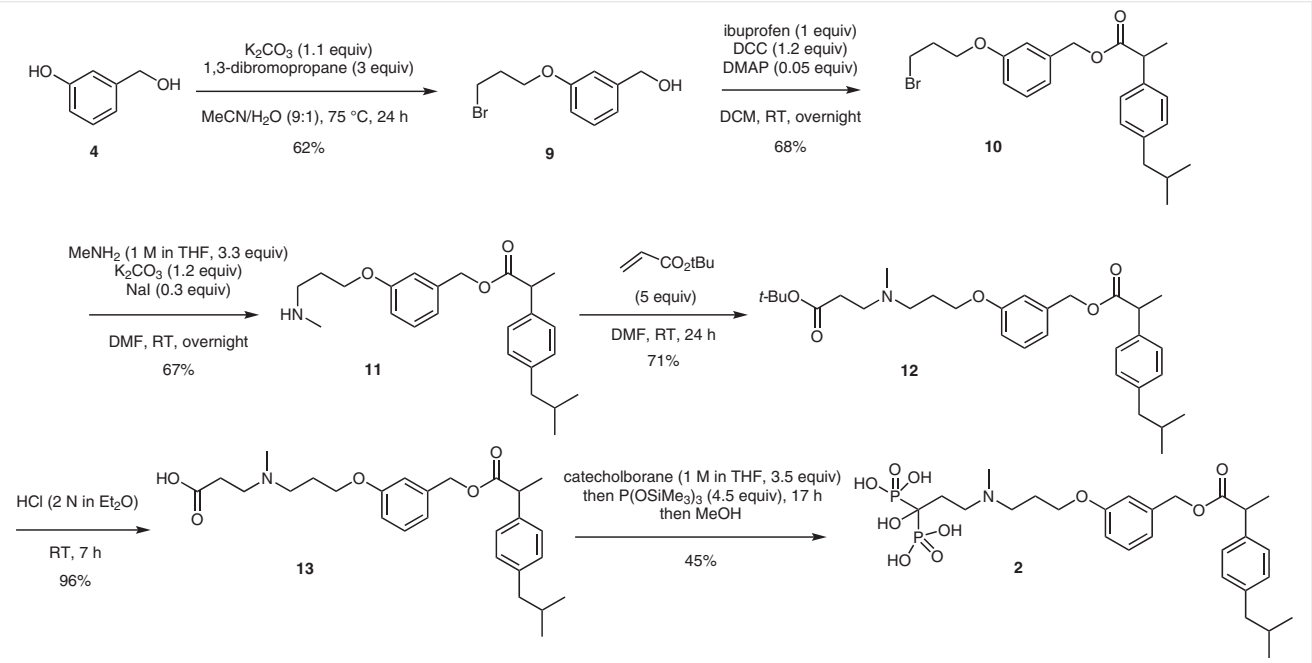
To open the route to a more straightforward approach to prepare similar HBP prodrugs, we explored a convergent strategy, based upon Huisgen 1,3-dipolar cycloaddition and access so to the compound **3** (Figure 3). Indeed, it was shown by Novartis group that the replacement of the basic tertiary nitrogen of the olpadronate **J** by the nitrogen of a heteroaromatic ring system such as in compound **K**, gave analogues with quite similar activity (Figure 3).[22] We therefore supposed that a 1,4-disubstituted-1,2,3-triazole analogue of compound **2**, such as compound **3** could also be designed as a promising antiresorptive and anti-inflammatory prodrug.

According to the literature data there are still only very few examples of Huisgen 1,3-dipolar cycloaddition involving an alkyne as well as an azide bearing functions such as hydroxy-bisphosphonic esters[27] or hydroxy-bisphosphonic acids.[28] So we first explored the click reaction between azide **16** and free HBP alkyne substrate **15**. Because no reaction occurred between **16** and **15** in simple thermal conditions using acetonitrile as the solvent, and observing a degradation of the alkyne **15** in solution, the corresponding sodium salt was prepared.[28a] We then moved to reaction

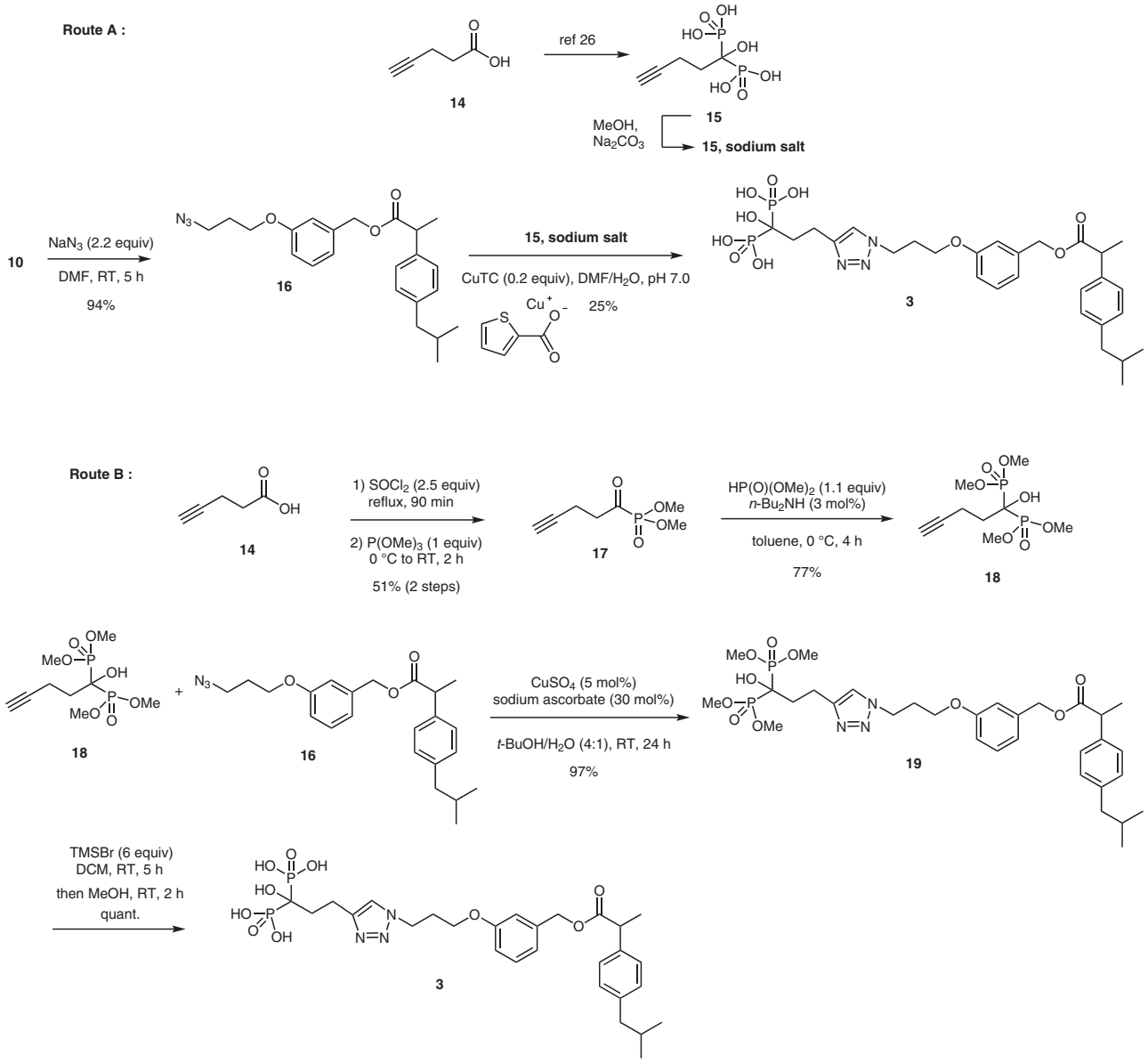
conditions inspired from those reported by Guénin and collaborators,[28a] and carried out the cycloaddition with $CuSO_4$ in a mixture of DMF/water, instead of *t*-BuOH/water, due to poor solubility of compound **16**.[29] After 48 hours at room temperature, some conversion occurred, but the expected compound **3** seemed to be copper complexed[30] and no clear resolved ^{1}H NMR analysis could be obtained. However, the formation of some HBP derivative **3** was confirmed by mass spectrometry analysis. The copper(I) thiophene-2-carboxylate (CuTC) was then tested, which was previously identified as a good Cu(I) catalyst in difficult CuAAC reactions.[31] To the best of our knowledge, this copper salt has never been tested with HBP substrates. In similar reaction conditions, the compound **3** was obtained in low yield, after successive precipitations in a mixture of methanol/diethyl ether (Scheme 3, Route A), and recovering also a large part of the azide starting material **16**. We suspected that this specific pentynyl-HBP substrate **15** underwent side reaction such as intramolecular P–OH addition into alkyne in the presence of Cu(I).[32] Undesirable side reactions were also observed by Mindt and collaborators with the 4-pentynoic acid, which mainly gave enol lactone in similar aqueous click reaction conditions.[33] So we turned to the preparation of the targeted compound **3** from the alkynyl tetramethylphosphonate **18** and azide **16** (Scheme 3, Route B).

The compound **18** was prepared in three steps starting from commercially available 4-pentynoic acid (**14**). The latter was activated as its acyl chloride form before being engaged in an Arbuzov reaction with $P(OMe)_3$ to furnish acylphosphonate **17** in 51% yield. As recently published by Turhanen,[27a] reaction of **17** with dimethyl phosphite under neat conditions always afforded a mixture of the expected compound **18** in ca. 30% yield due to the partial formation of the corresponding phosphate-phosphonate. We did the reaction in toluene at 0 °C, and in the presence of a catalytic amount of *n*-Bu_2NH.[16c] The expected compound **18** precipitated out during the reaction and it could be obtained pure by simple filtration in 77% yield. Then, 1,3-dipolar cycloaddition between **16** and **18** in classical conditions of click chemistry gave triazole derivative **19** in 97% yield. The prodrug **3** was finally obtained by simple dealkylation with TMSBr, followed by methanolysis and isolated pure in a quantitative yield after removal of the volatiles.

In summary, we have proposed two complementary (linear and convergent) strategies towards the synthesis of bifunctional compounds bearing a bone-targeting hydroxybisphosphonic function. In the linear approach, we have shown that the hydroxy-bisphosphonic function could be introduced in the last step of the synthesis in mild conditions, from the carboxylic acid precursor, using catecholborane as a neutral activating agent. In the convergent approach, the CuAAC step starting with free hydroxy-bisphosphonic alkyne as the substrate was not satisfying compared to the same approach conducted on the corresponding hydroxybisphosphonate tetraester. Both strategies could be applied to selected drugs bearing a carboxylic acid function for the anchorage to the HBP-linker. Moreover, the cleavable ester bond and the specific structure of the HBP linker for



Scheme 2 Synthetic linear pathway to prepare the free HBP compound **2**



Scheme 3 Convergent routes to prepare HBP prodrug **3** with triazole ring containing linker starting with hydroxybisphosphate **15** (Route A) or tetramethyl hydroxybisphosphonate **18** (Route B)

the compounds designed in this study, could be in favor of a putative dual antiresorptive and anti-inflammatory activity.

All solvents used were reagent grade and TLC was performed on silica-covered aluminum sheets (Kieselgel 60F254, MERCK). Eluted TLC was revealed using UV radiation (λ = 254 nm), or molybdate solution. Flash chromatography was performed on silica gel (60 ACC 40–63 µm, SDS-CarloErba) and low pressure chromatography column on C18 reversed-phase (FlashPure cartridge 40 µM Büchi). Melting points were determined on a Stuart Scientific apparatus 7SMP3. IR spectra were recorded on a Bruker Vector 22 spectrometer. NMR spectra were recorded on a Bruker AC 300 (300 MHz for ^{1}H) or on a Bruker 400 (400 MHz for ^{1}H) at RT, on samples dissolved in an appropriate deuterated solvent. Used references were TMS for ^{1}H NMR, deuterated solvent signal for ^{13}C NMR and 85% aq H_3PO_4 for ^{31}P NMR. Chemical displacement values (δ) are expressed in parts per million (ppm), and coupling constants (*J*) in hertz (Hz). Low-resolution mass spectra (MS) were recorded in the CEISAM laboratory on a Thermo-Finnigan DSQII quadripolar at 70 eV (CI with NH_3 gas). High-resolution mass spectrometry (HRMS in Da unit) analyses were recorded on an LC-Q-TOF (Synapt-G2 HDMS, Waters) in the IRS-UN center (Mass Spectrometry platform, Nantes) or on a MALDI-TOF-TOF apparatus (Autoflex III from Bruker) in the INRA center (BIBS platform, Nantes).

3-Hydroxybenzyl Alcohol (4)[34]

To a solution of the commercial 3-hydroxybenzaldehyde (5 g, 40.94 mmol) in EtOH (25 mL) was cautiously added $NaBH_4$ (774 mg, 20.47 mmol) in small portions at 0 °C under argon. The mixture was stirred at 0 °C for 1 h. Aq 2 N HCl was then added stepwise until pH 3. After stirring for 10 min, sat. aq $NaHCO_3$ was added to obtain a neutral solution (pH 7). The organic phase was dried (anhyd Na_2SO_4), filtered, and concentrated under reduced pressure to afford pure **4** (5.06 g, quant.) as a viscous brown oil, which crystallized at 0 °C.

^{1}H NMR (300 MHz, MeOD): δ = 7.14 (t, *J* = 7.8 Hz, 1 H_{arom}), 6.82–6.80 (m, 2 H_{arom}), 6.70 (dd, *J* = 7.3, 1.9 Hz, 1 H_{arom}), 4.53 (s, 2 H, CH_2).

^{13}C NMR (75 MHz, MeOD): δ = 158.3, 144.1, 130.3, 119.1, 115.1, 114.7, 65.1.

MS (CI): *m*/*z* = 142 $[M + NH_4]^{+\cdot}$

[3-(Pent-4-enyloxy)phenyl]methanol (5)

To a solution of **4** (250 mg, 2.01 mmol) in a mixture of MeCN/H_2O (1.5 mL, 9:1) at room temperature was added K_2CO_3 (305 mg, 2.21 mmol). After 10 min, 5-bromo-1-pentene (715 µL, 6.03 mmol) was added and the reaction mixture was heated at 75 °C during 24 h. After cooling to RT, Et_2O was added and the organic layer washed with brine (3 ×), dried (anhyd Na_2SO_4), filtered,and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (DCM) to give pure **5** (300 mg, 78%) as a colorless oil.

IR (film): 3345, 2936, 1641, 1602, 1585, 1449, 1264 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.25 (t, *J* = 8.1 Hz, 1 H_{arom}), 6.91–6.89 (m, 2 H_{arom}), 6.81 (dd, *J* = 8.2, 2.3 Hz, 1 H_{arom}), 5.85 (ddt, *J* = 17.0, 10.3, 6.7 Hz, 1 H, CH_2=C*H*), 5.10–4.98 (m, 2 H, CH_2=CH), 4.63 (s, 2 H, CH_2OH), 3.96 (t, *J* = 6.4 Hz, 2 H, CH_2OPh), 2.27–2.20 (m, 2 H, CH_2CH=CH_2), 1.97 (br s, 1 H, OH), 1.92–1.83 (m, 2 H, CH_2CH_2O).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.4, 142.6, 137.9, 129.7, 119.1, 115.3, 113.9, 113.0, 67.2, 65.3, 30.2, 28.5.

MS (ESI): *m*/*z* = 175 $[M + H - H_2O]^+$; 215 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{12}H_{16}O_2Na$: 215.1042; found: 215.1046.

3-(Pent-4-enyloxy)benzyl 2-(4-Isobutylphenyl)propanoate (6)

To a solution of DCC (300 mg, 1.45 mmol) in anhyd DCM (10 mL) at RT was added the commercial ibuprofen (250 mg, 1.21 mmol), followed by compound **5** (279 mg, 1.45 mmol) and DMAP (0.3 mL of a freshly prepared 0.2 M solution of DMAP in anhyd DCM, 0.06 mmol). After completion of the reaction as monitored by TLC, the organic layer was washed with H_2O (3 ×), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (PE/Et_2O, 98:2 to 90:10) to afford pure **6** (376 mg, 81%) as a colorless oil.

IR (film): 2953, 2932, 2868, 1736, 1603, 1586, 1452, 1267, 1160 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.22–7.17 (m, 3 H_{arom}), 7.10–7.07 (m, 2 H_{arom}), 6.82–6.78 (m, 3 H_{arom}), 5.85 (ddt, *J* = 17.1, 10.3, 6.6 Hz, 1 H, CH_2=C*H*), 5.11–4.98 [m, 4 H, CH_2=CH and CH_2OC(O)], 3.90 (t, *J* = 6.4 Hz, 2 H, CH_2O), 3.75 [q, *J* = 7.2 Hz, 1 H, CH_3C*H*C(O)], 2.44 [d, *J* = 7.2 Hz, 2 H, CH_2CH(CH_3)$_2$], 2.26–2.19 (m, 2 H, CH_2CH=CH_2), 1.90–1.77 [m, 3 H, CH_2CH_2O and C*H*(CH_3)$_2$], 1.51 [d, *J* = 7.2 Hz, 3 H, CH_3CHC(O)], 0.89 [d, *J* = 6.6 Hz, 6 H, CH(CH_3)$_2$].

^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.6, 159.3, 140.7, 137.9, 137.7 (2 C), 129.6, 129.4 (2 C), 127.3 (2 C), 119.9, 115.3, 114.3, 113.8, 67.2, 66.3, 45.3, 45.2, 30.3, 30.2, 28.5, 22.5 (2 C), 18.6.

MS (CI): *m*/*z* = 398 $[M + NH_4]^+$.

HRMS (MALDI, DHB, PEG 400): *m*/*z* $[M + Na]^+$ calcd for $C_{25}H_{32}O_3Na$: 403.2244; found: 403.2247.

3-(4-Oxobutoxy)benzyl 2-(4-Isobutylphenyl)propanoate (7)

A solution of **6** (369 mg, 0.97 mmol) in DCM/MeOH (50 mL, 15:1) at –78 °C, was stirred through an argon flow during 15 min. Then O_3 was bubbled into the solution until a blue color persisted. Me_2S (2.15 mL, 29.1 mmol) was added and the mixture was allowed to warm to RT overnight. After concentration in vacuo, the oil was dissolved in DCM and the organic layer was washed with brine (3 ×), dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (DCM to DCM/MeOH 95:5) to afford **7** (251 mg, 68%) as a colorless oil.

IR (film): 2954, 2931, 2724, 1732, 1603, 1586, 1453, 1267, 1160 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.81 (t, *J* = 1.1 Hz, 1 H, CHO), 7.24–7.16 (m, 3 H_{arom}), 7.10–7.07 (m, 2 H_{arom}), 6.80–6.75 (m, 3 H_{arom}), 5.06 [AB system, J_{AB} = 12.7 Hz, $\Delta\nu_{AB}$ = 15.4 Hz, 2 H, CH_2OC(O)], 3.92 (t, *J* = 6.0 Hz, 2 H, CH_2O), 3.75 [q, *J* = 7.2 Hz, 1 H, CH_3C*H*C(O)], 2.63 (td, *J* = 7.0, 1.1 Hz, 2 H, CH_2CHO), 2.44 [d, *J* = 7.2 Hz, 2 H, CH_2CH(CH_3)$_2$], 2.08 (qt, *J* = 6.5 Hz, 2 H, CH_2CH_2O), 1.84 [nonet, *J* = 6.8 Hz, 1 H, C*H*(CH_3)$_2$], 1.51 [d, *J* = 7.2 Hz, 3 H, CH_3CHC(O)], 0.89 [d, *J* = 6.6 Hz, 6 H, CH(CH_3)$_2$].

^{13}C NMR (75 MHz, $CDCl_3$): δ = 201.7, 174.5, 158.8, 140.6, 137.7 (2 C), 129.6, 129.4 (2 C), 127.3 (2 C), 120.1, 114.2, 113.6, 66.6, 66.1, 45.2, 45.1, 40.7, 30.2, 22.4 (2 C), 22.0, 18.5.

MS (CI): *m*/*z* = 400 $[M + NH_4]^+$.

HRMS (MALDI, DHB, PEG 400): *m*/*z* $[M + Na]^+$ $C_{24}H_{30}O_4Na$: 405.2036; found: 405.2039.

4-(3-{[2-(4-Isobutylphenyl)propanoyloxy]methyl}phenoxy)butanoic Acid (8)

To a solution of the aldehyde **7** (731 mg, 1.91 mmol) in *t*-BuOH (40 mL) was added 2-methyl-2-butene (9.5 mL, 89.77 mmol) at RT under an argon atmosphere. NaH_2PO_4 (1.6 g, 13.37 mmol) and $NaClO_2$ (1.94 g, 17.2 mmol) were dissolved in H_2O and introduced into the reaction mixture. After stirring overnight, sat. aq $NaHCO_3$ was added and the resulting mixture was extracted with Et_2O (3 ×). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (DCM to DCM/MeOH 95:5) to give pure **8** (745 mg, 98%) as a white solid; mp 49–52 °C.

IR (film): 3200, 2953, 2869, 1719, 1585, 1452, 1274, 1159, 1059 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.24–7.16 (m, 3 H_{arom}), 7.10–7.07 (m, 2 H_{arom}), 6.81–6.76 (m, 3 H_{arom}), 5.06 [AB system, J_{AB} = 12.7 Hz, $\Delta\nu_{AB}$ = 15.5 Hz, 2 H, CH_2OC(O)], 3.95 (t, *J* = 6.0 Hz, 2 H, CH_2O), 3.75 [q, *J* = 7.2 Hz, 1 H, CH_3C*H*C(O)], 2.57 (t, *J* = 7.2 Hz, 2 H, CH_2CO_2H), 2.44 [d, *J* = 7.2 Hz, 2 H, CH_2CH(CH_3)$_2$], 2.09 (qt, *J* = 6.7 Hz, 2 H, CH_2CH_2O), 1.84 [nonet, *J* = 6.7 Hz, 1 H, C*H*(CH_3)$_2$], 1.51 [d, *J* = 7.2 Hz, 3 H, CH_3CHC(O)], 0.89 [d, *J* = 6.6 Hz, 6 H, CH(CH_3)$_2$].

^{13}C NMR (75 MHz, $CDCl_3$): δ = 179.4, 174.7, 158.9, 140.7, 137.7 (2 C), 129.6, 129.4 (2 C), 127.3 (2C), 120.2, 114.3, 113.7, 66.5, 66.3, 45.2, 45.1, 30.6, 30.3, 24.4, 22.5 (2 C), 18.6.

MS (CI): *m*/*z* = 416 $[M + NH_4]^+$.

HRMS (MALDI, DHB, PEG 200): *m*/*z* $[M + Na]^+$ $C_{24}H_{30}O_5Na$: 421.1985; found: 421.1981.

1-Hydroxy-4-(3-{[2-(4-isobutylphenyl)propanoyloxy]methyl}phenoxy)butane-1,1-bis(phosphonic acid) (1)

A catecholborane solution (1 M solution in THF, 1.36 mL, 1.36 mmol) was added to neat carboxylic acid **8** (155 mg, 0.39 mmol) under an argon atmosphere at RT. The mixture was stirred for 1 h at RT until no more gas evolution. Then $P(OSiMe_3)_3$ (585 µL, 1.75 mmol) was added without solvent, and stirred for 16 h. MeOH (1.3 mL) was added, and after stirring for 1 h, the solvents were evaporated under reduced pressure. The crude product was taken up in DCM and a large amount of Et_2O was added to give an oil, which separated. It was purified by low pressure C18 reversed-phase chromatography (MeCN/MeOH, 100:0 to 70:30) to afford the pure compound **1** (170 mg, 64%) as an amorphous white solid. Following Lecouvey's method,[25] purification could be done by successive precipitations of the residue in a mixture of Et_2O/PE to give **1** (62%) with an inseparable amount of H_3PO_3 (see SI).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.20–7.17 (m, 3 H_{arom}), 7.11–7.09 (m, 2 H_{arom}), 6.85–6.81 (m, 2 H_{arom}), 6.75–6.73 (m, 1 H_{arom}), 5.04 (AB system, J_{AB} = 13.2 Hz, $\Delta\nu_{AB}$ = 13.3 Hz, 2 H, PhCH_2O), 3.88 (t, J = 5.6 Hz, 2 H, CH_2OPh), 3.82 [q, J = 7.1 Hz, 1 H, CH_3CHC(O)], 2.41 [d, J = 7.1 Hz, 2 H, CH_2CH(CH_3)$_2$], 2.01 [m, 4 H, CH_2C(OH)(PO_3H_2)$_2$ and CH_2CH_2O], 1.80 [nonet, J = 6.8 Hz, 1 H, CH(CH_3)$_2$], 1.40 [d, J = 7.1 Hz, 3 H, CH_3CHC(O)], 0.85 [d, J = 6.6 Hz, 6 H, CH(CH_3)$_2$].

^{13}C NMR (125 MHz, DMSO-d_6): δ = 173.7, 158.7, 139.8, 137.7, 137.6, 129.4, 129.1 (2 C), 127.1 (2 C), 119.2, 113.9, 113.4, 72.0 (t, $^1J_{CP}$ = 140.8 Hz), 68.2, 65.4, 44.1 (2 C), 29.7, 29.5, 23.3 (t, $^3J_{CP}$ = 6.5 Hz), 22.1 (2 C), 18.4.

^{31}P NMR (121.5 MHz, DMSO-d_6): δ = 20.9 (s, 2 P).

MS (ESI): m/z = 545 [M + H]$^+$.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{24}H_{35}O_{10}P_2$: 545.1711; found: 545.1702.

[3-(3-Bromopropoxy)phenyl]methanol (9)

The compound **9** was prepared according to the method described for the preparation of **5**, starting with **4** (3 g, 24.17 mmol) and 1,3-dibromopropane (7.4 mL, 72.5 mmol) as the alkylating agent. The crude product was purified by flash chromatography on silica gel (DCM to DCM/MeOH 97:3) to give a mixture of bromo compound **9** (3.97 g, 62%) as a brown viscous oil, which slowly crystallized to give beige or brown crystals.

IR (film): 3300, 2949, 2875, 1585, 1451, 1261, 1150, 1033 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.25 (m, 1 H_{arom}), 6.92–6.90 (m, 2 H_{arom}), 6.81 (m, 1 H_{arom}), 4.61 (s, 2 H, CH_2OH), 4.08 (t, J = 5.8 Hz, 2 H, CH_2O), 3.59 (t, J = 6.4 Hz, 2 H, CH_2Br), 2.29 (qt, J = 6.1 Hz, 2 H, CH_2CH_2Br), 2.24 (br s, 1 H, OH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.0, 142.7, 129.7, 119.4, 113.8, 112.9, 65.3, 65.1, 32.4, 30.2.

MS (CI): m/z = 262 [M + NH_4]$^+$.

HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{10}H_{13}{}^{79}BrO_2Na$: 266.9991; found: 266.9992.

3-(3-Bromopropoxy)benzyl 2-(4-Isobutylphenyl)propanoate (10)

The compound **10** was prepared according to the coupling method described for the preparation of compound **6**, starting from **9** (2.75 g, 11.3 mmol). The crude product was purified by flash chromatography on silica gel (PE/Et_2O, 98:2 to 90:10) to afford **10** (3.16 g, 68%) as a yellow oil.

IR (film): 2954, 2868, 1735, 1604, 1453, 1268, 1160 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.22–7.17 (m, 3 H_{arom}), 7.10–7.07 (m, 2 H_{arom}), 6.81–6.77 (m, 3 H_{arom}), 5.06 (AB system, J_{AB} = 12.9 Hz, $\Delta\nu_{AB}$ = 14.0 Hz, 2 H, CH_2O), 4.01 (t, J = 5.8 Hz, 2 H, CH_2CH_2O), 3.75 [q, J = 7.2 Hz, 1 H, CH_3CHC(O)], 3.57 (t, J = 6.4 Hz, 2 H, CH_2Br), 2.44 [d, J = 7.2 Hz, 2 H, CH_2CH(CH_3)$_2$], 2.27 (qt, J = 6.1 Hz, 2 H, CH_2CH_2Br), 1.84 [nonet, J = 6.8 Hz, 1 H, CH(CH_3)$_2$], 1.50 [d, J = 7.2 Hz, 3 H, CH_3CHC(O)], 0.89 [d, J = 6.6 Hz, 6 H, CH(CH_3)$_2$].

^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.5, 158.8, 140.6, 137.8, 137.7, 129.6, 129.4 (2 C), 127.3 (2 C), 120.2, 114.2, 113.7, 66.1, 65.2, 45.2, 45.1, 32.4, 30.3, 30.0, 22.5 (2 C), 18.5.

MS (CI): m/z = 450 [M + NH_4]$^+$.

HRMS (MALDI, DHB, PEG 400): m/z [M + Na]$^+$ calcd for $C_{23}H_{29}{}^{79}BrO_3$-Na: 455.1192; found: 455.1195.

3-[3-(Methylamino)propoxy]benzyl 2-(4-Isobutylphenyl)propanoate (11)

K_2CO_3 (1.55 g, 11.2 mmol) followed by NaI (460 mg, 3.1 mmol) were successively added to a solution of **10** (4.43 g, 9.29 mmol, 1 equiv) in DMF (90 mL) at RT. After 20 min, $MeNH_2$ (15.3 mL of a 2 M solution in THF, 30.66 mmol) was added. The reaction mixture was stirred at RT overnight and diluted with Et_2O. The organic phase was washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography on neutral alumina (DCM/MeOH, 100:0 then 95:5) to give pure **11** (2.63 g, 67%) as a yellow amorphous compound.

IR (film): 3331, 2951, 2790, 1734, 1449, 1271, 1161, 1054 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.22–7.17 (m, 3 H_{arom}), 7.10–7.07 (m, 2 H_{arom}), 6.83–6.79 (m, 3 H_{arom}), 5.06 [AB system, J_{AB} = 12.6 Hz, $\Delta\nu_{AB}$ = 20.0 Hz, 2 H, CH_2OC(O)], 4.57 (br s, 1 H, NH), 3.99 (t, J = 6.1 Hz, 2 H, CH_2CH_2O), 3.75 [q, J = 7.2 Hz, 1 H, CH_3CHC(O)], 2.88 (t, J = 7.1 Hz, 2 H, CH_2NHCH_3), 2.53 (s, 3 H, NHCH_3), 2.44 [d, J = 7.2 Hz, 2 H, CH_2CH(CH_3)$_2$], 2.07 [qt, J = 6.8 Hz, 2 H, CH_2CH_2O], 1.84 [nonet, J = 6.7 Hz, 1 H, CH(CH_3)$_2$], 1.50 [d, J = 7.2 Hz, 3 H, CH_3CHC(O)], 0.89 [d, J = 6.6 Hz, 6H, CH(CH_3)$_2$].

^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.6, 158.9, 140.6, 137.7 (2 C), 129.6, 129.4 (2 C), 127.3 (2 C), 120.1, 114.2, 113.8, 66.2, 65.8, 48.5, 45.2, 45.1, 35.6, 30.3, 28.6, 22.5 (2 C), 18.6.

MS (CI): m/z = 384 [M + H]$^+$.

HRMS (MALDI, DHB, PEG 400): m/z [M + H]$^+$ calcd for $C_{24}H_{34}NO_3$: 384.2533; found: 384.2526.

***tert*-Butyl {3-[3-(3-{[2-(4-Isobutylphenyl)propanoyloxy]methyl}phenoxy)propyl](methyl)amino}propanoate (12)**

To a solution of amine **11** (3.35 g, 8.73 mmol) in DMF (14 mL) was added *tert*-butyl acrylate (6.35 mL, 43.66 mmol). The reaction mixture was stirred for 24 h at RT under an argon atmosphere. After dilution with Et_2O, the organic phase was washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (DCM/MeOH, 100:0 to 95:5) to afford pure **12** (3.16 g, 71%) as a brownish oil.

IR (film): 2954, 2925, 2869, 2849, 1732, 1454, 1367, 1268, 1160 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.22–7.16 (m, 3 H_{arom}), 7.09–7.07 (m, 2 H_{arom}), 6.82–6.77 (m, 3 H_{arom}), 5.06 [AB system, J_{AB} = 12.6 Hz, $\Delta\nu_{AB}$ = 18.4 Hz, 2 H, CH_2OC(O)], 3.94 (t, J = 6.3 Hz, 2 H, CH_2CH_2O), 3.75 [q, J = 7.2 Hz, 1 H, CH_3CHC(O)], 2.68 (t, J = 7.2 Hz, 2 H, C$H_2CH_2CO_2t$Bu), 2.52 [t, J = 7.0 Hz, 2H, CH_2(CH_2)$_2$O], 2.44 [d, J = 7.2 Hz, 2 H, CH_2CH(CH_3)$_2$], 2.38 (t, J = 7.2 Hz, 2 H, CH_2CO_2tBu), 2.25 (s, 3 H, NCH_3), 1.92 (qt, J = 6.7

Hz, 2 H, CH_2CH_2O), 1.84 [nonet, J = 6.8 Hz, 1 H, $CH(CH_3)_2$], 1.50 [d, J = 7.2 Hz, 3 H, $CH_3CHC(O)$], 1.43 [s, 9 H, $C(CH_3)_3$], 0.89 [d, J = 6.6 Hz, 6 H, $CH(CH_3)_2$].

^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.5, 172.0, 159.2, 140.6, 137.7, 137.6, 129.5, 129.4 (2 C), 127.3 (2 C), 119.9, 114.2, 113.8, 80.3, 66.2, 66.0, 54.1, 53.1, 45.2, 45.1, 42.0, 33.8, 30.2, 28.2 (3 C), 27.3, 22.5 (2 C), 18.5.

MS (CI^+): m/z = 512 $[M + H]^+$.

HRMS (MALDI, DHB, PEG 400): m/z $[M + H]^+$ calcd for $C_{31}H_{46}NO_5$: 512.3370; found: 512.3364.

3-{[3-(3-{[2-(4-Isobutylphenyl)propanoyloxy]methyl}phenoxy)propyl](methyl)amino}propanoic Acid (13)

A solution of dry HCl (3.9 mL of a 2 N solution in Et_2O, 7.8 mmol) was added at 0 °C to the neat ester **12** (135 mg, 0.26 mmol) and the mixture was stirred at RT for 7 h. The solvent was concentrated under reduced pressure to give a white precipitate, which was purified by flash chromatography on silica gel (DCM/MeOH, 100:0 to 90:10) to give **13** (116 mg, 96%) as an amorphous yellow compound.

IR (film): 3400, 2955, 2869, 1734, 1587, 1454, 1268, 1162 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.21–7.17 (m, 3 H_{arom}), 7.10–7.08 (m, 2 H_{arom}), 6.83 (dd, J = 8.0, 2.1 Hz, 1 H_{arom}), 6.79–6.75 (m, 2 H_{arom}), 5.05 [AB system, J_{AB} = 13.2 Hz, $\Delta\nu_{AB}$ = 13.3 Hz, 2 H, $CH_2OC(O)$], 3.94 (t, J = 6.3 Hz, 2 H, CH_2CH_2O), 3.81 [q, J = 7.1 Hz, 1 H, $CH_3CHC(O)$], 2.86 (t, J = 7.2 Hz, 2 H, $CH_2CH_2CO_2H$), 2.75 [t, J = 7.3 Hz, 2 H, $CH_2(CH_2)_2O$], 2.49 (t, J = 7.2 Hz, 2 H, CH_2CO_2H), 2.41–2.39 [m, 5 H, $CH_2CH(CH_3)_2$ and NCH_3], 1.95 (qt, J = 7.0 Hz, 2 H, CH_2CH_2O), 1.80 [nonet, J = 6.7 Hz, 1 H, $CH(CH_3)_2$], 1.39 [d, J = 7.1 Hz, 3 H, $CH_3CHC(O)$], 0.84 [d, J = 6.6 Hz, 6 H, $CH(CH_3)_2$].

^{13}C NMR (100 MHz, DMSO-d_6): δ = 173.7, 173.0, 158.4, 139.8, 137.7 (2 C), 129.4, 129.0 (2 C), 127.1 (2 C), 119.5, 113.9, 113.4, 65.3 (2 C), 52.8, 51.9, 44.2, 44.1, 40.4, 30.8, 29.5, 25.2, 22.1 (2 C), 18.3.

MS (ESI): m/z = 456 $[M + H]^+$.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{27}H_{38}NO_5$: 456.2750; found: 456.2741.

1-Hydroxy-3-{[3-(3-{[2-(4-isobutylphenyl)propanoyloxy]methyl}phenoxy)propyl](methyl)amino}propane-1,1-bis(phosphonic acid) (2)

The compound **2** was prepared according to the method described for the preparation of the analogue **1**, starting from **13** (270 mg, 0.6 mmol) in the presence of catecholborane (3.5 equiv) and $P(OSiMe_3)_3$ (4.5 equiv). The crude product was taken up in DCM and a large amount of Et_2O was added to give an oil which separated. It was purified by low pressure C18 reversed-phase chromatography (MeCN/MeOH, 100:0 to 50:50) to give **2** (160 mg, 45%) as an amorphous white solid. The oil could also be taken up in a mixture of MeOH/Et_2O until a white precipitate appeared, which was filtered. After evaporation of the filtrate, **2** (37%) could be obtained with an inseparable amount of H_3PO_3 (see SI).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.19 (d, J = 8 Hz, 2 H_{arom}), 7.10 (d, J = 8 Hz, 2 H_{arom})–6.85 (m, 3 H_{arom}), 5.04 [s, 2 H, $CH_2OC(O)$], 4.00 (m, 2 H, CH_2CH_2O), 3.81 [q, J = 7.1 Hz, 1 H, $CH_3CHC(O)$], 3.29 [m, 2 H, $CH_2N(CH_3)$], 3.13 [m, 2 H, $N(CH_3)CH_2$], 2.71 [s, 3 H, $N(CH_3)$], 2.40 [d, J = 7.1 Hz, 2 H, $CH_2CH(CH_3)_2$], 2.26–2.11 [m, 4 H, CH_2CH_2O and $CH_2C(OH)(PO_3H_2)_2$], 1.80 [nonet, J = 6.8 Hz, 1 H, $CH(CH_3)_2$], 1.39 [d, J = 7.1 Hz, 3 H, $CH_3CHC(O)$], 0.84 [d, J = 6.6 Hz, 6 H, $CH(CH_3)_2$].

^{13}C NMR (100 MHz, DMSO-d_6): δ = 173.6, 158.2, 139.7, 137.6 (2 C), 129.4, 128.9 (2 C), 127.0 (2 C), 119.5, 113.8, 113.6, 65.3, 64.9, 52.4, 51.7, 44.1, 44.0, 39.4, 29.4, 27.6, 23.5, 22.0 (2 C), 18.5; one C_q signal missing.

^{31}P NMR (121.5 MHz, DMSO-d_6): δ = 20.4 (2 P).

MS (ESI): m/z = 600 $[M - H]^-$.

HRMS (ESI): m/z $[M - H]^-$ calcd for $C_{27}H_{40}NO_{10}P_2$: 600.2127; found: 600.2132.

3-(3-Azidopropoxy)benzyl 2-(4-Isobutylphenyl)propanoate (16)

NaN_3 (44 mg, 0.67 mmol) was added to bromide **10** (146 mg, 0.31 mmol) in DMF (3 mL), at RT. The resulting mixture was stirred for 4 h and diluted with Et_2O. The organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification by flash chromatography on silica gel (PE/Et_2O, 100:0 to 90:10) gave pure azide **16** (116 mg, 94%) as a colorless oil.

IR (film): 2955, 2870, 2099, 1735, 1452, 1266, 1160 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.12–7.05 (m, 3 H_{arom}), 6.99–6.96 (m, 2 H_{arom}), 6.71–6.67 (m, 3 H_{arom}), 4.96 [AB system, J_{AB} = 13.3 Hz, $\Delta\nu_{AB}$ = 13.3 Hz, 2 H, $CH_2OC(O)$], 3.84 (t, J = 5.9 Hz, 2 H, CH_2O), 3.64 [q, J = 7.1 Hz, 1 H, $CH_3CHC(O)$], 3.36 (t, J = 6.6 Hz, 2 H, CH_2N_3), 2.34 [d, J = 7.2 Hz, 2 H, $CH_2CH(CH_3)_2$], 1.88 (qt, J = 6.3 Hz, 2 H, CH_2CH_2O), 1.74 [nonet, J = 6.8 Hz, 1 H, $CH(CH_3)_2$], 1.40 [d, J = 7.2 Hz, 3 H, $CH_3CHC(O)$], 0.79 [d, J = 6.6 Hz, 6 H, $CH(CH_3)_2$].

^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.4, 158.7, 140.5, 137.7, 137.6, 129.5, 129.3 (2 C), 127.2 (2 C), 120.1, 114.1, 113.5, 66.0, 64.3, 48.2, 45.1, 45.0, 30.2, 28.7, 22.4 (2 C), 18.5.

MS (CI): m/z = 413 $[M + NH_4]^+$.

HRMS (MALDI, DHB, PEG 400): m/z $[M + Na]^+$ calcd for $C_{23}H_{29}N_3O_3Na$: 418.2101; found: 418.2101.

Dimethyl Pent-4-ynoylphosphonate (17)[35]

Freshly distilled $SOCl_2$ (11.1 mL, 152.9 mmol) was added to the commercial 4-pentynoic acid (**14**; 6 g, 61.16 mmol) and the resulting mixture was heated to reflux for 90 min. Distillation under reduced pressure afforded pure expected acyl chloride (3.6 g, 51%) as a colorless oil; bp 51 °C/30 mbar.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.14 [t, J = 7.1 Hz, 2 H, $CH_2C(O)Cl$], 2.57 [td, J = 7.1, 2.7 Hz, 2 H, $CH_2CH_2C(O)Cl$], 2.05 (t, J = 2.7 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.3, 80.5, 70.4, 45.7, 14.8.

To the above neat acyl chloride (2.1 g, 17.88 mmol) cooled at 0 °C was added dropwise trimethyl phosphite (2.11 mL, 17.88 mmol) with vigorous stirring. After complete addition, the reaction mixture was stirred for 2 h at RT, while monitoring by ^{31}P NMR spectroscopy. After evaporation of the volatiles, acyl phosphonate **17** was obtained as a yellow oil (3.43 g, ~100%) and used without further purification.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.89 (d, $^3J_{HP}$ = 10.7 Hz, 6 H, 2 × OCH_3), 3.10 [td, J = 7.1, 1.6 Hz, 2 H, $CH_2C(O)$], 2.50 [td, J = 7.1, 2.6 Hz, 2 H, $CH_2CH_2C(O)$], 1.99 (t, J = 2.6 Hz, 1 H, CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 208.4 (d, $^1J_{CP}$ = 171.3 Hz), 81.9, 69.4, 54.1 (d, $^2J_{CP}$ = 7.1 Hz, 2 C), 42.4 (d, $^2J_{CP}$ = 56.4 Hz), 11.8 (d, $^3J_{CP}$ = 4.5 Hz).

^{31}P NMR (121.5 MHz, $CDCl_3$): δ = –1.2.

Tetramethyl 1-Hydroxy-4-pentylidene-1,1-bis(phosphonate) (18)

To a solution of the acyl phosphonate **17** (1.91 g, 10.04 mmol) in freshly distilled toluene (9 mL) was added dimethyl phosphite (1.06 mL, 11.55 mmol) and a catalytic amount of n-Bu_2NH (55 µL, 0.32

mmol) at 0 °C. A white solid began to form 20 min after the introduction of the base. Stirring was continued for 4 h. After completion of the reaction (^{31}P NMR monitoring), the precipitate was filtered to give pure hydroxy-bisphosphonate **18** (2.3 g, 77%) as a white powder; mp 81–83 °C.

IR (film): 3224, 2961, 1247, 1217, 1037 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.08 (br s, 1 H, OH), 3.90–3.87 (m, 12 H, 4 × OCH_3), 2.57 [td, *J* = 8.1, 2.6 Hz, 2 H, $CH_2CH_2C(OH)$], 2.37–2.26 [m, 2 H, $CH_2C(OH)$], 1.98 (t, *J* = 2.6 Hz, 1 H, CH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 84.0, 74.8 (t, $^1J_{CP}$ = 152.8 Hz), 69.0, 54.5 (m, 4 C), 33.0, 13.4 (t, $^3J_{CP}$ = 7.1 Hz).

^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 21.6 (2 P).

MS (ESI) : *m*/*z* = 323 [M + Na]$^+$.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_9H_{18}O_7P_2Na$: 323.0425; found: 323.0421.

Tetramethyl 1-Hydroxy-3-{1-[3-(3-{[2-(4-isobutylphenyl)propanoyloxy]methyl}phenoxy)propyl]-1*H*-1,2,3-triazol-4-yl}-1,1-bis(phosphonate) (19)

Alkyne phosphonate **18** (151 mg, 0.5 mmol) and azide **16** (218 mg, 0.55 mmol) were suspended in a 4:1 mixture of *t*-BuOH and H_2O (2 mL). The solution was degassed for 15 min and $CuSO_4$ (25 μL of freshly prepared 1 M solution in H_2O, 0.025 mmol) was added, followed by sodium L-ascorbate (75 μL of freshly prepared 2 M solution in H_2O, 0.15 mmol). The heterogeneous mixture was stirred vigorously for 24 h, until TLC analysis indicated complete consumption of the alkyne. The reaction mixture was diluted with brine (8 mL) and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by flash chromatography on silica gel (DCM/MeOH, 100:0 to 96:4) gave pure compound **19** (338 mg, 97%) as a brownish gum.

IR (film): 3200, 2956, 1734, 1587, 1453, 1252, 1050 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33 (s, 1 $H_{triazolyl}$), 7.23–7.19 (m, 3 H_{arom}), 7.09–7.07 (m, 2 H_{arom}), 6.83–6.76 (m, 3 H_{arom}), 5.07 [AB system, J_{AB} = 12.7 Hz, $\Delta\nu_{AB}$ = 16.8 Hz, 2 H, $CH_2OC(O)$], 4.52 (t, *J* = 6.9 Hz, 2 H, CH_2N), 3.92–3.87 (m, 14 H, CH_2O and 4 × OCH_3), 3.75 [q, *J* = 7.2 Hz, 1 H, $CH_3CHC(O)$], 3.12 [t, *J* = 7.1 Hz, 2 H, $CH_2CH_2C(OH)(PO_3H_2)_2$], 2.49 [tt, J_{HP} = 14.6 Hz, J_{HH} = 7.2 Hz, 2 H, $CH_2C(OH)(PO_3H_2)_2$], 2.44 [d, *J* = 7.2 Hz, 2 H, $CH_2CH(CH_3)_2$], 2.35 (qt, *J* = 6.0 Hz, 2 H, CH_2CH_2O), 1.84 [nonet, *J* = 6.8 Hz, 1 H, $CH(CH_3)_2$], 1.51 [d, *J* = 7.2 Hz, 3 H, $CH_3CHC(O)$], 0.89 [d, *J* = 6.6 Hz, 6 H, $CH(CH_3)_2$].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.5, 158.6, 147.0, 140.6, 137.9, 137.7, 129.7, 129.4 (2 C), 127.3 (2 C), 121.5, 120.5, 114.1, 113.7, 75.3 (t, $^1J_{CP}$ = 155.4 Hz), 66.1, 64.0, 54.5 (4 C), 47.2, 45.2, 45.1, 32.5, 30.2, 30.0, 22.4 (2 C), 20.6 (t, $^3J_{CP}$ = 8.0 Hz), 18.6.

^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 22.1 (2 P).

MS (ESI) : *m*/*z* = 694 [M – H]$^-$, 730 [M – Cl]$^-$.

HRMS (ESI): *m*/*z* [M – H]$^-$ calcd for $C_{32}H_{46}N_3O_{10}P_2$: 694.2664; found: 694.2647; [M + Cl$^-$]$^-$ calcd for $C_{32}H_{47}N_3O_{10}P_2Cl$: 730.2431; found: 730.2431.

1-Hydroxy-3-{1-[3-(3-{[2-(4-isobutylphenyl)propanoyloxy]methyl}phenoxy)propyl]-1*H*-1,2,3-triazol-4-yl}-1,1-bis(phosphonic acid) (3)

*From **16***: To a solution of the azide **16** (200 mg, 0.5 mmol) in DMF (5 mL) was added an aqueous solution of the sodium salt of **15** (150 mg, 0.5 mmol in 1 mL of H_2O at pH 7) to give a milky solution. Solid CuTC was then added (20 mg, 0.1 mmol) and the reaction mixture was stirred for 18 h. After addition of MeOH followed by a large amount of Et_2O, a brownish precipitated appeared, which was collected. It was dissolved in MeOH and acidified with HCl (1 mL of a 2 M HCl solution in anhyd Et_2O) to give a yellowish solution. After concentration, the residue was dissolved in a minimum of MeOH and a large amount of Et_2O was added to give the compound **3** as a colored powder, which was filtered (80 mg, 25%).

*From **19***: To a solution of phosphonate **19** (287 mg, 0.41 mmol) in DCM (4 mL) was added TMSBr (377 mg, 2.46 mmol). After stirring for 5 h at RT, volatile fractions were eliminated by concentration in vacuo. MeOH (4 mL) was added to the isolated silylated intermediate and the solution was stirred for 2 h at RT. Concentration under reduced pressure afforded pure hydroxy-bisphosphonic compound **3** (260 mg, ~100%) as a beige hygroscopic powder.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.92 (s, 1 $H_{triazolyl}$), 7.22–7.08 (m, 5 H_{arom}), 6.83–6.76 (m, 3 H_{arom}), 5.05 [AB system, J_{AB} = 13.5 Hz, $\Delta\nu_{AB}$ = 13.5 Hz, 2 H, $CH_2OC(O)$], 4.49 (t, *J* = 6.9 Hz, 2 H, CH_2N), 3.91 (t, *J* = 6.0 Hz, 2 H, CH_2O), 3.82 [q, *J* = 7.1 Hz, 1 H, $CH_3CHC(O)$], 2.97–2.92 [m, 2 H, $CH_2CH_2C(OH)(PO_3H_2)_2$], 2.40 [d, *J* = 7.1 Hz, 2 H, $CH_2CH(CH_3)_2$], 2.28–2.17 [m, 4 H, CH_2CH_2O and $CH_2C(OH)(PO_3H_2)_2$], 1.79 [nonet, *J* = 6.7 Hz, 1 H, $CH(CH_3)_2$], 1.39 [d, *J* = 7.1 Hz, 3 H, $CH_3CHC(O)$], 0.83 [d, *J* = 6.6 Hz, 6 H, $CH(CH_3)_2$].

^{13}C NMR (100 MHz, DMSO-d_6): δ = 173.7, 158.3, 146.9, 139.8, 137.8, 138.7, 129.5, 129.1 (2 C), 127.1 (2 C), 122.1, 119.6, 113.9, 113.4, 72.0 (t, $^1J_{CP}$ = 143.2 Hz), 65.3, 64.4, 46.6, 44.2, 44.1, 32.8, 29.6, 29.4, 22.1 (2 C), 19.7 (t, $^3J_{CP}$ = 6.9 Hz), 18.4.

^{31}P NMR (121.5 MHz, DMSO-d_6): δ = 20.6 (2 P).

MS (ESI) : *m*/*z* = 638 [M – H]$^-$.

HRMS (ESI): *m*/*z* [M – H]$^-$ calcd for $C_{28}H_{38}N_3O_{10}P_2$: 638.2038; found: 638.2021.

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Supporting Information

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(29) Note : In these Huisgen cycloaddition conditions ($CuSO_4$, 0.2 equiv) and AscNa (1 equiv) in DMF/H_2O after 48 h at RT, less than 50% of the starting material **16** was consumed and no HBP compound **3** was isolated pure.
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