Four-fold click reactions: Generation of tetrahedral methane- and adamantane-based building blocks for higher-order molecular assemblies†

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A modular concept for the generation of achiral and chiral non-racemic tetrahedral tectons from common precursors was developed. The tectons presented here are based on tetraphenylmethane or 1,3,5,7-tetraphenyladamantane core structures. They are obtained through high-yielding four-fold click reactions, using either the tetraazido or the tetraalkyne precursors. In most cases, the tetratriazoles are obtained as pure products after simple washing with water and methanol. The side chains of the tectons prepared include a self-complementary DNA dimer, obtained from a 3′-azidonucleoside and a phosphoramidite. The concept allows for a variation of the "sticky ends", leading to tecton or ligand libraries.

Introduction

Recently, we initiated a program on the syntheses of organic building blocks or ligands for higher-order molecular assemblies.[1] Organic tectons – from the Greek word for 'builder' – have been specifically designed to self-assemble either through hydrogen bonding[2] or, in the presence of metal ions, *via* coordination bonds,[3] leading to higher-order molecular assemblies.[4] Amongst the different possible molecular networks, diamondoid ones, based on tetrahedral tectons, figure among the best known examples.[5] Other 3-D lattices are conceivable based on the self-assembly of tetrahedral tectons. Their formation can be expected to be dependent on the flexibility of the tectons in question. Undesirable flexibility may be avoided by choosing rigid core stuctures,[2c,6] favouring the better-studied diamondoid networks.[7]

In order to develop an efficient strategy for the preparation of diverse rigid 3-D tetrahedral building blocks, based on identical core structures, we sought a general method for attaching different "sticky ends" – functional groups enabling the supramolecular self-assembly – onto tetrakisphenylmethane and 1,3,5,7-tetrakisphenyladamantane core structures. The sticky ends were to include short DNA chains that allow the generation of assemblies based on the formation of Watson–Crick duplexes.[8] We decided to explore the so-called click chemistry[9] – a Huisgen 1,3-dipolar cycloaddition reaction between organic azides[10] and alkynes – in order to generate different building blocks using common precursors. This copper-catalyzed cycloaddition reaction – leading exclusively to 1,4-substituted triazoles – has already served for the polyfunctionalization of rigid structures[11] and the synthesis of higher-order interlocked structures.[12] Numerous examples of the formation of dendrimers are known;[13] even six-[1b] and twelve-fold[14] derivatization reactions of T_h-symmetric C_{60} fullerene cores have been achieved *via* click chemistry. However, to the best of our knowledge, this reaction has not yet been used to decorate tetrahedral core structures with diverse sticky sites in a modular fashion.

We have previously reported on the synthesis of tetrakis(4-azidophenyl) compounds and their energetic potential.[15] Here we describe an optimized synthesis of methane- and adamantane-based tetraphenylazides and their use in four-fold click reactions. Furthermore, access to the corresponding tetrakis(4-ethynylphenyl)methane and their four-fold click reaction has also been investigated.

Results and discussion

Synthesis of tetrakis(4-azidophenyl)methane or -adamantane

In a previous communication in this journal,[15] we presented four-fold azidation of tetrakis(4-iodophenyl)methane and -adamantane. These transformations, however, provided the desired tetraazides in moderate yields only in some cases, along with lower-substituted homologues. As a consequence, we sought a more efficient route to prepare the respective tetraazides. We started to explore tetraazidation reactions *via* the tetradiazonium salts, generated from the corresponding tetraamines. The latter have been obtained according to literature-known procedures (see ESI†).[16]

First, tetraazidation of the 4,4′,4″,4‴-methanetetrayltetraaniline (**5**) was investigated (Table 1, entries 1–3). Using trimethylsilyl azide either in the presence of isoamyl nitrite and sulfuric acid (entry 1), or in combination with *t*-butyl nitrite without acid (entry 2), gave compound **7** in moderate to acceptable yield. The best results were achieved under classical

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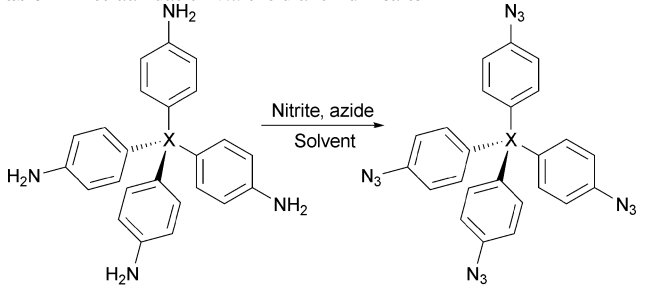
† Electronic supplementary information (ESI) available: Detailed experimental procedures for compounds **5**, **6**, **9** and **10**; NMR spectra of **5g,h** and MALDI-TOF-MS of **5i,j**. CCDC reference numbers 734783 (**1a**), 734784 (**4a**), and 734785 (**7**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b912189g

Table 1 Tetraazidation *via* the diazonium salts



5 (X = C) **7** (X = C)

6 (X = adamant-1,3,5,7-tetrayl) **8** (X = adamant-1,3,5,7-tetrayl)

Entry	Reactant	Nitrite	Azide	Acid	Solvent	Yield (%)
1	**5**	$C_5H_{11}ONO$	$TMSN_3$	H_2SO_4	DMF	16
2	**5**	*t*-BuONO	$TMSN_3$	—	MeCN	55
3	**5**	$NaNO_2$	NaN_3	HCl	H_2O	79
4	**6**	$NaNO_2$	NaN_3	HCl	H_2O	0
5	**6**	*t*-BuONO	$TMSN_3$	—	MeCN	80

conditions with sodium azide and sodium nitrite in the presence of hydrochloric acid (entry 3). **Caution**: *sodium azide is potentially explosive. Furthermore, the evolution of hydrazoic acid is possible under acidic conditions.* Tetraazide **7** was obtained as a pure product in 79% yield after extraction. No further purification by column chromatography was necessary. The structure of **7** was confirmed by X-ray crystallography (Fig. 2).‡ Surprisingly, when the optimized conditions established for the methane core were applied to the adamantane derivative, complete decomposition of the starting material was observed (entry 4). Fortunately, the desired tetraazido adamantane derivative could be obtained in high yield in the presence of trimethylsilyl azide and *t*-butyl nitrite (entry 5).

‡ Crystal structure determinations: All single-crystal X-ray diffraction studies were carried out on a Nonius Kappa-CCD diffractometer at 123(2) K using MoKα radiation ($\lambda = 0.71073$ Å). Direct methods (SHELXS-97)[20] were used for structure solution and refinement was carried out using SHELXL-97[20] (full-matrix least-squares on F^2). Hydrogen atoms were localized by difference electron density determination and refined using a riding model. A semi-empirical absorption correction was applied for **4a**. The absolute structure of **4a** was determined by refinement of Flack's *x*-parameter ($x = 0.01(6)$).[21] **1a**: pale yellow, $C_{57}H_{40}N_{12} - 2C_3H_7NO$, $M = 1039.20$, crystal size $0.40 \times 0.16 \times 0.04$ mm, monoclinic, space group $C2/c$ (No. 15): $a = 29.701(6)$ Å, $b = 8.996(2)$ Å, $c = 20.844(4)$ Å, $\beta = 109.53(2)°$, $V = 5248.9(19)$ Å^3, $Z = 4$, ρ(calcd) = 1.315 Mg m^{-3}, $F(000) = 2184$, $\mu = 0.084$ mm^{-1}, 20477 reflexes ($2\theta_{max} = 50$ °), 4625 unique [$R_{int} = 0.073$], 356 parameters, 37 restraints, $R1$ ($I > 2\sigma(I)$) = 0.085, $wR2$ (all data) = 0.231, GOOF = 1.05, largest diff. peak and hole +1.173/–0.824 e Å^{-3} (in the solvent DMF). **4a**: colorless crystals, $C_{66}H_{52}N_{12} - 4CHCl_3$, $M = 1490.67$, crystal size $0.40 \times 0.25 \times 0.15$ mm, tetragonal, space group $P\bar{4}$ (No. 81): $a = 21.970(3)$ Å, $c = 6.972(1)$ Å, $V = 3365.3(8)$ Å^3, $Z = 2$, ρ(calcd) = 1.471 Mg m^{-3}, $F(000) = 1528$, $\mu = 0.547$ mm^{-1}, 17869 reflexes ($2\theta_{max} = 55$ °), 7550 unique [$R_{int} = 0.034$], 425 parameters, $R1$ ($I > 2\sigma(I)$) = 0.050, $wR2$ (all data) = 0.132, GOOF = 1.06, largest diff. peak and hole +0.909/–0.456 e Å^{-3} (near the solvent $CHCl_3$). **7**: yellow crystals, $C_{25}H_{16}N_{12}$, $M = 484.50$, crystal size $0.30 \times 0.15 \times 0.10$ mm, monoclinic, space group $C2/c$ (No. 15), $a = 18.878(1)$ Å, $b = 7.137(1)$ Å, $c = 18.265(1)$ Å, $\beta = 111.37(1)°$, $V = 2273.5(4)$ Å^3, $Z = 4$, ρ(calcd) = 1.416 Mg m^{-3}, $F(000) = 1000$, $\mu = 0.094$ mm^{-1}, 8191 reflexes ($2\theta_{max} = 55$ °), 2578 unique [$R_{int} = 0.046$], 168 parameters, $R1$ ($I > 2\sigma I$)) = 0.051, $wR2$ (all data) = 0.116, GOOF = 1.01, largest diff. peak and hole +0.287/–0.252 e Å^{-3}.

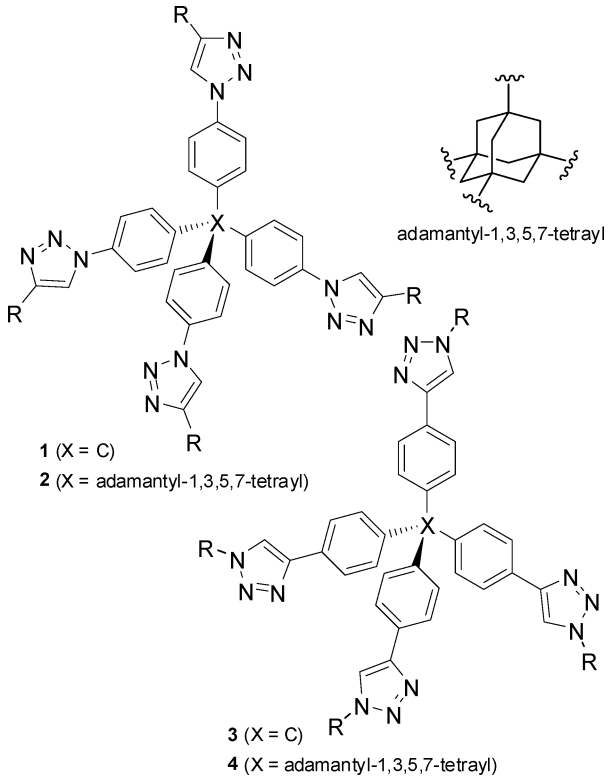


Fig. 1 Structures of target compounds **1**–**4**.

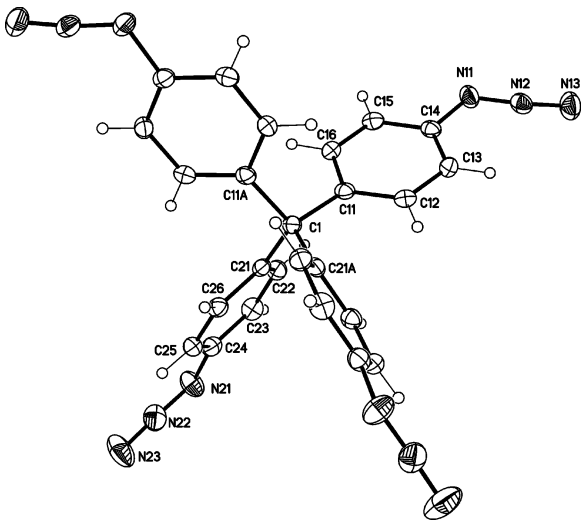


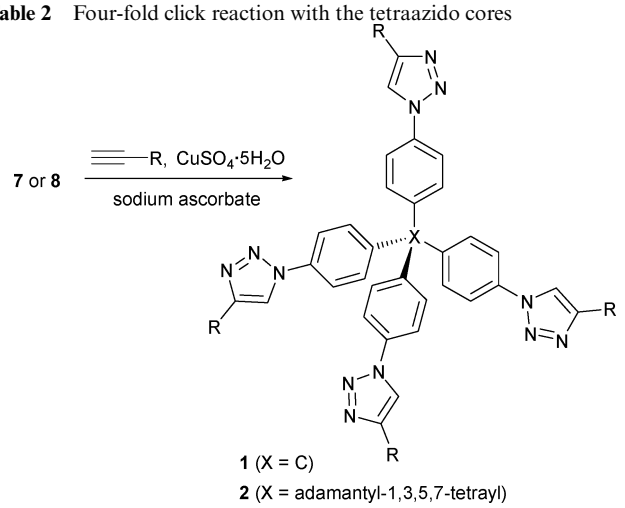
Fig. 2 Molecular structure of tetrakis(4-azidophenyl)methane (**7**) (displacement parameters are drawn at the 50% probability level).

Synthesis of tetrakis(4-ethynylphenyl)methane and adamantane derivatives

For the syntheses of tetraalkynes **9** and **10**, literature known procedures were employed, yielding the desired products in excellent overall yields (see ESI).[16c]

With both types of organic building block precursors in hand, we began to explore suitable protocols for the four-fold click reactions.

Table 2 Four-fold click reaction with the tetraazido cores



Entry	Reactant	R	Solvent	Product	Yield (%)
1	**7**	Ph	*t*-BuOH/H_2O	**1a**	97
2	**8**	Ph	*t*-BuOH/H_2O	**2a**	0
3	**8**	Ph	DMSO/H_2O	**2a**	99
4	**7**	CH_2OH	*t*-BuOH/H_2O	**1b**	76
5	**8**	CH_2OH	DMSO/H_2O	**2b**	11[a]
6	**7**	(*S*)-CHOHMe	*t*-BuOH/H_2O	**1c**	92
7	**8**	(*R*)-CHOHMe	DMSO/H_2O	**2c**	88[b]
8	**7**	*p*-C_6H_4CN	*t*-BuOH/H_2O	**1d**	91
9	**8**	*p*-C_6H_4CN	DMSO/H_2O	**2d**	90[c]
10	**7**	CH_2NH_2	*t*-BuOH/H_2O	**1e**	94
11	**8**	CH_2NH_2	DMSO/H_2O	**2e**	Trace

[a] Ref. 15. [b] Based on recovery of the starting material. [c] Yield determined by NMR.

Click reactions with tetrakis(4-azidophenyl) cores

Initially, the original click conditions developed by Fokin and Sharpless[9b,c] (sodium ascorbate, copper sulfate pentahydrate in *t*-BuOH/H_2O 1:1) were explored (Table 2). When tetrakis(4-azidophenyl)methane was reacted with ethynylbenzene, the desired tetrakistriazole **1a** was obtained in excellent yield (entry 1). Single crystals of **1a** were grown in a solution of DMF/acetone by slow evaporation of the solvents, and its structure was confirmed by X-ray crystallography (Fig. 3).‡ Running the same reaction with adamantane derivative **8** resulted in complete recovery of the starting materials (entry 2). Only when *t*-BuOH was replaced by DMSO was 1,3,5,7-tetrakis(4-(4-phenyl-1,2,3-triazol-1-yl)phenyl)adamantane (**2a**) formed, in nearly quantitative yield (entry 3).

With the conditions optimized for both cores, a series of different alkynes were "clicked" with both tetraazides. In the methane core series, the corresponding tetraazides were obtained in good to excellent yields in all cases (entries 4, 6, 8 and 10). These examples show once more the compatibility of the click reaction conditions with a wide range of functional groups. For the adamantane core, the same tolerance was observed; the yields of the tetraazido-adamantanes are, however, generally lower mainly due to solubility problems, which increase with increasing polarity of the product (entries 7 and 9). Tetraol **2b** was only obtained in 11%, mostly due to loss of product during column chromatography (entry 5). Tetraamine **2e** probably formed in trace amounts according to NMR of the crude mixture, but could not be isolated (entry 11).

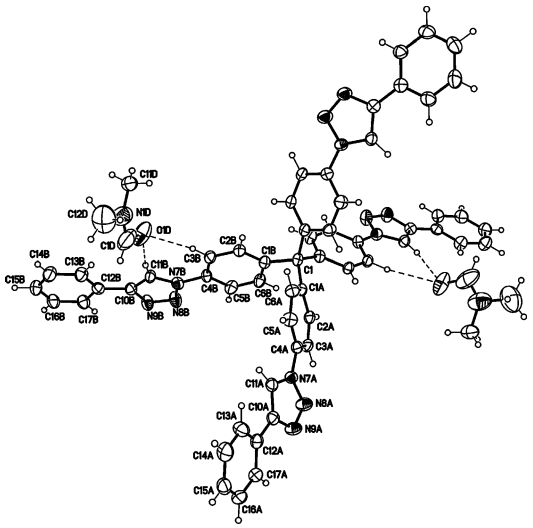
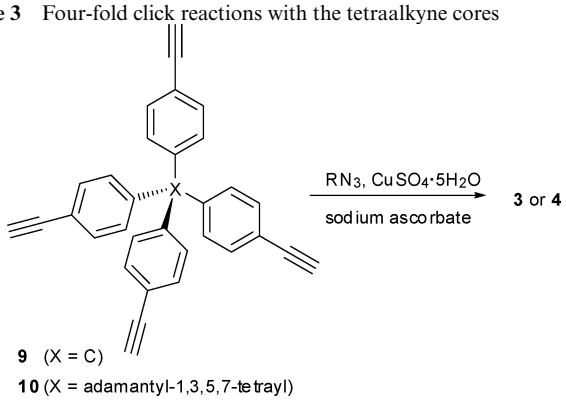


Fig. 3 Molecular structure of **1a** (displacement parameters are drawn at the 50% probability level).

Click reactions with the tetrakis(4-ethynylphenyl) cores

Next, the four-fold click reaction was performed with the tetrakis(4-ethynylphenyl) cores **9** and **10** and a series of commercial or readily available azides (Table 3). To start with, the previously optimized conditions were tested. Tetrakis(4-ethynylphenyl)methane was reacted in a mixture of *t*-BuOH/H_2O, whereas for the adamantane derivative, a DMSO/H_2O mixture was used. When reacted with phenylazide, both cores delivered the

Table 3 Four-fold click reactions with the tetraalkyne cores



Entry	Reactant	R	Solvent	Product	Yield (%)
1	**9**	Ph	*t*-BuOH/H_2O	**3a**	99
2	**10**	Ph	DMSO/H_2O	**4a**	72
3	**9**	*p*-C_6H_4F	*t*-BuOH/H_2O	**3b**	97
4	**10**	*p*-C_6H_4F	DMSO/H_2O	**4b**	86
5	**9**	*p*-$C_6H_4NO_2$	*t*-BuOH/H_2O	**3c**	92
6	**10**	*p*-$C_6H_4NO_2$	DMSO/H_2O	**4c**	Trace
7	**9**	(*S*)-BnCHCO$_2$Et	*t*-BuOH/H_2O	**3d**	85
8	**10**	(*S*)-BnCHCO$_2$Et	DMSO/H_2O	**4d**	64
9	**9**	(*S*)-BnCHCO$_2$H	*t*-BuOH/H_2O	**3e**	88
10	**10**	(*S*)-BnCHCO$_2$H	DMSO/H_2O	**4e**	0
11	**9**	*m*,*m*-$C_6H_3(CO_2H)_2$	*t*-BuOH/H_2O	**3f**	82
12	**10**	*m*,*m*-$C_6H_3(CO_2H)_2$	DMSO/H_2O	**4f**	60

corresponding tetratriazoles **3a** and **4a** in nearly quantitative yield (entries 1 and 2). Single crystals of compound **4a** were obtained by slow evaporation of a saturated solution of **4a** in chloroform, and the X-ray crystallographic structure was determined (Fig. 4).‡ Subsequently, a series of different azides were clicked onto our cores. The methane core delivered as before the four-fold click products in good to excellent yields after simple washing of the crude product with water and methanol (entries 1, 3, 5, 7, 9 and 11). It is worth mentioning that even tetraacids (entry 9) and octaacids (entry 12) can be prepared in high yields. For the adamantane core, we observed generally good to excellent yields of the corresponding tetratriazoles, except when solubility problems of the reactants or the products occurred. This resulted in either very low yields or no reaction at all (entries 6 and 10). We were, however, surprised to observe that tetradicarboxyphenyl derivative **4f** could be isolated in 60% yield (entry 12). This is all the more satisfying as these octaacids represent an interesting building block for higher-order molecular assemblies.

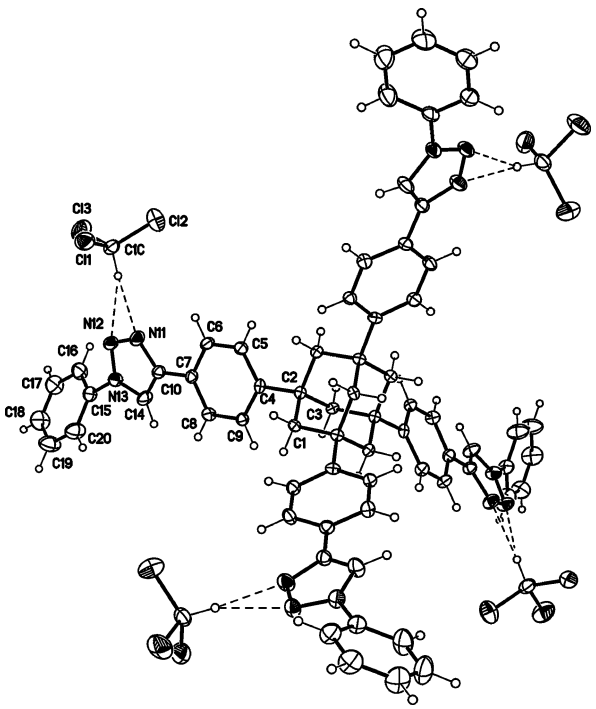


Fig. 4 Molecular structure of one independent molecule of **4a** (displacement parameters are drawn at the 50% probability level).

In the light of using our tetratriazoles as building blocks for porous periodic networks, we were also interested in the packing of our molecules in the crystalline state. Fig. 5 shows the space-filling representation of the unit cells of azide **7** and triazoles **1a** and **4a**. The respective apparent porosities[22,23] of 22% (**1a**) and 30% (**4a**) are very high, and clearly indicate a high potential of these compounds to act as building blocks in highly porous networks, once equipped with suitable sticky sites.

Click reactions to introduce self-complementary DNA chains

Finally, our methodology was extended to the four-fold cycloaddition of 3′-azido-2′,3′-dideoxynucleosides to tetraethynyl core **10** (Scheme 1). Both 3′-azido-2′,3′-dideoxythymidine (AZT)

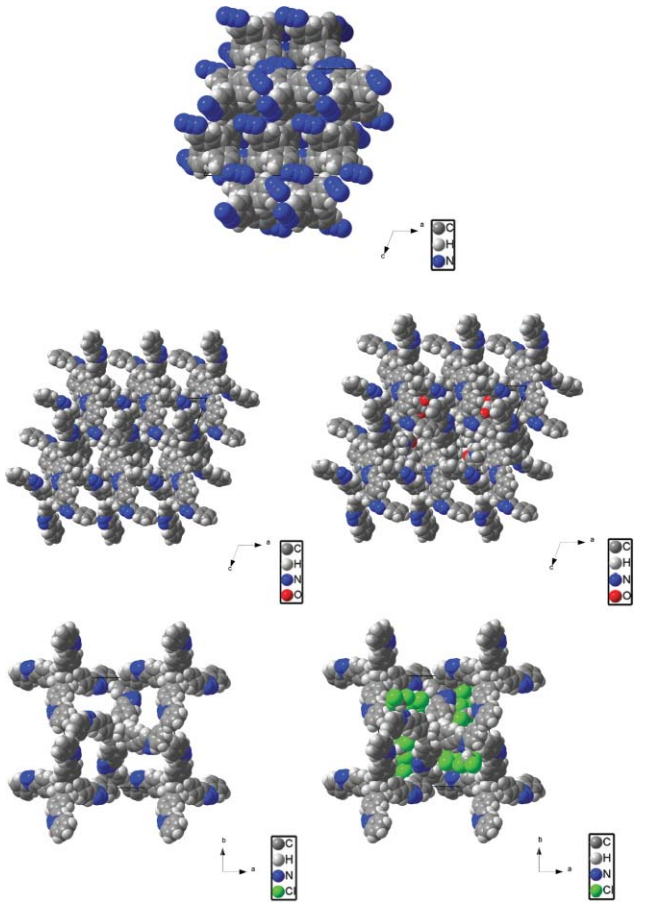
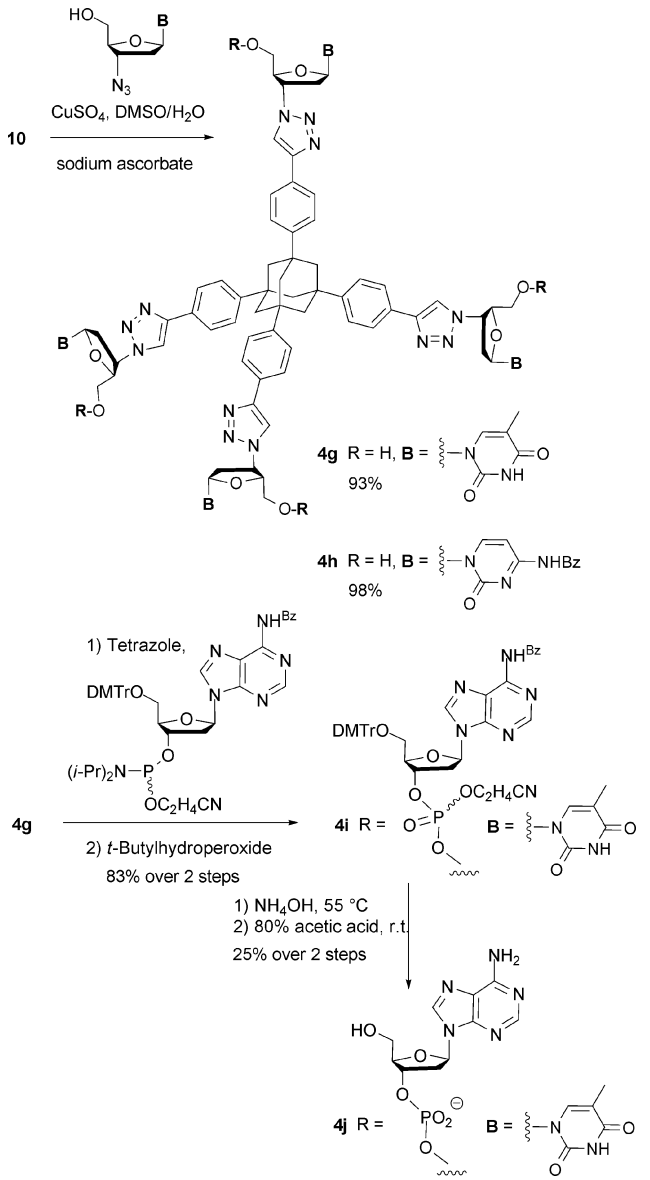


Fig. 5 Space-filling representation of the unit cells of **7** parallel to the *b*-axis (top), **1a** parallel to the *b*-axis (middle left without solvent, middle right with included solvent DMF) and **4a** parallel to the *c*-axis (bottom left without solvent, bottom right with included solvent $CHCl_3$).

and 3′-azido-N^6-benzoyl-2′,3′-dideoxycytidine[17] were thus added four times to this core to give **4g** and **4h** in high yields.[18] To explore the synthesis of tectons with DNA chains in solution, tetranucleoside **4g** was coupled to the 3′-phosphoramidite of 2′-deoxyadenosine, following a modification of a protocol for solution-phase DNA syntheses.[19] *In situ* oxidation led to fully protected octanucleoside **4i**, which proved easy to isolate, as it formed a solid at the organic–aqueous interface during aqueous extraction. Two-step deprotection of **4i** then gave **4j** with four self-complementary DNA chains in moderate yield after HPLC purification of an analytical sample. These results demonstrate the versatility of the current approach and open up a new avenue to DNA-based nanostructuring.[8]

Conclusions

We have used and adapted click chemistry for a highly effective and modular approach to generate different organic tectons based on common precursors. The tetrakis[(triazolyl)phenyl]methane and -adamantane derivatives **1**–**4** were obtained in excellent yields and purities, in most cases after simple washing with water and methanol, without need for further purification by column chromatography (Fig. 1). Some of these structures represent interesting building blocks for the generation of molecular architectures. Both routes offer access to similar triazoles having virtually the same



Scheme 1 Synthesis of tetrahedral tectons with nucleosidic "sticky ends".

angles in good to excellent yields. Therefore, depending on the accessibility of starting materials, either one of the precursors (azide or alkyne) can be chosen for tecton design.

Experimental

General methods

^{1}H NMR spectra were recorded on a Bruker AVANCE 400 (400 MHz) or AVANCE DRX 500 (500 MHz) spectrometer as solutions in $CDCl_3$, DMSO-d_6 or MeOH-d_4. Chemical shifts are expressed in parts per million (ppm, δ) downfield from tetramethylsilane (TMS) and are referenced to $CHCl_3$ (7.26 ppm), DMSO (2.50 ppm) or MeOH (3.31 ppm) as the internal standard. All coupling constants are absolute values and *J* values are expressed in Hertz (Hz). The description of signals include: s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, m = multiplet. The data are described according to a first-order analysis. The signal abbreviations include: Ar-H = aromatic proton.

^{13}C NMR spectra were recorded on a Bruker AVANCE 400 (100 MHz) or AVANCE DRX 500 (125 MHz) spectrometer as solutions in $CDCl_3$, DMSO-d_6 or MeOH-d_4. Chemical shifts are expressed in parts per million (ppm, δ) downfield from tetramethylsilane (TMS) and are referenced to $CHCl_3$ (77.4 ppm), DMSO (39.5 ppm) or MeOH (49.1 ppm) as internal standard. The multiplicity was analyzed by DEPT and is described as follows: + = primary or tertiary C-atom (positive signal), – = secondary C-atom (negative signal) and q = quaternary C-atom (no signal).

MS (EI) (electron impact mass spectrometry): Finnigan MAT 90 (70 eV). The molecular fragments are quoted as the relation between mass and charge (*m*/*z*), the intensities as a percentage value relative to the intensity of the base signal (100%). The abbreviation [M^+] refers to the molecular ion.

MALDI-TOF mass spectra were acquired on a Bruker REFLEX IV spectrometer using a nitrogen laser (λ = 337 nm) and software XACQ 4.0.4 and XTOF 5.1.0. Fully protected DNA hybrids were measured in linear, positive mode. Deprotected DNA hybrids were measured in linear, negative mode. MALDI matrix mixture for DNA hybrids was 2,4,6-trihydroxyacetophenone (0.3 M in EtOH) and diammonium citrate (0.1 M in H_2O) at a ratio of 2/1 (v/v). Calculated masses are average masses (*m*/*z*) found are those for the unresolved pseudomolecular ion peaks ([M + H]$^+$ or [M – H]$^-$). The accuracy of mass determination with the external calibration used is approximately ± 0.1.

UV-VIS spectra were recorded on a Lambda 25 spectrometer from Perkin Elmer, using the software Lambda. The detection was at 259.8 nm, using quartz cuvettes with a thickness of 1 cm.

IR (infrared spectroscopy) was performed on a FT-IR Bruker IFS 88 instrument. IR spectra of solids were recorded in KBr, and as thin films on KBr for oils and liquids. The position of the absorption band is given in wave numbers $\tilde{\nu}$ in cm^{-1}. The forms and intensities of the bands were characterized as follows: vs = very strong (0–10% T), s = strong (10–40% T), m = medium (40–70% T), w = weak (70–90% T), vw = very weak (90–100% T), br = broad.

Routine monitoring of reactions was performed using silica gel coated aluminium plates (Merck, silica gel 60, F254), which were analyzed under UV-light at 254 nm and/or dipped into a solution of molybdatophosphate (5% phosphomolybdic acid in ethanol, dipping solution) or ninhydrin solution (3 g of ninhydrin in 100 mL of ethanol) and heated with a heat gun. Solvent mixtures are given as volume/volume. DNA hybrids were purified on Nucleosil 120-5 reverse-phase C4 HPLC column (250 × 4.6; Macherey-Nagel, Düren, Germany) at a flow rate of 1 mL min^{-1} and detection at 260 nm. Solvents, reagents and chemicals were purchased from Aldrich, Fluka and Acros. Standard nucleosides 3′-phosphoramidites were obtained from Proligo (Hamburg, Germany). Tetrazole solution (0.45 M in acetonitrile, for DNA synthesis) and *t*-butyl hydroperoxide solution (5.5 M in decane over 4 Å molecular sieves) were from Sigma/Aldrich (Deisenhofen, Germany). Tetrahydrofuran was distilled from sodium/benzophenone under argon prior to use. Dichloromethane, ethyl acetate and diethyl ether were distilled from calcium hydride. Solid materials were powdered. All reactions involving moisture-sensitive reactants were executed under an argon atmosphere using oven-dried and/or flame-dried glassware. All other solvents, reagents and chemicals were used as purchased unless stated otherwise.

Tetrakis(4-azidophenyl)methane (7). 4,4′,4″,4‴-Methanetetrayltetraaniline (**5**) (1.50 g, 3.93 mmol, 1.0 equiv.) was suspended in water (30 mL) and the reaction mixture was cooled to –5 °C. At this temperature conc. sulfuric acid (15 mL) was added slowly and the suspension turned to a dark clear solution. Then, a solution of sodium azide (1.23 g, 17.7 mmol, 4.5 equiv.) in water (9 mL) was added dropwise under a strong evolution of gas. **Caution**: *sodium azide is potentially explosive. Furthermore, the evolution of hydrazoic acid is possible under acidic conditions.* The reaction mixture was stirred for 2 h at room temperature. After this, the formed precipitate was filtered off, washed with water (100 mL) and dried *in vacuo* to give tetrakis(4-azidophenyl)methane (**7**) (1.43 g, 75%) as a grey solid. R_f 0.30 (cyclohexane/EtOAc 25:1); δ_H (400 MHz; $CDCl_3$) 6.86 (8 H, d, *J* 8.8, Ar_m-*H*), 7.06 (8 H, d, *J* 8.8, Ar_o-*H*) ppm; δ_C (100 MHz; $CDCl_3$) 63.3 (C_q(Ar)$_4$), 118.4 (+, C_o-Ar), 132.1 (+, C_m-Ar), 138.2 [C_q-Ar(N_3)], 142.9 [C_q-Ar(C)] ppm; ν/cm^{-1} (DRIFT) 3032wv, 2544vw, 2412vw, 2252w, 2124s, 1601m, 1577w, 1501s, 1413w, 1290s, 1192 m, 1130w, 1119w, 1017w, 945vw, 911vw, 829m, 757vw, 701vw, 671w, 634vw, 555m, 538m, 414vw; *m*/*z* (EI) 484 (M^+, 100%), 456 (35), 317 (M^+ – 12N, 12), 240 (M^+ – $C_6H_4N_{12}$, 9); $C_{25}H_{16}N_{12}$ calcd. 484.1621; found 484.1623 [M^+].

1,3,5,7-Tetrakis(4-azidophenyl)adamantane (8). 1,3,5,7-Tetrakis(4-aminophenyl)adamantane (**6**) (96.0 mg, 0.19 mmol, 1.0 equiv.) was dissolved under argon in acetonitrile (10 mL) at 0 °C. ^{t}BuONO (0.14 mL, 119 mg, 1.15 mmol, 6.0 equiv.) and $TMSN_3$ (0.13 mL, 114 mg, 0.99 mmol, 5.0 equiv.) were added dropwise and the reaction mixture was stirred for several hours at room temperature until the reaction was complete (controlled by TLC). The solvent was removed under reduced pressure and the crude product purified by flash chromatography on silica gel using cyclohexane/CH_2Cl_2 (2:1) as eluent to give 1,3,5,7-tetrakis(4-azidophenyl)adamantane (**8**) (98.0 mg, 80%) as a yellowish solid. R_f 0.28 (cyclohexane/CH_2Cl_2 1:1); δ_H (400 MHz; $CDCl_3$) 2.10 (12 H,s, Ad-CH_2), 7.02 (8 H, d, *J* 8.5, Ar_o-*H*), 7.45 (8 H, d, *J* 8.5, Ar_m-*H*); δ_C (100 MHz; $CDCl_3$) 39.0 (C_q-Ad), 47.2 (–, C_s-Ad), 118.7 (+, C_m-Ar), 126.3 (+, C_o-Ar), 138.1 (C_q, Ar-Ad), 145.8 (C_q, Ar_p-N_3); ν/cm^{-1} (DRIFT) 3395vw, 3244vw, 3033w (C_{Ar}-H), 2929w, 2851w, 2574vw, 2419w, 2326vw, 2259w, 2127m, 1953vw, 1893vw, 1768vw, 1604w, 1575w, 1508m, 1445w, 1413w, 1356w, 1296m, 1190w, 1130w, 1014w, 892vw, 822m, 770w, 671w, 561w, 532w; λ ($CHCl_3$)/nm 256 (ε/dm^3 mol^{-1} cm^{-1} 6568).

General procedure for the synthesis of tetrakis(1,2,3-triazol-1-yl)-phenyl derivatives 1, methane series

Tetrakis(4-azidophenyl)methane (**7**) (0.10 g, 0.21 mmol, 1.0 equiv.) was suspended in 10 mL ^{t}BuOH/H_2O. Then $CuSO_4 \cdot 5H_2O$ (5.20 mg, 0.02 mmol, 0.1 equiv.), sodium ascorbate (16.4 mg, 0.08 mmol, 0.4 equiv.) and the corresponding alkyne (1.26 mmol, 6.0 equiv.) were added subsequently. The reaction mixture was stirred for 72 h at 70 °C. Then the precipitate was filtered off and washed with H_2O (20 mL) and methanol (10 mL) to give the four-fold click product.

General procedure for the synthesis of tetrakis(1,2,3-triazol-1-yl)-phenyl derivatives 2, adamantane series

1,3,5,7-Tetrakis(4-azidophenyl)adamantane (**8**) (40.0 mg, 0.07 mmol, 1.0 equiv.) were solved in DMSO (10 mL) under argon at 100 °C. $CuSO_4 \cdot 5H_2O$ (3.60 mg, 0.01 mmol, 0.2 equiv.), sodium ascorbate (5.20 mg, 0.03 mmol, 0.4 equiv.), solved in H_2O (0.5 mL), and the corresponding alkyne (0.83 mmol, 12 equiv.) were added slowly. It was stirred for 48 h at 100 °C, taken-up in $CHCl_3$ (20 mL) and washed with H_2O (2 × 20 mL), brine (2 × 20 mL) and H_2O (2 × 20 mL). The solvent was removed under reduced pressure. The crude product was taken-up in $CHCl_3$ (30 mL) and dried over $MgSO_4$.

General procedure for the synthesis of tetrakis(1,2,3-triazol-4-yl)-phenyl derivatives 3, methane series

Tetrakis(4-ethynylphenyl)methane (**9**) (0.10 g, 0.24 mmol, 1.0 equiv.) was suspended in 10 mL ^{t}BuOH/H_2O. Then $CuSO_4 \cdot 5H_2O$ (6.00 mg, 0.02 mmol, 0.1 equiv.), sodium ascorbate (19.0 mg, 0.10 mmol, 0.4 equiv.) and the corresponding azide (1.44 mmol, 6.0 equiv.) were added subsequently. The reaction mixture was stirred for 72 h at 70 °C. Then the precipitate was filtered off and washed with H_2O (20 mL) and methanol (10 mL) to give the four-fold click product.

General procedure for the synthesis of tetrakis(1,2,3-triazol-4-yl)-phenyl derivatives 4, adamantane series

1,3,5,7-Tetrakis(4-ethynylphenyl)adamantane (**10**) (70.0 mg, 0.13 mmol, 1.0 equiv.) were dissolved in DMSO (10 mL) under argon at 100 °C. $CuSO_4 \cdot 5H_2O$ (6.50 mg, 0.03 mmol, 0.2 equiv.), sodium ascorbate (10.3 mg, 0.05 mmol, 0.4 equiv.), solved in H_2O (0.5 mL), and the corresponding alkyne (0.78 mmol, 6.0 equiv.) were added slowly. It was stirred for 48 h at 100 °C, taken-up in $CHCl_3$ (20 mL) and washed with H_2O (2 × 20 mL), brine (2 × 20 mL) and H_2O (2 × 20 mL). The solvent was removed under reduced pressure. The crude product was taken-up in $CHCl_3$ (30 mL) and dried over $MgSO_4$.

Tetrakis(4-(4-phenyl-1,2,3-triazol-1-yl)phenyl)methane (1a). The product was isolated after filtration and washing as a yellow solid (179 mg, 97%). δ_H (400 MHz; DMSO-d_6) 7.39 (4 H, t, *J* 7.5, Ar_p-*H*), 7.51 (8 H, t, *J* 7.5, Ar_m-*H*), 7.64 (8 H, d, *J* 8.8, Ar_o(N)-*H*), 7.96 (8 H, d, *J* 7.5, Ar_o-*H*), 8.02 (8 H, d, *J* 8.8, Ar_m(N)-*H*), 9.33 (4 H, s, *H*-triazole) ppm; δ_C (100 MHz; DMSO-d_6) 63.9 (C_q-(Ar)$_4$), 119.6 (*C*H-triazole), 120.1 [+, C_m-Ar(N)], 125.3 (+, C_o-Ar), 126.3 (+, C_p-Ar), 129.0 (+, C_m-Ar), 130.2 (+, C_q-Ar), 131.7 [+, C_o-Ar(N)], 134.8 [C_q-Ar(N)], 146.00 [C_q-Ar(C)], 147.30 (C_q-triazole) ppm; ν/cm^{-1} (DRIFT) 3127vw, 3064vw, 2926vw, 2269vw, 1922vw, 1711vw, 1606vw, 1514w, 1482w, 1457vw, 1433vw, 1410vw, 1351vw, 1230w, 1184vw, 1121vw, 1093vw, 1073vw, 1038w, 1027w, 993w, 916vw, 830w, 765w, 695w, 678vw, 631vw, 561vw, 504vw, 460vw; *m*/*z* (FAB): 893 ([MH^+], 100%), 865 ([MH^+ – N_2], 11), 588 ([MH^+–$C_{24}H_{16}$], 40); $C_{57}H_{41}N_{12}$: calcd. 893.3577, found 893.3569 [MH^+].

1,3,5,7-Tetrakis(4-(4-phenyl-1,2,3-triazol-1-yl)phenyl)adamantane (2a). The product was isolated in quantitative yields (254 mg, 99%) as a bright-yellow solid. R_f 0.69 (*n*-pentane/EtOAc 200:1); δ_H (400 MHz; $CDCl_3$) 2.30 (12 H, s, Ad-CH_2), 7.44–7.57 (20 H, m, C_6H_5), 7.92 (8 H, d, *J* 7.2, Ar_m-*H*), 7.80 (8 H, d, *J* 7.2, Ar_o-*H*), 8.20 (4 H, s, triazole-*H*); δ_C (100 MHz; $CDCl_3$) 39.4 (C_q, Ad), 46.9 (–, C_s, Ad-CH_2), 117.6 (+, *C*-5, triazole-C*H*), 120.5 (+, *C*-8, C_o-Ph), 125.8 (+, *C*-3, Ar_m-Ph), 128.4 (+, *C*-10, C_p-Ph), 128.9 (+, *C*-9, C_m-Ph), 129.7 (+, *C*-2, Ar_o-triazole), 135.4 (C_q, *C*-7, C_6H_5),

137.0 (C_q, *C*-4, Ar-triazole), 148.4 (C_q, *C*-1, Ar-Ad), 149.3 (C_q, C-6, triazole); ν/cm^{-1} (DRIFT) 3439vw, 3122w (C_{Ar}-H), 3098w, 3056w, 2928vw (C=CH), 1600w (N=N), 1556w, 1505w, 1482w, 1353w, 1229w, 1074w, 1042w, 994w, 910w, 827w, 758m, 691m, 661w, 538w, 520w; *m/z* (FAB) 1014 ([MH$^+$], 100%), 1015 (78), 1016 (26), 985 ([M – C_4H_3]+Na, 15); $C_{66}H_{53}N_{12}$ calcd. 1013.4516; found 1013.4530 [MH$^+$].

Tetrakis(4-(4-hydroxymethyl-1,2,3-triazol-1-yl)phenyl)methane (1b). The crude product was purified by washing with an additional 20 mL of dichloromethane and could be isolated as a yellowish solid (111 mg, 76%). δ_H (400 MHz; DMSO-d_6) 4.58–4.62 (8 H, m, CH_2), 5.32–5.37 (4 H, m, O*H*), 7.50–7.54 (8 H, m, Ar_o-*H*), 7.92–7.95 (8 H, m, Ar_m-*H*), 8.67 (4 H, s, *H*-triazole); δ_C (100 MHz; DMSO-d_6) 55.0 (–, *C*H_2OH), 62.8 (C_q-(Ar)$_4$), 119.8 (+, *C*H–triazole), 120.9 (+, C_m-Ar), 131.7 (+, C_o-Ar), 137.4 [C_q-Ar(N)], 142.8 (C_q–triazole), 146.0 [C_q-Ar(C)]; ν/cm^{-1} (DRIFT) 3315br (OH), 2410vw, 2320vw, 2251vw, 2123w, 2083w, 1911vw, 1601vw, 1577vw, 1502w, 1413vw, 1289vw, 1192vw, 1130vw, 1017vw, 911vw, 829vw, 731vw, 670vw, 671vw, 623vw, 555vw, 537vw, 452vw, 442vw, 407vw; *m/z* (FAB) 709 ([MH$^+$], 8%); $C_{37}H_{33}O_4N_{12}$ calcd. 709.2748; found 709.2750 [MH$^+$].

1,3,5,7-Tetrakis(4-(4-hydroxymethyl-1,2,3-triazol-1-yl)phenyl)-adamantane (2b)[15]. The crude product was purified by flash chromatography on silica gel using CH_2Cl_2/MeOH (5:1) as eluent and could be isolated as a bright yellow solid (6 mg, 11% yield). R_f 0.40 (CH_2Cl_2/MeOH 5:1). δ_H (400 MHz; $CDCl_3$/MeOH-d_4) 2.15 (12 H, s, Ad-CH_2), 4.61 (8 H, s, CH_2OH), 7.53 (8 H, d, *J* 8.8, Ar_o-*H*), 7.60 (8 H, d, *J* 8.8, Ar_m-*H*), 7.98 (4 H, s, *H*-triazole) ppm; δ_C (100 MHz; $CDCl_3$) 39.1 (C_q, Ad), 46.5 (–, C_s, Ad-*C*H$_2$), 55.3 (–, C_s, *C*H$_2$OH), 120.2 (C_t, *C*H=CCH$_2$OH), 120.3 (+, C_m, Ar), 126.3 (+, C_o, Ar), 135.0 (C_q, Ar_p), 148.4 (C_q, Ar-Ad), 149.3 (CH=*C*CH$_2$OH) ppm; ν/cm^{-1} (DRIFT) 3365w, 2923w, 2853w, 1609vw, 1519w, 1378w, 1262w, 1238w, 1184w, 1040w, 836w, 788w, 761vw, 700vw, 560w; UV/VIS ($CHCl_3$): λ_{max} (A) = 227 (0.015), 255 (0.028), 472 (0.011) nm; *m/z* (FAB) 829 ([MH$^+$], 100%), 733 (10), 731 (22), 573 (26), 529 (32), 485 (30), 419 (100); $C_{46}H_{45}O_4N_{12}$: calcd. 829.3681, found 829.3694 [MH$^+$]. $C_{46}H_{45}O_4N_{12}$ calcd. 829.3687; found 829.3694 [MH$^+$].

Tetrakis(4-(4-(2-(*S*)-hydroxyethyl)l-1,2,3-triazol-1-yl)phenyl)-methane (1c). The product was obtained as a brown powder (146 mg, 92%). δ_H (400 MHz; DMSO-d_6) 1.47 (12 H, d, *J* 6.4, CH_3), 4.88–4.96 (4 H, m, C*H*OH), 5.42 (4 H, d, *J* 4.3, O*H*), 7.50 (8 H, d, *J* 8.7, Ar_o-*H*), 7.95 (8 H, d, *J* 8.7, Ar_m-*H*), 8.64 (4 H, s, *H*-triazole); δ_C (100 MHz; DMSO-d_6) 23.6 (+, *C*H$_3$), 61.4 (+, *C*HOH), 63.6 (C_q-(Ar)$_4$), 119.5 (+, *C*H–triazole), 119.6 (+, C_m-Ar), 131.5 (+, C_o-Ar), 134.9 [C_q-Ar(N)], 145.4 [C_q-Ar(C)], 153.7 (C_q–triazole); ν/cm^{-1} (DRIFT): 3369w, 2976vw, 2898vw, 1776vw, 1606vw, 1551vw, 1512w, 1441vw, 1410vw, 1370vw, 1324vw, 1233vw, 1182vw, 1103vw, 1085vw, 1041w, 988vw, 894vw, 817vw, 744vw, 673vw, 625vw, 561vw, 541vw, 465vw; *m/z* (FAB) 765 ([MH$^+$], 18%), 719 ([MH$^+$ – C_2H_5O], 4), 577 ([MH$^+$ – $C_{10}H_9N_3$], 2), 492 ([$C_{28}H_{26}N_7O_2^+$], 5); $C_{41}H_{41}N_4O_{12}$ calcd. 765.3374; found 765.3380 [MH$^+$].

1,3,5,7-Tetrakis(4-(4-(2-(*R*)-hydroxyethyl)-1,2,3-triazol-1-yl)-phenyl)adamantane (2c). 23.0 μmol of the azide were used following the general procedure with identical equivalents. The product was isolated as a crude product (50% conversion) as reddish oil (18 mg, 88%). δ_H (400 MHz; $CDCl_3$/MeOH-d_4) 1.58 (12 H, d, *J* 6.5, CH_3), 2.10 (12 H, s, Ad-CH_2), 5.06 [4 H, q, *J* 6.1, CH_3C*H*(OH)], 7.58–7.60 (8 H, m, Ar_o-*H*), 7.66–7.68 (8 H, m, Ar_m-*H*), 7.95 (4 H, s, triazole-*H*); δ_C (100 MHz; $CDCl_3$/MeOH-d_4) 23.0 [+, *C*H$_3$CH(OH)], 39.2 (C_q, Ad), 48.7 (–, C_s, Ad-CH$_2$), 62.5 (+, *C*H(OH)), 120.4 (+, *C*-5, triazole-*C*H), 126.3 (+, *C*-2, C_o-Ar), 126.6 (+, *C*-3, C_m-Ar), 137.9 (C_q, *C*-4, Ar-triazole), 145.4 (C_q, *C*-6, triazole), 149.4 (C_q, Ar-Ad); ν/cm^{-1} (KBr) 3356br (OH), 2975w (C_{Ar}-H), 2927 m (C=CH), 2852 m (CH_3), 2414w, 2258w, 2125m, 1902 vw, 1688w, 1605 w (N=N), 1576w, 1509m, 1445w, 1411m, 1358m, 1291m, 1230m, 1190w, 1107m, 1042m, 989w, 951w, 893w, 835m, 785m, 735w, 702w, 672w, 563w; *m/z* (FAB) 885 (24) ([MH$^+$], 24%) 815 (M – C_4H_5O, 73), 774 (M – $C_4H_7ON_3$, 15), 745 (M – $C_8H_{13}O_2$, 100), 675 (M – $C_{12}H_{18}O_3$, 79); $C_{50}H_{53}O_4N_{12}$: calcd. 885.4313; found 885.4315 [MH$^+$].

Tetrakis(4-(4-(4-cyanophenyl)-1,2,3-triazol-1-yl)phenyl)methane (1d). The product was isolated as a brownish solid (186 mg, 91%). δ_H (400 MHz; DMSO-d_6) 7.65 (8 H, d, *J* 8.8, Ar_o(N)-*H*), 7.98–8.07 (16 H, m, Ar_m(N)-*H*, Ar_m(CN)-*H*), 8.12 (8 H, d, *J* 8.4, Ar_o(CN)-*H*), 9.33 (4 H, s, *H*-triazole); δ_C (100 MHz; DMSO-d_6) 64.0 (C_q-(Ar)$_4$), 110.5 (C_q-CN), 118.8 (*C*N), 120.2 [+, C_m-Ar(N)], 121.4 (+, *C*H-triazole), 125.9 [+, C_o-Ar(CN), C_q-Ar(CN)], 131.8 [+, C_o-Ar(N)], 133.1 [+, C_m-Ar(CN)], 134.6 [C_q-Ar(N)], 145.7 (C_q-triazole), 146.2 [C_q-Ar(C)]; ν/cm^{-1} (DRIFT) 3423vw, 3136vw, 2225w, 2125vw, 1919vw, 1780vw, 1614w, 1558vw, 1514w, 1490w, 1443vw, 1409vw, 1346vw, 1275vw, 1237vw, 1180vw, 1142vw, 1036vw, 994vw, 969vw, 919vw, 830w, 748vw, 625vw, 577vw, 554vw, 509vw, 451vw, 429vw, 419vw; *m/z* (FAB): 993 ([MH$^+$], 7%), 965 ([MH$^+$ – N_2], 2), 91 ([$C_7H_7^+$], 25); $C_{61}H_{37}N_{16}$ calcd. 993.3387, found 993.3393 [MH$^+$].

1,3,5,7-Tetrakis(4-(4-(4-cyanophenyl)-1,2,3-triazol-1-yl)phenyl)-adamantane (2d). 21.0 μmol of the azide were used following the general procedure with identical equivalents and the product was isolated as a bright yellow solid (10 mg, 40% yield) after successive washing with methanol. δ_H (500 MHz; $CDCl_3$/MeOH-d_4) 2.34 (12 H, s, Ad-CH_2), 7.73 (8 H, d, *J* 9.5, Ar_o(Ad)-*H*), 7.75 (8 H, d, *J* 9.0, Ar_m(CN)-*H*), 7.85 (8 H, d, *J* 8.7, Ar_m(Ad)-*H*), 8.04 (8 H, d, *J* 8.2, Ar_o(CN)-*H*), 8.30 (4 H, s, triazole-*H*); δ_C (125 MHz; $CDCl_3$) 39.5 (C_q, Ad), 46.9 (–, C_s, Ad-*C*H$_2$), 111.9 [+, C_q, Ar(CN)], 118.0 (C_q, *C*N), 118.6 (+, *C*H-triazole), 120.7 [C_o-Ar(Ad)], 126.1 [+, C_m-Ar(CN)], 126.6 [+, C_m-Ar(Ad)], 132.8 [+, C_o-Ar(CN)], 134.5 [C_q, triazole-Ar(CN)], 135.2 (C_q, Ar(Ad)-triazole), 146.7 (C_q, triazole), 149.6 (C_q, Ar-Ad); ν/cm^{-1} (DRIFT) 3418vw, 3092vw, 3066vw, 2928vw, 2853vw, 2228w, 1926vw, 1685vw, 1613w, 1601w (N=N), 1521w, 1495w, 1442vw, 1405w, 1360vw, 1271w, 1176vw, 1105vw, 1036w, 1016w, 993w, 840w, 828w, 654w, 553w; *m/z* (FAB) 1113 ([MH$^+$], 100%), 1115 (41), 1114 (87), 1085 (15), 990 (21).

Tetrakis(4-(4-aminomethyl-1,2,3-triazol-1-yl)phenyl)methane (1e). The product was isolated as a brown solid (136 mg, 94%). δ_H (400 MHz; DMSO-d_6) 4.18 (8 H, s, CH_2), 7.48–7.58 (8 H, m, Ar_o-*H*), 7.81–7.89 (8 H, m, Ar_m-*H*, 8.73 (s, 8 H, NH_2), 8.90 (4 H, s, *H*-triazole) ppm; δ_C (100 MHz; DMSO-d_6) 41.7 (*C*H$_2$), 62.8 (C_q-(Ar)$_4$), 119.8 (+, *C*H-triazole), 120.9 (+, C_m-Ar), 131.7 (+, C_o-Ar), 132.9 (C_q-triazole), 137.4 [C_q-Ar(N)], 146.0 [C_q-Ar(C)] ppm; ν/cm^{-1} (DRIFT) 3279w, 3139w, 1668w, 1606w, 1513w, 1439w, 1412w, 1349w, 1232w, 1181w, 1044w, 990w, 826w, 745vw, 615vw,

560w, 414vw; *m/z* (FAB) 705 ([MH$^+$], 1%); $C_{37}H_{37}N_{16}$ calcd. 705.3387; found 705.3384 [MH$^+$].

Tetrakis(4-(1-phenyl-1,2,3-triazol-4-yl)phenyl)methane (3a). The product was isolated following the general procedure as a yellow solid (212 mg, 99%). δ_H (400 MHz; DMSO-d_6) 7.47 (8 H, d, *J* 8.5, Ar_o-*H*), 7.52 (4 H, t, *J* 7.5, Ar_p(N)-*H*), 7.64 (8 H, d, *J* 7.5, Ar_m(N)-*H*), 7.93–7.99 (16 H, m, Ar_m-*H*, Ar_o(N)-*H*), 9.31 (4 H, s, *H*-triazole) ppm; δ_C (100 MHz; DMSO-d_6) 64.3 (C_q-$(Ar)_4$), 119.7 (+, *C*H-triazole), 112.0 [+, C_o-Ar(N)], 125.1 (+, C_m-Ar), 128.1 [C_q-Ar(triazole)], 128.7 [+, C_p-Ar(N)], 129.9 [+, C_m-Ar(N)], 131.0 (+, C_o-Ar), 136.6 [C_q-Ar(N)], 146.1 [C_q-Ar(C)], 146.9 (C_q-triazole) ppm; ν/cm^{-1} (DRIFT) 3065vw, 1722vw, 1598vw, 1504vw, 1488vw, 1466vw, 1427vw, 1348vw, 1230vw, 1192vw, 1154vw, 1039vw, 993vw, 970vw, 914vw, 829vw, 758vw, 689vw, 614vw, 561vw, 527vw, 497vw; *m/z* (FAB) 893 ([MH$^+$], 48%), 865 ([MH$^+$ – N_2], 10), 588 ([M$^+$ – $C_{24}H_{16}$], 55); $C_{57}H_{40}N_{12}$ calcd. 893.3572; found 893.3580 [MH$^+$].

1,3,5,7-Tetrakis(4-(1-phenyl-1,2,3-triazol-4-yl)phenyl)adamantane (4a). The product was isolated as yellow oil without further purification (95 mg, 72% yield). R_f 0.22 (CH_2Cl_2/cyclohexane 3:1); δ_H (400 MHz; $CDCl_3$) 2.13 (12 H, s, Ad-CH_2), 7.43–7.51 (20 H, m, C_6H_5), 7.77 (8 H, d, *J* 8.0, Ar_o-*H*), 7.90 (8 H, d, *J* 8.0, Ar_m-*H*), 8.23 (4 H, s, triazole-*H*-*6*); δ_C (100 MHz; $CDCl_3$) 39.1 (C_q, Ad), 46.9 (–, C_s, Ad-*C*H_2), 117.5 (+, *C*-6, triazole-*C*H), 120.3 (+, *C*-8, C_o-Ph), 125.6 (+, *C*-3, C_m(Ar)-Ad), 125.8 (+, *C*-2, C_o(Ar)-Ad), 128.1 (+, *C*-10), 128.6 (C_q, *C*-1, Ar-Ad), 129.6 (+, *C*-9), 136.9 (C_q, *C*-4, Ar_p-triazole), 148.0 (C_q, *C*-7), 149.3 (C_q, *C*-7, triazole); ν/cm^{-1} (DRIFT) 3141w, 3052w (C_{Ar}-H), 2927 m (C=CH), 2898w, 2850w (C_{Ad}-H), 2125vw, 1670w, 1597 m (N=N), 1493m, 1465m, 1426m, 1408m, 1349m, 1290w, 1228m, 1118w, 1037m, 1018m, 993m, 909w, 837m, 783m, 758m, 689m, 554w; *m/z* (FAB) 1013 ([MH$^+$], 100%), 1015 (77), 1016 (33), 985 ([M – C_4H_3]+Na, 10), 895 (9); $C_{66}H_{53}N_{12}$ calcd. 1013.4516; found 1013.4510 [MH$^+$].

Tetrakis(4-(1-(4-fluorophenyl)-1,2,3-triazol-4-yl)phenyl)methane (3b). The product was isolated as a yellowish solid without further purification (225 mg, 97%). δ_H (400 MHz; DMSO-d_6) 7.46 (8 H, d, *J* 8.6, Ar_o-*H*), 7.48–7.53 (8 H, m, Ar_m(F)-*H*), 7.93 (8 H, d, *J* 8.6, Ar_m-*H*), 7.98–8.03 (8 H, m, Ar_o(F)-*H*), 9.28 (4 H, s, *H*-triazole) ppm; δ_C (100 MHz; DMSO-d_6) 64.2 (C_q-$(Ar)_4$), 116.7 [+, $J_{C\text{-}F}$ 23, C_m-Ar(F)], 119.9 (+, *C*H-triazole), 122.2 [+, $J_{C\text{-}F}$ 9, C_o-Ar(F)], 125.1 (+, C_m-Ar), 128.0 [C_q-Ar(triazole)], 130.9 (+, C_o-Ar), 133.1 [$J_{C\text{-}F}$ 3, C_q-Ar(F)], 146.1 [C_q-Ar(C)], 146.9 (C_q-triazole), 161.6 ($J_{C\text{-}F}$ 246, C_q-F) ppm; δ_F ([1H]; 376 MHz; DMSO-d_6) –112.88 (s, F-Ar); ν/cm^{-1} (DRIFT) 3462vw, 3142vw, 2265vw, 1605vw, 1516m, 1490w, 1446vw, 1410vw, 1345vw, 1294vw, 1227m, 1191vw, 1157w, 1121vw, 1091vw, 1036w, 1020w, 994w, 969vw, 836m, 791w, 749vw, 706vw, 519w, 559vw, 524vw; *m/z* (FAB) 965 ([MH$^+$], 25%); $C_{57}H_{37}F_4N_{12}$ calcd. 965.3195; found 965.3211 [MH$^+$].

1,3,5,7-Tetrakis(4-(1-(4-fluorophenyl)-1,2,3-triazol-4-yl)phenyl)-adamantane (4b). 65.0 μmol of the alkyne were used following the general procedure and the same equivalents. The product was isolated as cream-colored solid (61 mg, 86% yield). R_f 0.22 (CH_2Cl_2/cyclohexane, 3:1); δ_H (400 MHz; $CDCl_3$) 2.27 (12 H, s, Ad-*H*), 7.24 (8 H, m, Ar_F-*H*), 7.62 (8 H, d, *J* 8.5, Ar_m-*H*), 7.78 (8 H, m, Ar_F -*H*), 7.92 (8 H, d, *J* 8.5, Ar_o-*H*), 8.16 (4 H, s, triazole-*H*); δ_C (100 MHz; $CDCl_3$) 39.3 (C_q, Ad), 47.1 (–, C_s, Ad-CH_2), 116.6 (+, *C*H-triazole), 116.7 (+, $J_{C\text{-}F}$ 23, *C*-8, Ar_m-F), 122.4 (+, *C*-2, C_o-Ar), 122.5 (+, *C*-3, C_m-Ar), 125.8 (+, $J_{C\text{-}F}$ 25, *C*-9, Ar_o-F), 128.1 (C_q, *C*-4, Ar_p-triazole), 133.3 (C_q, $J_{C\text{-}F}$ 3, *C*-7, ArF), 148.3 (C_q, *C*-5, triazole), 149.5 (C_q, *C*-1, Ar-Ad), 162.4 (C_q, $J_{C\text{-}F}$ 249, *C*-10, Ar_F); δ_F ([1H]; 376 MHz; $CDCl_3$) –111.97 (s, F-Ar); ν/cm^{-1} (DRIFT) 3415w, 3140w (C_{Ar}-H), 2926w (C=CH), 2852w (C_{Ad}-H), 1606w (N=N), 1517m, 1496m, 1446w, 1409w, 1356w, 1228 m (C-F), 1156w, 1093w, 1037w, 994w, 837m, 782w, 790vw, 619w, 533w; *m/z* (FAB) 1085 ([MH$^+$], 95%), 1086 (76), 1087 (27), 647 (53), 136 (67).

Tetrakis(4-(1-(4-nitrophenyl)-1,2,3-triazol-4-yl)phenyl)methane (3c). The product was isolated as a reddish solid without further purification (237 mg, 92%). δ_H (400 MHz; DMSO-d_6) 7.34 (8 H, d, *J* 8.8, Ar_o-*H*), 7.94 (8 H, d, *J* 8.8, Ar_m-*H*), 8.25 (8 H, d, *J* 8.6, $Ar_o(NO_2)$-*H*), 8.49 (8 H, d, *J* 8.6, Ar_m-(NO_2)-*H*), 9.50 (4 H, s, *H*-triazole) ppm; δ_C (100 MHz; DMSO-d_6) 64.2 (C_q-$(Ar)_4$), 120.1 (+, *C*H-triazole), 120.4 [+, C_o-Ar(NO_2)], 125.5 (+, C_m-Ar), 125.6 [+, C_m-Ar(NO_2)], 128.3 [C_q-Ar(triazole)], 131.0 (+, C_o-Ar), 140.8 [C_q-Ar(N)], 146.0 [C_q-Ar(C)], 146.7 (C_q-triazole), 147.4 (C_q-NO_2) ppm; ν/cm^{-1} (DRIFT) 3378m, 3087m, 2932m, 2450vw, 2255vw, 2123m, 2089w, 1925vw, 1781vw, 1597m, 1524 s, 1441w, 1408m, 1344 s, 1311m, 1229m, 1176w, 1111m, 1030m, 1017m, 991 s, 854m, 828m, 750m, 686w, 633w, 558w, 534w; *m/z* (FAB) 1072 ([M$^+$], 1%).

(*S*,*S*,*S*,*S*)-4,4′,4″,4‴-Methanetetrayltetra-4-phenyl-1*H*-1,2,3-triazole-1-acetic acid tetraethyl ester (3d). The product was isolated as brown solid (264 mg, 85%). δ_H (400 MHz; DMSO-d_6) 1.16 (t, 12 H, *J* 7.1, CH_3), 3.29–3.68 (8 H, m, CH_2-Ph), 4.18 (q, 8 H, *J* 7.1, CH_2CH$_3$) 5.87–5.91 (4 H, m, NC*H*CH$_2$), 7.14–7.25 (20 H, m, Ar_p(Ph)-*H*, Ar_o(Ph)-*H*, Ar_o-*H*), 7.30 (8 H, d, *J* 8.3, Ar_m(Ph)-*H*), 7.77 (8 H, d, *J* 8.4, Ar_m-*H*), 8.72 (4 H, s, *H*-triazole) ppm; δ_C (100 MHz; DMSO-d_6) 13.9 (+, *C*H$_3$), 36.6 (–, *C*H$_2$Ph), 61.8 (–, *C*H$_2$CH$_3$), 64.3 (C_q-$(Ar)_4$), 70.7 (+, *C*HCO), 121.5 (+, *C*H-triazole), 124.7 (+, C_p-Ar(Ph), C_m-Ar), 126.9 [Cq-Ar(triazole)], 128.3 [+, C_o-Ar(Ph)], 128.9 [+, C_m-Ar(Ph)], 130.9 (+, C_o-Ar), 135.9 [C_q-Ar(Ph)], 146.1 [C_q-Ar(C)], 147.3 (C_q-triazole), 168.9 (C_q-*C*O) ppm; ν/cm^{-1} (DRIFT) 3139vw, 3062w, 3029w, 2980w, 2936vw, 1745m, 1604w, 1494w, 1455w, 1372w, 1336w, 1231w, 1194w, 1080w, 1019w, 976w, 909vw, 830w, 750w, 701w, 608vw, 560vw, 543vw, 477vw, 415vw; *m/z* (FAB): 1293 ([MH$^+$], 4%), 1265 ([MH$^+$ – N_2], 8).

(*S*,*S*,*S*,*S*)-4,4′,4″,4‴-(1,3,5,7-Adamantane)tetrayltetra-4-phenyl-1*H*-1,2,3-triazole-1-acetic acid tetraethyl ester (4d). The crude triazole could be purified by flash chromatography on silica gel using cyclohexane/EtOAc (1:1) as eluent and isolated as colorless oil (118 mg, 64% yield). R_f 0.29 (cyclohexane/EtOAc 1:1); δ_H (400 MHz; $CDCl_3$) 1.21 (12 H, t, *J* 7.1, CH_2CH_3) 2.21 (12 H, s, Ad-CH_2), 3.54 (8 H, d, *J* 6.5, CH_2Ph), 4.21 (8 H, q, *J* 7.1, CH_2CH$_3$), 5.64 (4 H, t, *J* 7.5, NC*H*CH$_2$), 7.08–7.25 (20 H,m, C_6H_5), 7.55 (8 H, d, *J* 8.5, Ar_o-*H*), 7.83 (8 H, d, *J* 8.5, Ar_m-*H*), 7.90 (4 H, s, triazole-*H*); δ_C (100 MHz; $CDCl_3$) 13.8 (+, CH_2CH_3), 38.8 (–, C_s, CH_2Ph), 39.1 (C_q, Ad), 46.94 (–, Ad-CH_2), 62.3 (–, C_s, CH_2CH_3), 63.9 (+, *C*HCH$_2$Ph), 119.4 (+, *C*H-triazole), 125.4 (+, *C*-2, C_o-Ar), 125.6 (+, *C*-3, C_m-Ar), 127.4 (+, C_p-Ph), 128.3 (C_q, Ar-triazole), 128.6 (+, C_o-Ph), 128.8 (+, C_m-Ph), 134.6 (C_q, Ar-Ad), 147.2 (C_q, C_6H_5), 149.1 (C_q, triazole), 168.1 (C_q, C=O); ν/cm^{-1} (DRIFT) 3464vw, 3141w (C_{Ar}-H), 3031w, 2981w, 2932w (C=CH), 2852w (C_{Ad}-H), 1745 m (C=O), 1605w (N=N), 1496m,

1454 m (CH2), 1409w, 1357w, 1196m, 1115w, 1080w, 1018m, 976w, 894vw, 840w, 785w, 751w, 701m, 571w, 514w; *m/z* (FAB) 1413 (59%), 1414 ([MH$^+$], 57), 154 (100).

(*S*,*S*,*S*,*S*)-4,4′,4″,4‴-Methanetetrayltetra-4-phenyl-1*H*-1,2,3-triazole-1-acetic acid (3e). The desired click product was obtained without further purification (241 mg, 85%). δ_H (400 MHz; DMSO-d_6) 3.21–3.58 (8 H, m, CH_2-Ph), 5.42–5.68 (4 H, m, CHCH$_2$), 7.03–7.18 (20 H, m, Ar$_o$(Ph)-*H*, Ar$_p$(Ph)-*H*, Ar$_o$-*H*), 7.21–7.26 (8 H, m, Ar$_m$(Ph)-*H*), 7.63–7.76 (8 H, m, Ar$_o$-*H*), 8.63 (4 H, s, *H*-triazole); δ_C (100 MHz; DMSO-d_6) 31.2 (–, *C*H$_2$Ph), 64.4 (C_q-(Ar)$_4$), 66.8 (+, *C*HCO), 119.7 (+, *C*H-triazole), 124.6 [+, C_p-Ar(Ph), C$_m$-Ar)], 126.5 [C$_q$-Ar(triazole)], 128.1 [+, C_o-Ar(Ph)], 128.7 [(C_m-Ar(Ph)], 130.8 (+, C_o-Ar), 131.4 [C_q-Ar(Ph)], 145.4 [C_q-Ar(C)], 146.0 [C_q-triazole], 169.6 (C$_q$-*C*O); ν/cm^{-1} (DRIFT) 3283m, 3030m, 2972m, 1742m, 1604w, 1497m, 1455w, 1367w, 1195m, 1082w, 1019w, 978w, 897w, 827m, 749w, 701m, 674w, 571w, 428vw, 415vw; *m/z* (FAB): 1181 (M$^+$, 1%).

Tetrakis(4-(1-(3,5-dicarboxyphenyl)-1,2,3-triazol-4-yl)phenyl)-methane (3f). The product was isolated as a brownish solid (245 mg, 82%). δ_H (400 MHz; DMSO-d_6) 7.24–7.30 (8 H, m, Ar$_o$-*H*,), 7.78–7.81 (8 H, m, Ar$_m$-*H*), 8.38 (4 H, s, Ar(CO$_2$H)$_2$-*H*), 8.53 (8 H, s, Ar(N)-*H*), 9.38 (4 H, s, *H*-triazole), 13.71 (8 H, s, CO$_2$*H*) ppm; δ_C (100 MHz; DMSO-d_6): 64.5 (C_q-(Ar)$_4$), 119.9 (+, *C*H-triazole), 121.1 [*C*-Ar(CCO$_2$H)] 125.2 [+, C_m-Ar], 127.9 [C_q-Ar(triazole)], 128.0 [C_q-Ar(N)] 131.0 (+, C_o-Ar), 131.1 [*C*-Ar(CCO$_2$H)$_2$, *C*-Ar(CO$_2$H)], 146.2 [C_q-Ar(C)], 147.3 (C_q-triazole), 168.6 (*C*O$_2$H) ppm; ν/cm^{-1} (DRIFT) 3088w, 2124w, 1718w, 1602w, 1460w,1414w, 1224w, 1060vw, 1017vw, 898vw, 827vw, 760w, 670vw, 536vw, 440vw, 412vw; *m/z* (FAB) 1245 ([MH$^+$], 1%), 232 ($C_{10}H_6N_3O_4^+$, 54).

1,3,5,7-Tetrakis(4-(1-(3,5-dicarboxyphenyl)-1,2,3-triazol-4-yl)-phenyl)adamantane (4f). The pure product was separated after the reaction *via* filtration as a grey solid and washed with MeOH and CHCl$_3$ (106 mg, 60%). δ_H (500 MHz; CDCl$_3$) 2.23 (12 H, s, Ad-CH$_2$), 7.76 (8 H, d, *J* 7.8, Ar$_m$-*H*), 7.99 (8 H, d, *J* 7.7, Ar$_o$-*H*), 8.52 (4 H, s, C*H*C(CO$_2$H)$_2$), 8.69 (8 H, s, 2 × C*H*C(CO$_2$H)), 9.58 (4 H, s, triazole-*H*); δ_C (125 MHz; CDCl$_3$) 39.1 (–, Ad-*C*H$_2$), 46.2 (–, C_q), 119.5 (+, *C*H-triazole), 123.5 (+, 2 × *C*H(CCO$_2$H), 125.2 (+, *C*-2, C_o-Ar), 125.9 (+, *C*-3, C_m-Ar), 127.7 (+, *C*-4, Ar-triazole), 133.9 (C_q, Ar-Ad), 137.2 [C_q, *C*(CO$_2$H)], 147.6 (C_q, CH(*C*CO$_2$H), 149.8 (C_q, triazole), 165.9 (C_q, *C*=O); ν/cm^{-1} (DRIFT) 3070w (C$_{Ar}$-H), 1714m, 1602w (N=N), 1461w, 1422w, 1237m, 1059w, 1016w, 902w, 762w, 705w, 672w, 578w; *m/z* (FAB) 1365 ([MH$^+$], 100%), 1356 (74), 1357 (41).

1,3,5,7-Tetrakis[4-(1-2′,3′-dideoxythymidin-3′-yl-1,2,3-triazol-4-yl)phenyl]adamantane (4g). 3′-Azido-2′,3′-dideoxythymidine (199 mg, 0.75 mmol) and 1,3,5,7-tetrakis(4-ethynylphenyl)-adamantane (**10**) (100 mg, 0.19 mmol) were dried for 1 h at 0.1 Torr, and then dissolved in DMSO (1.5 mL). A slurry of CuSO$_4$·5 H$_2$O (18.6 mg, 0.07 mmol) and sodium ascorbate (29.2 mg, 0.15 mmol) in water (500 μL) was added, and the resulting mixture was stirred for 10 h at r.t. After TLC analysis showed full conversion of 1,3,5,7-tetrakis(4-ethynylphenyl)adamantane, the reaction mixture was diluted with ethyl acetate (5 mL), and added to water (10 mL) in a centrifuge vial. A precipitate formed that was isolated by centrifugation. The solid was washed with ethyl acetate (3 × 15 mL) and water (2 × 15 mL), leading to a product that was dried at 0.1 Torr over silica, yielding 279 mg (0.17 mmol, 93%) of the title compound as a colorless solid. δ_H (500 MHz; DMSO-d_6) 1.82 (12 H, s, CH_3), 2.20 (12 H, bs, CH_2), 2.71, 2.83 (2 × 4 H, 2 m, *H2′*,*H2″*), 3.69, 3.73 (2 × 4 H, 2 m, *H5′*,*H5″*), 4.30 (4 H, m, *H4′*), 5.28 (4 H, t, *J* 5.1, O*H*), 5.40 (4 H, m, *H3′*), 6.46 (4 H, t, *J* 6.5, *H1′*), 7.72 (8 H, d, *J* 7.7, Ar-*H*), 7.84 (4 H, s, *H6*), 7.85 (8 H, d, *J* 7.7, Ar-*H*), 8.77 (4 H, s, *H5*-triazole), 11.36 (4 H, s, N*H*); δ_C (125 MHz; DMSO-d_6) 12.2 (*C*-Me), 37.1 (*C2′*), 39.2 (*Cq*-ad, hidden under the solvent peak), 46.2 (*C*-ad), 59.3 (*C3′*), 60.7 (*C5′*), 83.8 (*C1′*), 84.3 (*C4′*), 109.6 (C_q-*C*5), 120.7 (*C4*-triazole), 125.0 (*C*-Ar), 125.8 (*C*-Ar), 128.2 (C_q-Ar), 136.2 (*C6*), 146.5, 149.4 (2C_q, triazole,Ar), 150.4, 163.7 (2C_q, CO); HRMS (APCI) m/z: $C_{82}H_{85}N_{20}O_{16}$ calcd 1605.6447; found 1605.6448 [MH$^+$].

Tetrakis[4-(1-*N4*-benzoyl-2′,3′-dideoxycytidine-3′-yl-1,2,3-triazol-4-yl)phenyl]adamantane (4h). Samples of 3′-azido-*N*4-benzoyl-2′,3′-dideoxycytidine (267 mg, 0.75 mmol) and tetrakis(4-ethynylphenyl)adamantane (**10**) (100 mg, 0.19 mmol) were dissolved in DMSO (4.5 mL). A mixture of CuSO$_4$·5H$_2$O (18.6 mg, 75.0 μmol) and sodium ascorbate (29.2 mg, 0.15 mmol) in water (500 μL) was added, and the reaction mixture was stirred for 10 h at r.t. After TLC analysis (cyclohexane/CH$_2$Cl$_2$, 1:1 and CHCl$_3$/MeOH, 85:15) showed disappearance of the starting material, CH$_2$Cl$_2$ (50 mL) was added. The resulting mixture was transferred to a centrifuge vial, and the resulting precipitate isolated after centrifugation. The crude product was washed with CH$_2$Cl$_2$ (2 × 10 mL) and water (2 × 10 mL). The product thus obtained was dried over silica at 0.1 Torr, yielding 357 mg (0.18 mmol, 98%) of a slightly yellow solid. δ_H (500 MHz; DMSO-d_6) 2.21 (12H, bs, CH$_2$), 2.75, 3.07 (2 × 4 H, 2 m, H2′,H2″), 3.72, 3.82 (2 × 4 H, 2 m, *H5′*,*H5″*), 4.47 (4 H, bs, *H4′*), 5.41–5.39 (8 H, m, O*H*, *H3′*), 6.41 (4 H, m, *H1′*), 7.43 (4H, bs, *H5*), 7.52 (8 H, t, *J* 7.3, Bz-*H*), 7.63 (4H, t, *J* 7.3, Bz-*H*), 7.73 (8 H, d, *J* 7.7, Ar-*H*), 7.87 (8 H, d, *J* 7.7, Ar-*H*), 8.03 (8 H, d, *J* 7.3, Bz-*H*), 8.54 (4 H, d, *J* 6.6, *H6*), 8.77 (4 H, s, *H5*-triazole), 11.27 (4 H, bs, N*H*); δ_C (125 MHz; DMSO-d_6) 38.4 (*C2′*), 39.2 (C_q-ad, hidden under the solvent peak), 46.2 (*C*-ad), 58.8 (*C3′*), 60.3 (*C5′*), 85.3 (*C4′*), 86.4 (*C1′*), 96.2 (*C5*), 120.7 (*C4*-triazole), 125.0 (*C*-Ar), 125.8 (*C*-Ar), 128.2 (C_q-Ar), 128.3 (*C*-Bz), 128.4 (*C*-Bz), 132.7 (*C*-Bz), 133.1 (C_q), 145.1 (*C6*), 146.5, 149.4 (2C_q, triazole, Ar), 154.2, 163.1, 167.3 (3C_q, 2*C*O, *C4*); HRMS (ESI) *m/z*: $C_{106}H_{96}N_{24}O_{16}Na_2$ calcd 1003.3610 [M + 2Na]$^{2+}$; found: 1003.3606.

(DMT-A$_{PCNE}$T)$_4$TTPA (4i). Tetranucleoside **4g** (52.0 mg, 32.4 μmol) and the 3′-β-cyanoethyl-*N*,*N*′-diisopropylphosphoramidite of N^6-benzoyl-2′-deoxy-5′*O*-(dimethoxytrityl)adenosine (169 mg, 194 μmol, 6.0 eq) were mixed, coevaporated from dry MeCN (3 × 2.5 mL), and dissolved in dry THF (2 mL) under argon. The stirred solution was treated dropwise with a solution of tetrazole (0.45 M, 2 mL). After 24 h, a solution of *t*-butylhydroperoxide (500 μL, 5.5 M in decane) was added dropwise, followed by stirring for 45 min. The reaction mixture was added to ethyl acetate (10 mL) in a centrifuge vial, leading to the precipitation of a solid that was isolated by centrifugation. The solid was washed with ethyl acetate (3 × 7 mL). The fully protected octanucleosidic product thus obtained (mixture of *R*P/*S*P diastereomers) was dried over silica at 0.1 Torr, yielding 127 mg (27 μmol, 83%) of a colorless solid. HRMS (ESI) *m/z*: calcd for $C_{246}H_{232}N_{44}O_{48}P_4$: 2348.8111 [M + 2H]$^{2+}$; found

2348.8115; MS (MALDI-TOF): calcd. for $C_{246}H_{232}N_{44}O_{48}P_4$ 4695 [MH^+]; found 4698.

$(AT)_4$TTPA (4j). A sample of fully protected DNA hybrid **4i** (55.0 mg, 11.7 μmol) was treated with saturated aqueous ammonia (25%, 1 mL) and heated to 55 °C for 24 h while stirring. **Caution**: *saturated aqueous ammonia builds up pressure when heated, and a pressure-resistant vessel should be employed.* The solution was allowed to cool to room temperature and water (2.5 mL) was added, followed by removal of remaining ammonia with a gentle stream of N_2, directed onto the surface of the solution. Lyophilization to dryness gave 54.0 mg of an intermediate free of base-labile protecting groups. A sample of this crude product (8.0 mg) was dissolved in acetic acid (3 mL, 80% aqueous solution, v/v) and stirred at r.t. for 1 h. After addition of H_2O/diethyl ether (18 mL, 1/1, v/v) and stirring for 30 min at r.t., a precipitate was isolated by centrifugation. The crude product was washed with water (5 mL) and diethyl ether (3 × 5 mL), followed by drying at 0.1 Torr, to yield 5.6 mg of fully deprotected hybrid. The solid was then dissolved in aqueous triethylammonium acetate buffer (0.1 M, pH 7.0, 1.5 mL) containing 15% CH_3CN. A sample of this solution (100 μL) was subjected to RP-HPLC (C4 column, gradient from 0% to 40% CH_3CN in 80 min) to yield the title compound **4j** at a retention time (t_R) of 50 min (yield 25%, as determined by its absorption at 260 nm in the HPLC trace of the crude); ε_{260} used = 167000 L mol^{-1} cm^{-1}; HRMS (ESI) m/z: calcd for $C_{122}H_{128}N_{40}O_{36}P_4Na$: 958.9436 $[M + Na]^{3-}$; found: 958.9435; MS (MALDI-TOF): calcd. for $C_{122}H_{128}N_{40}O_{36}P_4$ 2852 $[M - H]^-$; found 2855.

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