Synthesis of functionalized bisphosphonates *via* click chemistry

Hanna Skarpos,[b] Sergey N. Osipov,*[a] Daria V. Vorob'eva,[a] Irina L. Odinets,[a] Enno Lork[b] and Gerd-Volker Röschenthaler*[b]

Received 3rd April 2007, Accepted 31st May 2007
First published as an Advance Article on the web 21st June 2007
DOI: 10.1039/b705510b

An efficient general synthetic approach giving the possibility for facile, rapid and cheap access to a wide range of novel nitrogen-bisphosphonates (N-BPs) as potent drug candidates, based on the reaction of mono- and bis-propargyl-substituted bisphosphonates with a variety of azides under Cu(I) catalysis ("click" methodology), has been developed. The method allows the incorporation of two functionalities into the N-BP molecule simultaneously, as well as to ligate *in situ* two N-BPs to one another *via* the one-pot reaction of organic dibromides with propargyl-substituted bisphosphonates, generating both the diazide and Cu(I) moieties.

1. Introduction

Bisphosphonates (BPs), being analogs of naturally occurring diphosphates, are powerful inhibitors of bone resorption, and some of them are currently clinically applied to treat malignant hypercalcemia.[1] For this reason, their main therapeutic uses are in diseases connected with calcium disorders, such as Paget's disease, osteoporosis and bone tumoral metastasis.[2] BPs are also of interest in the context of cancer and immunotherapy, as they possess potent effects against the parasites responsible for sleeping sickness, Chagas' disease, malaria and leishmaniasis.[3]

To date, most of the highly potent third-generation BP drugs contain an additional moiety in the molecule, namely a nitrogen heterocycle,[4] as in risedronate and zoledronate (Fig. 1). These cyclic nitrogen bisphosphonates (N-BPs) are up to 10 000-fold more active[1b] than, for example, etidronate—the first BP used for treating humans. These drugs act by directly and selectively inhibiting the activity of osteoclasts, cells responsible for bone resorption. The detailed inhibitory mechanism of N-BPs is well documented in the literature.[5,6]

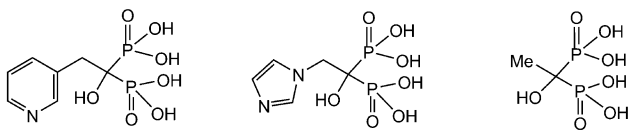


Fig. 1

The results obtained to date regarding the inhibitory potency of N-BPs indicate that: (1) the presence of two geminal phosphonate groups is responsible for interaction with the molecular target, (2) the presence of a basic nitrogen in the heterocyclic side chain affects potency, (3) the 3-dimensional orientation of this basic nitrogen atom is critical for effective inhibition, (4) the geminal hydroxy group does not influence the ability of N-BPs to act at the cellular level, and (5) the introduction of lipophilic groups into the N-BP backbone can significantly improve their pharmacokinetics, increasing their availability in soft tissues. Therefore, the purposeful synthesis of new members of the N-BP family is of current interest for further development of more potent drugs.

Modern drug discovery requires the identification and the optimization of synthetic routes to specifically acting low molecular weight molecules. That is why simple methods that can quickly and easily generate large libraries of compounds have become more and more used.[7] The "click" methodology recently introduced by Sharpless *et al.*[8] is one of these methods based on reactions which are of wide scope, give high yields, and use highly energetic reactants to form irreversible carbon–heteroatom bonds. The Huisgen 1,3-dipolar cycloaddition[9] perfectly illustrates this kind of reaction. It consists of the ligation of azides and terminal alkynes to give triazoles. As has been recently shown,[10] under copper(I) catalysis, the rate of this coupling event is dramatically accelerated and only the corresponding 1,4-disubstituted regioisomer is obtained. At the same time, 1,2,3-triazoles are versatile compounds, which have been applied for a variety of purposes, including as anticorrosive agents, dyes, agrochemicals and photographic materials.[11] Although the 1,2,3-triazole structural moiety does not occur in nature, it features in diverse biologically active substances, displaying anti-HIV and antimicrobial behavior as a selective β_3-adrenergic receptor agonist.[12]

Recently we have developed a simple method for the preparation of functionalized α-trifluoromethyl-substituted histidine aza analogs *via* Cu(I)-catalyzed 1,3-dipolar Huisgen cycloaddition between α-propargyl-α-trifluoromethyl-α-amino esters and organic azides.[13] In this paper we disclose an efficient general approach opening up the possibility for facile, rapid and cheap synthesis of a wide range of novel N-BPs (*e.g.* aza-analogs of zoledronate—the most potent drug to date among bisphosphonates[1b]) as potent drug candidates based on "click" methodology.

2. Results and discussion

Despite the synthesis of propargyl-substituted bisphosphonate **2** based on the alkylation of methylene bisphosphonate by propargyl

[a]*A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, 28 Vavilova, 119991, Moscow, Russia. E-mail: osipov@ineos.ac.ru*
[b]*Institute for Inorganic & Physical Chemistry, University of Bremen, Leobener Strasse., D-28334, Bremen, Germany. E-mail: gvr@chemie.uni-bremen.de*

bromide (with deprotonation by NaH) being reported in the literature,[14] in our experience this reaction is accompanied by substantial double alkylation (up to 35% of **3**). Moreover, separation of mono- and dipropargyl-substituted bisphosphonates **2** and **3** using column chromatography is not effective due to the similar R_f values of these compounds. Therefore, we developed an alternative method for the preparation of **2**, which comprises selective addition of sodium acetylenide to ethylidene bisphosphonate **4**. This reaction gives excellent results even on a multi-gram scale (Scheme 1). After ordinary work-up the product **2** obtained in 92% yield does not require additional purification and can be used directly in further transformations.

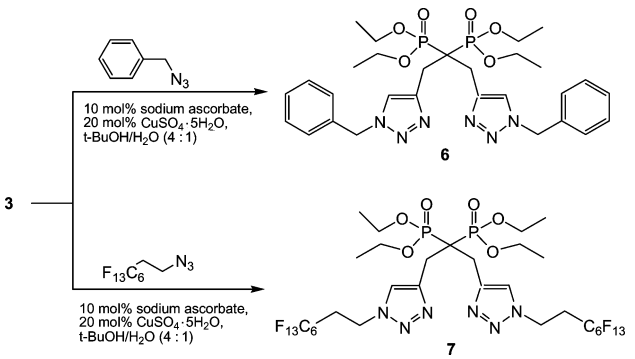
It should be noted that alkylation of methylene bisphosphonate **1** by 2 equivalents of propargyl bromide using deprotonation with NaH in THF is a facile route to disubstituted bisphosphonate **3**, as described by Choi *et al.*[15]

Thus, having in hand the mono- and dipropargyl-substituted bisphosphonates **2** and **3**, we investigated the possibility of their application in cycloadditions with a variety of azide-functionalized substrates. To the best of our knowledge, the alkene–azide type of 1,3-dipolar addition has not yet been applied in bisphosphonate chemistry.

In the standard procedure for regioselective Cu(I)-catalyzed alkyne–azide coupling, the catalyst can be directly introduced as a Cu(I) salt or generated *in situ* by reduction of Cu(II) salts,[16] usually in organic–aqueous systems. For the synthesis of the N-BPs **5** from propargyl-substituted bisphosphonate **2**, we have applied both of the above-mentioned procedures, namely: A) use of CuI as a catalyst in an organic solvent (THF) in the presence of an organic base (DIPEA); and B) generation of Cu(I) *in situ* from $CuSO_4$ and sodium ascorbate in a water–alcohol medium (Table 1).

1,3-Dipolar Huisgen cycloaddition of propargyl-containing bisphosphonate **2** with various azides was found to proceed smoothly at room temperature to afford functionalized 1,2,3-triazoles **5a–f** in high yields after 68 h. Even highly functionalised azides (Table 1, entries 5 and 6) are good partners for propargyl-bisphosphonate **2** in these copper-catalyzed reactions. In spite of the fact that both methods give good-to-excellent results, method B is preferable due to a simpler isolation procedure (in the majority of cases column chromatography was not required).

In a similar manner, Huisgen copper-catalyzed 1,3-dipolar cycloaddition of bisphosphonate **3** with azides was accomplished using method B (being more preferable in terms of purification) to afford the corresponding bistriazols **6** and **7** in a good yield (Scheme 2).



Scheme 2

The structure of bisphosphonate **6** was confirmed by X-ray data (Fig. 2). Molecules in the crystal have an approximately *C*2 symmetry (a two-fold axis passes through the C9 atom). The principal geometrical parameters of **6** are within the range of standard values.

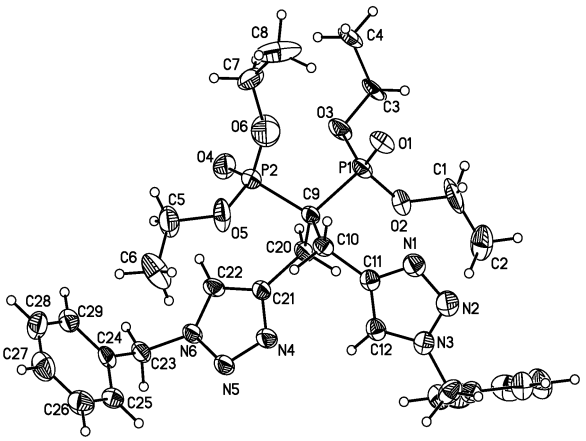
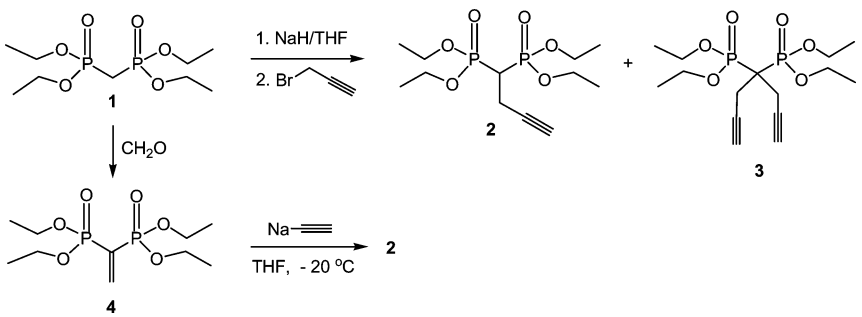


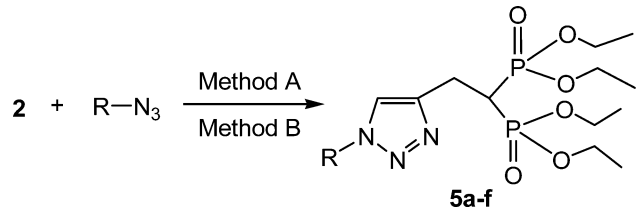
Fig. 2 A general view of **6**, representing atoms by thermal ellipsoids ($p = 50\%$). The disorder is omitted for clarity. Selected bond lengths (Å): P1–C9 1.837(4), P2–C9 1.837(4), P1–O1 1.458(3), P2–O4 1.456(3), C9–C10 1.572(5), C9–C20 1.571(5), C10–C11 1.503(5), C20–C21 1.500(5); bond angles (°): P1–C9–P2 109.7(2), P1–C9–C10 108.1(3), P1–C9–C20 109.3(3), P2–C9–C20 107.7(3), P2–C9–C10 109.7(2), C10–C9–C20 112.8(3).

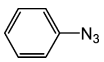
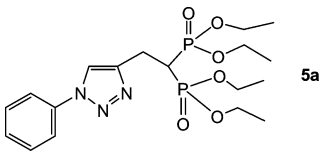
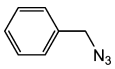
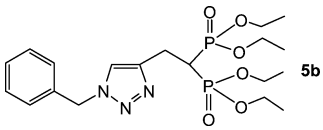
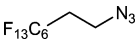
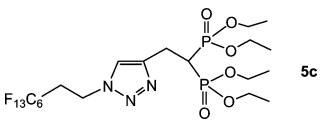
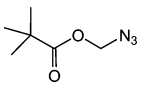
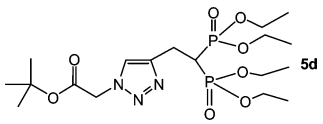
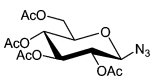
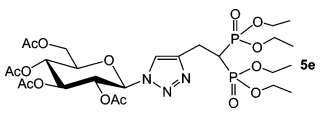
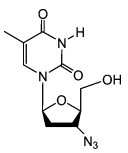
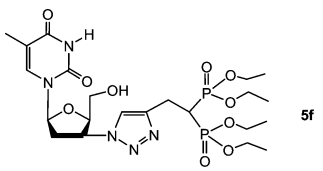
It should be noted that such a 1,3-cycloaddition can also be performed as a one-pot reaction starting from organic bromides and sodium azide (generation of the corresponding azide *in situ* normally takes about 12 hours) followed by propargyl-substituted



Scheme 1

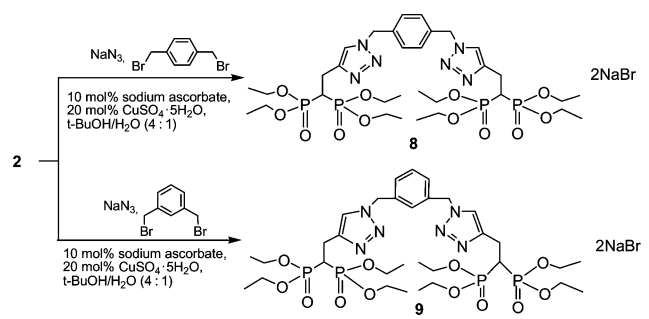
Table 1 Reaction of **2** with alkynes



Entry	R–N_3	Product	Method[a]	Yield (%)
1		 **5a**	A B	79 87
2		 **5b**	A B	73 80
3		 **5c**	A B	81 85
4		 **5d**	B	72
5		 **5e**	B	68
6		 **5f**	B	92

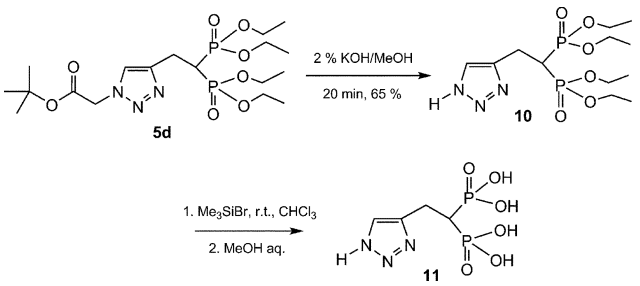
[a] Method A: CuI (10 mol%), DIPEA (3 equiv.), THF. Method B: $CuSO_4$ (5 mol%), sodium ascorbate (30 mol%), H_2O–*t*-BuOH.

bisphosphonate addition (Scheme 3). Thus, the above-mentioned bisphosphorylated triazole **5b** was obtained starting directly from benzyl bromide, while for the synthesis of tetraphosphonates **8** and **9** isomeric bis(bromomethyl)benzenes were used. Due to the complexing ability of the methylenebisphosphonate moiety towards metals, under these one-pot conditions tetraphosphonates **8** and **9** form strong chelates with sodium bromide (the side product of the reaction), and these complexes were isolated after column chromatography (Scheme 3).



Scheme 3

To obtain free N-BP **11**, the *N*-pivaloylmethyl derivative **5d** was selected as the most suitable precursor. We found that the pivaloylmethyl group could be selectively removed under basic conditions for few minutes at room temperature in methanol to afford **10** in good yield. Finally, hydrolysis of the ester groups at the phosphorus atoms was quantitatively performed by treatment of **10** with trimethylsilyl bromide in chloroform followed by treatment with aqueous MeOH (Scheme 4).



Scheme 4

Conclusion

In conclusion, we have developed an efficient general synthetic approach giving the possibility for the facile, rapid and cheap synthesis of a wide range of novel N-BPs as potent drug candidates based on "click" methodology. The method allows the incorporation of two functionalities into the N-BP molecule simultaneously, as well as the ligation of two N-BPs to one another by a one-pot reaction of organic dibromides with propargyl-substituted bisphosphonates, generating both the diazide and Cu(I) moiety *in situ*.

Experimental

General remarks

Solvents were freshly distilled from the appropriate drying agents before use. All other reagents were recrystallized or distilled when necessary. Syntheses of mono- and bispropargyl substituted bisphosphonates **2** and **3** were performed under an atmosphere of dry nitrogen. Analytical TLCs were performed with Merck silica gel 60 F_{254} plates. Visualization was accomplished by UV light or spraying by $Ce(SO_4)_2$ solution in H_2SO_4. Flash chromatography was carried out using Merck silica gel 60 (230–400 mesh ASTM). Melting points were determined with an Electrothermal IA9100 digital melting point apparatus and are uncorrected. NMR spectra were obtained on Bruker DPX-200 (^{1}H, 200.13, ^{31}P, 80.99, ^{19}F, 188.31, and ^{13}C, 50.32 MHz) and Bruker Avance-300 (^{1}H, 300.13, ^{31}P, 121.49 and ^{13}C, 75.47 MHz) spectrometers using the residual proton signals of the deuterated solvent as an internal standard (^{1}H, ^{13}C) relative to TMS, H_3PO_4 (^{31}P) or $CFCl_3$ (^{19}F) as external standards. High-resolution mass spectra were obtained on a Varian MAT CH7A instrument at 70 eV. IR spectra were recorded using a thin layer of the sample on a Fourier-transform "Magna-IR750" (Nicolet) spectrometer (resolution 2 cm^{-1}, 128 scans).

Tetraethyl but-3-yne-1,1-diyldiphosphonate (2)

To a solution of ethylidenbisphosphonate **1** (10 g, 34.4 mmol) in dry THF (100 mL) a slurry of sodium acetylenide in xylene (9.1 mL, 18% solution) was added dropwise at −15 °C. The reaction mixture was allowed to warm to r.t. and stirred overnight. To the reaction solution, ether (100 mL) and 1 N HCl (50 mL) were added. The organic layer was washed with 1 N HCl (50 mL), brine (2 × 50 mL) and dried over magnesium sulfate. After evaporation of the solvent under reduced pressure, the product was used for subsequent reactions without purification. Yield 92% (colorless oil). ^{31}P NMR (80.99 MHz, $CDCl_3$) δ: 22.8. ^{1}H NMR (200.13 MHz, $CDCl_3$) δ: 1.31 (t, 12H, CH_3, $^3J_{HH}$ = 7.2 Hz), 2.03 (s, 1H, C≡H), 2.61–2.92 (m, 3H, CHP + CH_2), 4.22–4.28 (m, 8H, OCH_2); ^{13}C (50.32 MHz, $CDCl_3$) δ: 16.7 (d, CH_3, $^3J_{CP}$ = 6.1 Hz), 39.6 (CH, t, $^1J_{CP}$ = 134.3), 63.3 (d, OCH_2, $^2J_{CP}$ = 6.5 Hz), 70.4 (HC≡), 81.6 (t, CH_2C≡, $^3J_{CP}$ = 9.4). IR (thin layer) ν/cm^{-1}: 1025 (P–O–C), 1249 (P=O), 2120 (C≡C). HRMS: calculated for $C_{12}H_{26}O_6P_2$ (M^+) 326.1048, found 326.1040.

Tetraethyl hepta-1,6-diyne-4,4-diyldiphosphonate (3)

Obtained according to the procedure described in ref. 15. Yield 78% (white crystals), mp 57–61 °C. ^{31}P NMR (80.99 MHz, $CDCl_3$) δ: 22.9. ^{1}H NMR (200.13 MHz, $CDCl_3$) δ: 1.34 (t, 12H, CH_3, $^3J_{HH}$ = 7.0), 2.04 (s, 1H, C≡H), 2.90 (dt, 4H, CH_2, $^3J_{HH}$ = 3.1, $^2J_{HP}$ = 15.9 Hz), 4.23 (quintet, 8H, OCH_2). ^{13}C (50.32 MHz, $CDCl_3$) δ: 14.3 (d, CH_3, $^3J_{CP}$ = 6.1 Hz), 19.0 (CH_2), 41.7 (t, $C(CH_2)_2$, $^1J_{CP}$ = 133.8 Hz), 61.1 (d, OCH_2, $^2J_{CP}$ = 7.2 Hz), 69.6 (HC≡), 76.8 (t, CH_2C≡, $^3J_{CP}$ = 10.9 Hz). IR (thin layer) ν/cm^{-1}: 1025 (P–O–C), 1255 (P=O), 2120 (C≡C). HRMS: calculated for $C_{15}H_{26}O_6P_2$ (M^+) 364.1205, found 364.1204.

Procedures for the synthesis of triazoles

Method A. A mixture of organic azide (1.0 mmol), acetylene **2** (1.0 mmol), DIPEA (2.0 mmol) and CuI (0.1 mmol) in THF (10 mL) was stirred at r.t. for 68 h. The resulting reaction mixture was treated with 1 N HCl (15 mL), and extracted with ether (3 × 15 mL). The combined organic layers were dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography on silica gel (acetone–petroleum ether).

Method B. The organic azide (2.0 mmol) and acetylene **2** (2.0 mmol) were suspended in 1 : 4 H_2O–*t*-BuOH (8 mL). To this was added $CuSO_4 \cdot 5H_2O$ (5 M solution, 0.1 mmol, 5 mol%) and sodium ascorbate (0.6 mmol). The mixture was stirred at r.t. for 24 h, after which time TLC (silica, acetone–petroleum ether) indicated complete conversion. The resulting solution was concentrated under reduced pressure (rotary evaporator). The residue was dissolved in 30 mL of brine and then extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with 5% aq. NH_4OH (2 × 10 mL), dried over $MgSO_4$, filtered, and the solvent removed under vacuum to give analytically pure product.

Tetraethyl 2-(1-phenyl-1*H*-1,2,3-triazol-4-yl)ethane-1, 1-diyldiphosphonate (5a)

Yield 87%, colorless oil. ^{31}P NMR (80.99 MHz, $CDCl_3$) δ: 23.7. ^{1}H NMR (200.13 MHz, $CDCl_3$) δ: 1.31 (t, 12H, CH_3, $^3J_{HH}$ = 7.1 Hz), 3.03 (tt, 1H, CHP, $^3J_{HH}$ = 6.4, $^2J_{HP}$ = 23.1 Hz), 3.40 (dt, 2H, CH_2, $^3J_{HH}$ = 6.4, $^3J_{HP}$ = 16.0 Hz), 4.22–4.31 (m, 8H, OCH_2), 7.45–7.55 (m, 5H, arom), 7.71 (s, 1H, CH). ^{13}C (50.32 MHz, $CDCl_3$) δ: 16.7 (d, CH_3, $^3J_{CP}$ = 3.0 Hz), 16.8 (d, CH_3, $^3J_{CP}$ = 2.5 Hz), 22.6 (CH_2), 37.1 (t, CP, $^1J_{CP}$ = 132.9 Hz), 62.9 (OCH_2), 63.3 (OCH_2), 120.8 (CH=), 128.9, 128.6, and 130.2 (CH_{Ar}), 137.6 ($C_{Ar}N$), 146.9 (C=). IR (thin layer) ν/cm^{-1}: 1023 (P–O–C), 1255 (P=O), 1597 (C=C), 1500 (N=N). HRMS: calculated for $C_{18}H_{29}N_3O_6P_2$ (M^+) 445.1532, found 445.1543.

Tetraethyl 2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)ethane-1, 1-diyldiphosphonate (5b)

Yield 89%, colorless oil. ^{31}P NMR (80.99 MHz, $CDCl_3$) δ: 23.6. ^{1}H NMR (200.13 MHz, $CDCl_3$) δ: 1.3 (t, 12H, CH_3, $^3J_{HH} = 6.5$ Hz), 2.91 (tt, 1H, CHP, $^3J_{HH} = 6.3$, $^2J_{HP} = 23.0$ Hz), 3.32 (dt, 2H, CH_2, $^3J_{HH} = 6.4$, $^3J_{HP} = 15.9$ Hz), 4.21–4.26 (m, 8H, OCH_2), 5.52 (s, 2H, CH_2), 7.30–7.33 (m, 5H, arom.), 7.52 (s, 1H, CH). ^{13}C (50.32 MHz, $CDCl_3$) δ: 16.7 (CH_3), 22.6 (CH_2), 37.1 (t, CP, $^1J_{CP} = 132.9$ Hz), 55.2 (NCH_2), 62.9 (d, OCH_2, $^2J_{CP} = 6.5$ Hz), 63.2 (d, OCH_2, $^2J_{CP} = 6.2$ Hz), 122.6 (CH=), 128.5 and 128.6 and 129.4 (C_{Ar}), 135.3 (C_{Ar}), 145.9 (C=). IR (thin layer) ν/cm^{-1}: 1024 (P–O–C), 1248 (P=O), 1498 (N=N), 1555 (C=C). HRMS: calculated for $C_{19}H_{31}N_3O_6P_2$ (M^+) 459.1688, found 459.1685.

Tetraethyl 2-[1-(4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluorononyl)-1*H*-1,2,3-triazol-4-yl]ethane-1,1-diyldiphosphonate (5c)

Yield 92%, colorless oil. ^{31}P NMR (80.99 MHz, $CDCl_3$) δ: 23.7. ^{1}H NMR (200.13 MHz, $CDCl_3$) δ: 1.31 (t, 12H, CH_3, $^3J_{HH} = 7.0$ Hz), 2.41–2.93 (m, 3H, CHP + CH_2), 3.40 (dt, 2H, CH_2, $^3J_{HH} = 6.1$ Hz, $^3J_{HP} = 16.1$ Hz), 4.22–4.31 (m, 8H, OCH_2), 4.72 (t, 2H, CH_2, $^3J_{HH} = 7.2$ Hz), 7.61 (s, 1H, CH), (m). ^{19}F NMR (188.34 MHz, $CDCl_3$) δ: −81.9 (m, 3F, CF_3), −114.3 (m, 2F, CF_2CH_2), −123.0 (m, 2F, CF_2CF_3), −124.0 (m, 2F, $CH_2CF_2CF_2CF_2$), −124.6 (m, 2F, $CH_2CF_2CF_2$), −127.2 (m, 2F, $CF_2CF_2CF_3$). ^{13}C (50.32 MHz, $CDCl_3$) δ: 16.6 (d, CH_3, $^3J_{CP} = 3.0$ Hz), 16.8 (d, CH_3, $^3J_{CP} = 2.5$ Hz), 22.5, 32.2 (t, CH_2CF_2, $^2J_{CF} = 21.7$ Hz), 37.0 (t, CP, $^1J_{CP} = 133.1$ Hz), 42.5 (NCH_2), 62.9 (d, OCH_2, $^2J_{CP} = 6.5$ Hz), 63.3 (d, OCH_2, $^2J_{CP} = 6.2$ Hz), 109.3, 121.1 (CH=), 123.4, 145.9 (C=). IR (thin layer) ν/cm^{-1}: 1028 (P–O–C), 1241 (P=O), 1367 and 1394 (CH_2), 1550 (C=C), 3460. HRMS: calculated for $C_{20}H_{28}N_3O_6P_2F_{13}$ (M^+) 715.1245, found 715.1235.

***tert*-Butyl {4-[2,2-bis(diethoxyphosphoryl)ethyl]-1*H*-1,2, 3-triazol-1-yl}acetate (5d)**

Yield 64%, oil. ^{31}P NMR (121.49 MHz, $CDCl_3$): δ 22.4. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 1.23 (s, 9H, CH_3), 1.34 (t, 12H, CH_3, $^3J_{HH} = 7.08$ Hz), 2.97–3.04 (m, 1H, CH), 3.38 (dt, 2H, CH_2, $^3J_{HH} = 16.20$ Hz), 4.15–4.22 (m, 8H, OCH_2), 6.24 (s, 2H, CH_2), 7.76 (s, 1H, CH). Calculated for $C_{18}H_{35}N_3O_8P_2$: C, 44.75; H, 7.24; N, 8.70. Found: C, 44.67; H, 7.31; N, 8.49.

Tetraethyl 2-[1-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-1*H*-1,2,3-triazol-4-yl]ethane-1,1-diyldiphosphonate (5e)

Yield 66%, oil. ^{31}P NMR (121.49 MHz, $CDCl_3$): δ 22.33. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 1.28–1.40 (m, 12H, CH_3), 1.93 (s, 3H, CH_3), 2.11 (d, 9H, CH_3, $^3J_{HH} = 11.2$ Hz), 2.89–3.09 (m, 1H, CH), 3.32–3.47 (m, 2H, CH_2), 4.01–4.29 (m, 8H, OCH_2, 3H), 5.28 (t, 1H, CH, $^3J_{HH} = 10.05$ Hz), 5.45 (t, 1H, CH, $^3J_{HH} = 9.12$ Hz), 5.54 (t, 1H, CH, $^3J_{HH} = 9.12$ Hz), 5.89 (d, 1H, $^3J_{HH} = 9.12$ Hz), 7.76 (s, 1H, CH). Calculated for $C_{26}H_{43}N_3O_{15}P_2$: C, 44.64; H, 6.15; N, 6.01. Found: C, 44.15; H, 6.14; N, 5.58.

Tetraethyl (2-{1-[3-(hydroxymethyl)-5-(5-methyl-2,4-dioxo-3, 4-dihydropyrimidin-1(2*H*)-yl)tetrahydrofuran-2-yl]-1*H*-1,2,3-triazol-4-yl}ethane-1,1-diyl)diphosphonate (5f)

Yield 92%, oil. ^{31}P NMR (80.99 MHz, $CDCl_3$): δ 24.73. ^{1}H NMR (200.13 MHz, $CDCl_3$) δ: 1.28–1.35 (m, 12H, CH_3), 1.96 (s, 3H, CH_3), 2.97–3.00 (m, 3H, CH_2CH), 3.35–3.37 (m, 3H, CH_2CH), 3.86 (dm, 1H, CH), 4.09–4.12 (dm, 1H, CH_2), 4.16–4.18 (m, 8H, OCH_2), 4.39–4.42 (m, 1H, CH_2), 5.35–5.39 (m, 1H, CH), 6.20–6.24 (m, 1H, CH), 7.43 (s, 1H, =CH), 7.75 (s, 1H, CH), 8.55 (br s, 1H, NH). ^{13}C (50.32 MHz, $CDCl_3$) δ: 12.9 (CH_3), 16.7 and 16.8 (CH_3CH_2O), 22.5 (CH_2), 37.0 (t, CP, $^1J_{CP} = 133.6$ Hz), 59.3 (CHN), 60.8 (CH_2OH), 63.3 (dd, OCH_2, $^2J_{CP} = 6.5$ Hz), 85.5 (NCH), 87.5 ($CHCH_2OH$), 111.2 (=CCH_3), 123.6 (NCH=C), 137.6 (=CH_2N), 145.5 and 145.6 and 145.7 (C_{Ar}), 151.0 (C=O), 164.8 (C=O). Calculated for $C_{22}H_{37}N_5O_{10}P_2$: C, 44.48; H, 6.23; N, 11.79. Found: C, 44.35; H, 6.24; N, 11.58.

Tetraethyl 1,3-bis(1benzyl-1*H*-1,2,3-triazol-4-yl)propane-2, 2-diyldipshopshonate (6)

Yield 88%, white crystals, mp 86–88 °C. ^{31}P NMR (80.99 MHz, $CDCl_3$) δ: 25.1. ^{1}H NMR (200.13 MHz, $CDCl_3$) δ: 1.33 (t, 12H, CH_3, $^3J_{HH} = 7.3$ Hz), 3.32 (dd, 4H, CH_2, $^3J_{HP(1)} = 16.0$ Hz $^3J_{HP(2)} = 12.2$ Hz), 4.21–4.27 (m, 8H, OCH_2), 5.52 (s, 4H, CH_2), 7.30–7.35 (m, 10H, arom.), 7.91 (s, 2H, CH). ^{13}C (50.32 MHz, $CDCl_3$) δ: 16.6 (d, CH_3, $^3J_{CP} = 3.3$ Hz), 16.7 (d, CH_3, $^3J_{CP} = 3.1$ Hz), 26.6 (PCH_2), 47.6 (t, CP, $^1J_{CP} = 130.9$), 54.2 (NCH_2), 63.1 & 63,2 ($POCH_2$), 125.0 (CH=), 128.5 and 128.9 and 129.4 (CH_{Ar}), 135.6 (*ipso*-C_{Ar}), 143.4 (C=). HRMS: calculated for $C_{29}H_{40}N_6O_6P_2$ (M^+) 630.2484, found 630.2480.

X-Ray crystallography. Crystals of **6** suitable for X-ray diffraction were grown from diethyl ether. Crystallographic data for **6** ($C_{29}H_{40}N_6O_6P_2$) at 173(2) K: Crystal size 0.42 × 0.30 × 0.22 mm, triclinic, space group $P\bar{1}$, $a = 8.615(6)$, $b = 12.829(4)$, $c = 14.996(5)$ Å, $\alpha = 88.06(3)$, $\beta = 78.28(4)$, $\gamma = 75.70(4)°$, $V = 1572.3(13)$ Å^3, $Z = 2$ ($Z' = 1$), $M = 630.61$, $d_{calc} = 1.332$ g m^{-3}, μ(MoKα) = 1.90 cm^{-1}, $F(000) = 668$. The intensities of 6834 reflections were measured with an Siemens P4 diffractometer at 173(2) K (λ(MoKα) = 0.71072 Å, $2\theta < 50°$, 2θ-scans), and 5524 independent reflections ($R_{int} = 0.0273$) were used in the further refinement. The structure was solved by direct methods and refined by the full-matrix least-squares technique against F^2 in the anisotropic-isotropic approximation. Analysis of Fourier density synthesis revealed that the ethyl groups (C(3)–C(4) and C(7)–C(8)) are disordered over two positions with equal occupancies. The positions of the hydrogen atoms were calculated from a geometrical point of view. The refinement converged to $wR_2 = 0.1940$ and GOF = 1.035 for all independent reflections ($R1 = 0.0702$ was calculated based on F for 3621 observed reflections with $I > 2\sigma(I)$). All calculations were performed using SHELXTL PLUS 5.0.[17] CCDC reference number 645541. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b705510b

Tetraethyl 1,3-bis[1-(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)-1*H*-1,2,3-triazol-4yl]propane-2,2-diyldiphosphonate (7)

Yield 92%, white crystals, mp 126–129 °C. ^{31}P NMR (80.99 MHz, $CDCl_3$) δ: 29.8. ^{1}H NMR (200.13 MHz, $CDCl_3$) δ: 1.30 (t, 12H,

CH_3, $^3J_{HH} = 7.1$ Hz), 2.91–2.95 (m, 4H, CH_2), 3.41 (dd, 4H, CH_2, $^3J_{HP} = 16.0$ Hz), 4.21–4.27 (m, 8H, OCH_2), 4.73 (t, 4H, CH_2, $^3J_{HH} = 7.4$ Hz), 8.01 (s, 2H, CH), (m). ^{19}F NMR (188.31 MHz, $CDCl_3$) δ: −76.9 (3F, m, CF_3), −110.3 (2F, m, CF_2CH_2), −117.9 (2F, m, CF_2CF_3), −118.9 (2F, m, $CH_2CF_2CF_2CF_2$), −119.6 (2F, m, $CH_2CF_2CF_2$), −122.2 (2F, m, $CF_2CF_2CF_3$). ^{13}C (50.32 MHz, $CDCl_3$) δ: 16.6 (d, CH_3, $^2J_{CP} = 6.2$ Hz), 26.5 ($PCCH_2$), 30.4 (t, CH_2CF_2, $^2J_{CF} = 21.9$ Hz), 41.6 (t, CP, $^1J_{CP} = 133.1$), 42.7 (NCH_2), 63.4 (d, OCH_2, $^2J_{CP} = 7.2$ Hz), 109.3–121.1, 125.6 (CH=), 142.7, 143.5 (C=). Calculated for $C_{31}H_{34}N_6O_6P_2F_{26}$: C, 32.59; H, 3.00. Found: C, 32.28; H, 3.21.

Octaethyl 2,2′-[1,1′-(1,4-phenylenebis(methylene)][bis(1*H*-1,2,3-triazol-4,1-diyl)]bis(ethane-2,1,1-triyl)tetraphosphonate (8)

Yield 67%, colorless oil. ^{31}P NMR (CD_3CN) δ: 29.3. ^{1}H NMR (CD_3CN) δ: 1.13–1.18 (m, CH_3, 24H), 3.00–3.05 (m, CHP + CH_2, 6H), 3.85–4.04 (m, OCH_2, 16H), 5.48 (s, CH_2, 4H), 7.32 (s, H_a, 4H), 7.63 (s, H_c, 2H). ^{13}C (50.32 MHz, $CDCl_3$) δ: 16.1 (d, CH_3, $^2J_{CP} = 6.1$ Hz), 22.0 (PCH_2), 37.1 (t, CP, $^1J_{CP} = 133.8$ Hz), 54.2 (NCH_2), 63.2 (d, OCH_2, $^2J_{CP} = 6.4$ Hz), 63.4 (d, OCH_2, $^2J_{CP} = 6.3$ Hz), 120.7 (CH=), 129.3 (C_{Ar}), 136.3 (C_{Ar}), 149.6 (C=). Calculated for $C_{32}H_{56}Br_2N_6O_{12}P_4Na_2$: C, 36.68; H, 5.35. Found: C, 37.11; H, 5.55.

Octaethyl 2,2′-[1,1′-(1,3-phenylenebis(methylene))bis(1*H*-1,2,3-triazol-4,1-diyl))bis(ethane-2,1,1-triyl]tetraphosphonate (9)

Yield 65%, colorless oil. ^{31}P NMR (CD_3CN) δ: 24.0. ^{1}H NMR (CD_3CN) δ: 1.30–1.33 (m, CH_3, 24H, $^3J_{HH} = 7.3$ Hz), 2.93–2.96 (m, CHP + CH_2, 6H), 3.82–4.13 (m, OCH_2, 16H), 5.50 (s, CH_2, 4H), 7.32 (s, H_a, 4H), 7.65 (s, H_c, 2H). Calculated for $C_{32}H_{56}Br_2N_6O_{12}P_4Na_2$: C, 36.68; H, 5.35. Found: C,37.18; H, 5.73.

Tetraethyl [2-(1*H*-1,2,3-triazol-4-yl)ethane-1,1-diyl]bis(phosphonate) (10)

To a solution of **5d** (0.48 g, 0.9 mmol) in MeOH (3.6 mL), NaOH (1 M aq. solution, 3.6 mL) was added. The reaction mixture was stirred at r.t. for 3 h and subsequently neutralized with 1 N HCl (5 mL), diluted with H_2O (20 mL) and extracted three times with ethyl acetate (45 mL). The organic layer was dried over $MgSO_4$ and evaporated under vacuum to yield the product in pure form. Yield 65%, oil. ^{31}P NMR (121.49 MHz, $CDCl_3$): δ 22.4. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 1.35 (t, 12H, CH_3, $^3J_{HH} = 7.08$ Hz), 2.93–3.01 (m, 1H, CH), 3.36–3.42 (m, 2H, CH_2), 4.17–4.23 (m, 8H, OCH_2), 5.77 (s, 1H, NH), 7.61 (d, 1H, CH, $^3J_{HH} = 10.95$ Hz). Calculated for $C_{12}H_{25}N_3O_6P_2$: C, 39.05; H, 6.77; N, 11.39. Found: C, 38.69; H, 6.72; N, 10.22.

[2-(1*H*-1,2,3-Triazol-4-yl)ethane-1,1-diyl]bis(phosphonic acid) (11)

A solution of trimethylsilyl bromide (0.54 g) in 2 mL of $CHCl_3$ was added dropwise to a solution of **10** (0.26 g) in $CHCl_3$ (7 mL). The reaction mixture was allowed to stir at r.t. overnight, then the solvent was removed under reduced pressure (rotary evaporator) and the residue was dissolved in methanol (10 mL). After stirring for 1 h, the methanol was removed in vacuum to give the crude product (0.14 g, 77%), mp 203–205 °C (ethanol–hexane). ^{31}P NMR (121.49 MHz, $CDCl_3$): δ 20.1. ^{1}H NMR (300.13 MHz, d_6-DMSO): δ 3.15–3.07 (m, 2H, CH_2), 3.88–3.84 (m, 1H, CH), 7.61 (s, 1H, CH). Calculated for $C_4H_9N_3O_6P_2$: C, 18.67; H, 3.50; N, 16.33. Found: C, 18.69; H, 3.52; N, 16.21.

Acknowledgements

This work was supported by the Deutsche Forschungsgemeinschaft (DFG no. 436 RUS 113/905/0-1) and the Russian Foundation of Basic Research (grant no. 06-03-04003).

References

1 (*a*) H. Fleisch, R. G. G. Russell and M. D. Francis, *Science*, 1996, **165**, 1262; (*b*) J. B. Catterall and T. E. Cawston, *Arthritis Res. Ther.*, 2002, **5**(1), 12.
2 (*a*) H. Fleisch, *Bisphosphonates in Bone Disease: From the Laboratory to the Patient*, The Parthenon Publishing Group, New York, 1995; (*b*) S. E. Papapoulos, J. O. Landman, O. L. M. Bijvoet, C. W. G. M. Loewik, R. Valkema, E. K. J. Pauwels and P. Vermeij, *Bone*, 1992, **13**, S41; (*c*) A. J. Yates and G. A. Rodan, *DDT*, 1998, **3**, 69; (*d*) E. Socrates and M. D. Papapoulos, *Am. J. Med.*, 1993, **95**, 48S; (*e*) S. Giannini, A. L. D'Angelo, G. L. Sartory, G. Passeri, L. D. Garbonare and C. Crebaldi, *Obstet. Gynecol. (Hagerstown, MD, U. S.)*, 1996, **88**, 431; (*f*) H. Uludag, *Curr. Pharm. Des.*, 2002, **8**, 99.
3 (*a*) S. H. Szajnman, A. Montalvetti, Y. Wang, R. Docampo and J. B. Rodriguez, *Med. Chem. Lett.*, 2003, **13**, 3231; (*b*) L. R. Garzoni, A. Caldera, L. Nazareth, M. Meirelles, S. L. Castro, R. Docampo, G. A. Meints, E. Oldfield and J. A. Urbina, *Int. J. Antimicrob. Agents*, 2004, **23**, 273; (*c*) L. R. Garzoni, M. C. Waghabi, M. M. Baptista, S. L. Castro, L. Nazareth, M. Meirelles, C. C. Britto, R. Docampo, E. Oldfield and J. A. Urbina, *Int. J. Antimicrob. Agents*, 2004, **23**, 286.
4 (*a*) J. M. Sanders, Y. Song, J. M. W. Chan, Y. Zhang, S. Jennings, T. Kosztowski, S. Odeh, R. Flessner, C. Schwerdtfeger, E. Kotsikorou, G. A. Meints, A. O. Gomez, D. Gonzalez-Pacanowska, A. M. Raker, H. Wang, E. R. van Beek, S. E. Papapoulos, C. T. Morita and E. Oldfield, *J. Med. Chem.*, 2005, **48**, 2957; (*b*) F. P. Coxon, F. H. Ebetino, E. H. Mules, M. C. Seabra, C. E. McKenna and M. J. Rogers, *Bone*, 2005, **37**, 349; (*c*) R. Engel, *Handbook of Organophosphorus Chemistry*, Marcel Dekker, New York, 1992, ch. 11.
5 (*a*) M. J. Rogers, *Curr. Pharm. Des.*, 2003, **9**, 2643; (*b*) M. Sato, W. Grasser, N. Endo, R. Akins, H. Simmons, D. D. Thompson, E. Golub and G. A. Rodan, *J. Clin. Invest.*, 1991, **88**, 2095; (*c*) P. Masarachia, M. Weinreb, R. Balena and G. A. Rodan, *Bone*, 1996, **19**, 281; (*d*) J. E. Dunford, K. Thompson, F. P. Coxon, S. P. Luckman, F. M. Hahn, C. D. Poulter, F. H. Ebetino and M. J. Rogers, *J. Pharmacol. Exp. Ther.*, 2001, **296**, 235.
6 (*a*) E. R. van Beek, C. Lowik, G. von der Pluijm and S. E. Papalous, *J. Bone Miner. Res.*, 1999, **14**, 722; (*b*) F. P. Coxon, M. H. Helfrich, R. Van't Hof, S. Sebti, S. H. Ralston, A. Hamilton and M. J. Rogers, *J. Bone Miner. Res.*, 2000, **15**, 1467.
7 (*a*) K. H. Bleicher, H. J. Boehm, K. Mueller and A. Alanine, *Nat. Rev. Drug Discovery*, 2003, **2**, 369; (*b*) J. F. Pritchard, M. Jurima-Komet, M. L. J. Reimer, E. Mortimer, B. Rolfe and M. N. Cayen, *Nat. Rev. Drug Discovery*, 2003, **2**, 542.
8 (*a*) H. Kolb and K. B. Sharpless, *Drug Discovery Today*, 2003, **24**, 1128; (*b*) H. C. Kolb, M. G. Finn and K. B. Sharpless, *Angew. Chem., Int. Ed.*, 2001, **40**, 2004.
9 R. Huisgen, in: *1,3-Dipolar Cycloaddition Chemistry*, ed. A. Padwa, Wiley, New York, 1984.
10 (*a*) V. V. Rostovtsev, L. G. Green, V. V. Fokin and K. B. Sharpless, *Angew. Chem., Int. Ed.*, 2002, **41**, 2596; (*b*) C. Tornoe, C. Christensen and M. Meldal, *J. Org. Chem.*, 2002, **67**, 3057.
11 (*a*) H. Wamhoff, in *Comprehensive Heterocyclic Chemistry*, ed. A. R. Katritzky and C. W. Rees, Pergamon, Oxford, 1984, vol. 5, pp. 669–732; (*b*) W.-Q. Fan, A. R. Katritzky, in *Comprehensive Heterocyclic Chemistry*, ed. A. R. Katritzky, C. W. Rees and C. W. V. Scriven, Elsevier Science, Oxford, 1996, vol. 4, pp. 1–126.
12 (*a*) R. Alvarez, S. Velazquez, A. San-Felix, S. Aquaro, E. D. Clercq, C. F. Perno, A. Karlesson, J. Balzarini and M. J. Camarasa, *J. Med. Chem.*, 1994, **37**, 4185; (*b*) M. J. Genin, D. A. Allwine, D. J. Anderson, M. R. Barbachyn, D. E. Emmert, S. A. Garmon, D. R. Graber, K. C. Greda, J. B. Hester, D. K. Hutchinson, J. Morris, R. J. Reischer, C. W.

Ford, G. E. Zurenco, J. C. Hamel, R. D. Schaadt, D. Stapert and B. H. Yagi, *J. Med. Chem.*, 2000, **43**, 953; (*c*) L. L. Brockunier, E. R. Parmee, H. O. Ok, M. R. Candelore, M. A. Cascieri, L. F. Colwell, L. Deng, W. P. Feeney, M. J. Forest, G. J. Hom, D. E. MacIntyre, L. Tota, M. J. Wyvratt, M. H. Fisher and A. E. Weber, *Bioorg. Med. Chem. Lett.*, 2000, **10**, 2111.
13 G. T. Shchetnikov, A. S. Peregudov and S. N. Osipov, *Synlett*, 2007, **1**, 136.
14 C. Li and C. Yuan, *Heteroat. Chem.*, 1993, **4**(5), 517.
15 H.-J. Lee, J.-M. Oh, S.-J. Choi, H.-K. Kim and S.-K. Choi, *Polym. Bull.*, 1994, **32**, 433.
16 (*a*) L. V. Lee, L. Mitchell, S.-J. Huang, V. V. Fokin, K. B. Sharpless and C.-H. Wong, *J. Am. Chem. Soc.*, 2003, **125**, 9588; (*b*) P. Appukkuttan, W. Dehaen, V. V. Fokin and E. von der Eycken, *Org. Lett.*, 2004, **6**, 4223; (*c*) A. K. Feldman, B. Colasson and V. V. Fokin, *Org. Lett.*, 2004, **6**, 3897.
17 G. M. Sheldrick, *SHELXTL-97, version 5.10*, Bruker AXS Inc., Madison, WI, USA, 1997.