Synthesis of Gd(III)-*C*-palmitamidomethyl-*C′*-DOTAMA-C_6-*o*-carborane: a new dual agent for innovative MRI/BNCT applications†‡

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C-(2-Benzyloxy)-ethyl-*C′*-*N*-*tert*-butoxycarbonyl-aminomethyl-*o*-carborane (**8**), a potentially useful intermediate for BNCT, has been synthesised. This intermediate can be readily functionalised with several biological vectors and MRI contrast agents. In this work intermediate **8** has been functionalised with a palmityl chain for lipophilic targeting and with Gd(III)-DOTAMA-C_6-NH_2 as MRI detector. This combination yielded Gd(III)-*C*-palmitamidomethyl-*C′*-DOTAMA-C_6-*o*-carborane (**14**) as a dual MRI-BNCT agent.

Introduction

BNCT (boron neutron capture therapy) is a type of binary radiation therapy for the treatment of cancer, especially of malignant brain tumors, based on the capture of thermal neutrons by boron-10 (^{10}B) nuclei that have been selectively delivered to tumor cells. The neutron capture event results in the formation of excited boron-11 nuclei that undergo fission to yield highly energetic $^4He^{2+}$ and $^7Li^{3+}$ ions. Cell death is triggered by the release of these charged particles which create ionisation tracks along their trajectories, resulting in cellular damage. It has been estimated that approximately 10–30 μg of boron for g of tumor mass is needed to attain an acceptable therapeutic advantage.[1]

Thus an important task relies on the possibility of delivery high payloads of boron-10 at the target sites. Although clinical exploitation of the BNCT strategy is currently being carried out with lower molecular weight boron delivery agents, it has been straightforward to consider polynuclear boron derivatives as potential candidates for BNCT applications.

In fact several readily functionalised carboranes have been employed to construct boron delivery vehicles for BNCT, because of their high content of boron and their stability in vivo.[2,3]

Furthermore, in order to improve boron delivery to the diseased cells, new higher molecular weight carriers are under study, with the main goal of increasing the tumor to healthy tissue accumulation ratio.[2b] Among them hyaluronan,[4] low density lipoprotein (LDL),[5] thymidine[6] and porphyrine[7] analogues have been considered.

An important issue is the assessment of the amount of boron-10 that has reached the target sites. This is important in order to proceed with the neutron irradiation step, because successful outputs can be expected only if the treshold boron concentration has been raised. One may envisage a route to this goal by means of the MRI detection provided by a boron-containing compound which is functionalised with the proper imaging reporter.[8]

With this goal in mind we have developed a synthesis of an *o*-carborane that bears, on one side a lipophilic chain and on the other side a gadolinium (III) ion complex which acts as an MRI contrast agent. As a matter of fact MRI (Magnetic Resonance Imaging) is a powerful, non-invasive, and widely applied diagnostic technique which permits the production of images of the inside of the human body.[9] Gadolinium increases the contrast in the image and can also be used to effectively quantify its concentration at the target. Furthermore, a dual gadolinium/boron compound will show an improved NCT efficiency in respect to a system containing boron alone. This is because gadolinium contains at least two stable isotopes (gadolinium-155 and gadolinium-157) that have high thermal neutron cross-sections. In particular, the gadolinium-157 thermal neutron cross-section provides a roughly 65-fold improvement upon boron-10.[10]

The lipophilic probe herein reported is expected to bind to LDLs (Low Density Lipoproteins) and to accumulate at tumor cells that overexpress transporters for these lipoproteins. In fact, it is well established that fast-dividing tumor cells avidly consume LDLs as suppliers of cholesterol and other lipidic components for the newly formed cell membranes. Alternatively, this lipid-based system may be used to form mixed micelles containing components that bear, on the outer surface of the particles, the synthons for the recognition of the cellular epitopes. Finally, the DOTA ligand may be used for the coordination of other metal ions besides Gd(III), as it forms very stable complexes with a variety of radiometals of interest to other imaging modalities such as SPECT and PET.[11]

Results and discussion

In order to obtain the bifunctionalised *o*-carborane, it was necessary to prepare the suitable internal alkyne from the commercially

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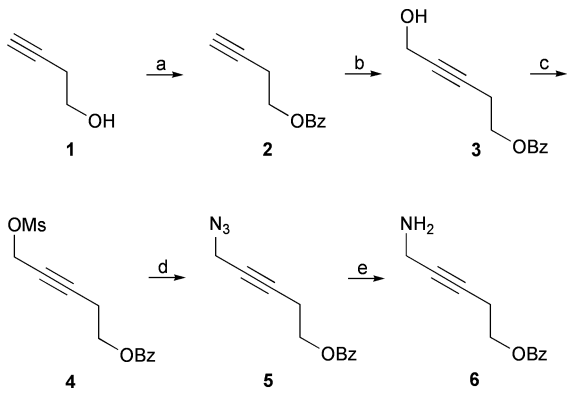
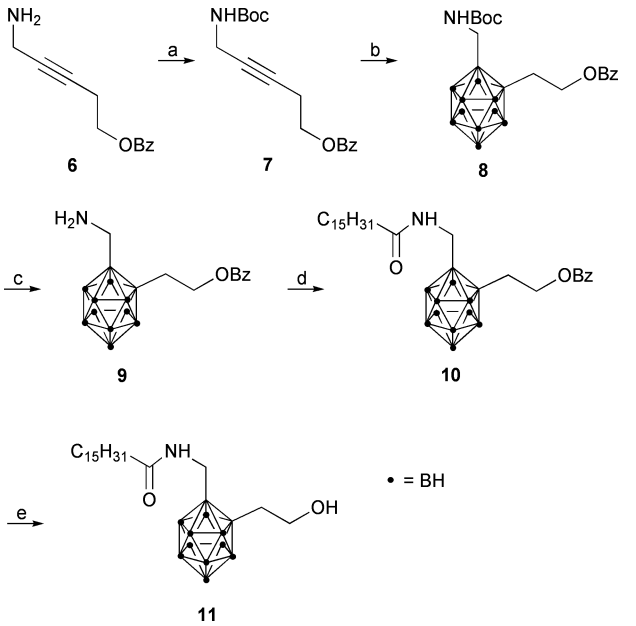
available 3-butyn-1-ol which was protected with benzyl bromide. Unfortunately all attempts to alkylate the protected butynol **2** with various electrophiles (alkyl halides, epoxides, and silanes) under different experimental conditions were unsuccessful. As shown in Scheme 1 only paraformaldehyde, as reported by Quintana *et al.*,[12] led to the desired 5-benzyloxy-pentyn-1-ol (**3**).



Scheme 1 Synthesis of 5-(benzyloxy)pent-2-yn-1-amine (**6**). *Reaction conditions and yields*: a) BnBr, NaH, THF, rt (90%); b) BuLi, $(CH_2O)_n$, THF, –20 °C → rt (65%); c) MsCl, TEA, Et_2O, 0 °C (98%); d) NaN_3, DMF, rt (92.5%); e) $SnCl_2$, MeOH, rt (99%).



Scheme 2 Synthesis of *C*-palmitamidomethyl-*C′*-2-hydroxyethyl-*o*-carborane (**11**). *Reaction conditions and yields*: a) (*tert*-Butoxycarbonyl)$_2$O, NH_2SO_3H, rt (99%); b) $B_{10}H_{14}$, $(bmim)^+Cl^-$, toluene, 120 °C (41%); c) CH_2Cl_2, CF_3COOH, rt (99%); d) CDMT, *N*-methylmorpholine, palmitic acid, CH_2Cl_2, – 5 °C → rt (64%); e) H_2, Pd/C, CH_3Cl/MeOH, rt (98%).

NMR evidence for the formation of the desired product has been gained from the disappearance of the triplet centered at 2.08 ppm corresponding to the acetylenic proton, and the concomitant appearance of the singlet at 4.23 ppm pertinent to the HOCH_2 group. Alcohol **3** was subsequently converted into the corresponding amine **6**, according to Scheme 1. Alcohol **3** was first transformed into azide **5** exploiting the intermediate mesylate **4** according to the procedures reported in literature.[13] Finally, treatment with $SnCl_2$ at room temperature afforded 5-benzyloxy-pent-1-inylamine (**6**), with an 90% overall yield.[14]

Reaction outcomes were confirmed by ^{1}H NMR analysis: the singlet at 4.23 ppm, assigned to the HOCH_2 group, shifted to 4.53 ppm for mesylate **4**, and to 3.91 and 3.39 ppm for azide **5** and amine **6**, respectively. In order to construct the carborane unit, a modification of the procedure proposed by Sneddon *et al.*[15] was used. The decaborane alkyne insertion reaction was carried out in a biphasic system, ionic liquid $(bmim)^+Cl^-$ (bmim = 1-butyl-3-methylimidazolium) and toluene, without the need of any catalyst.

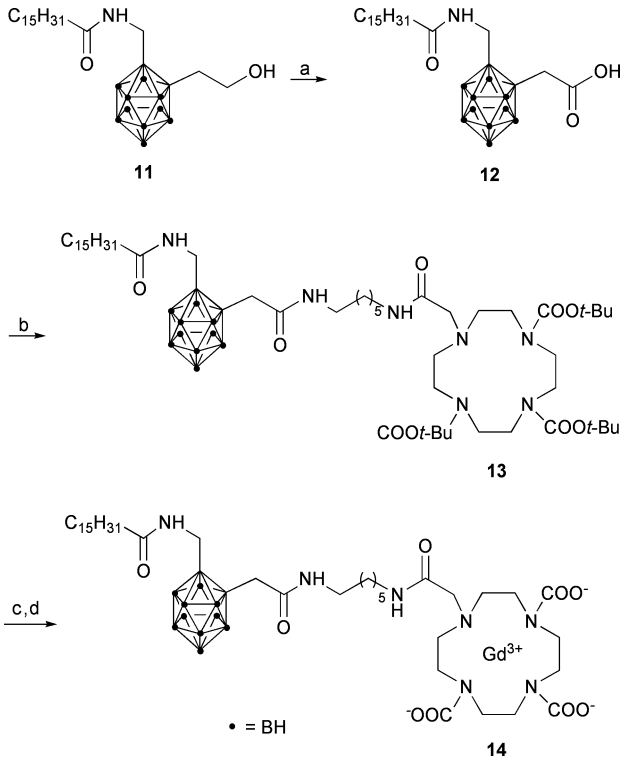
Intermediate amine **6** was protected as *tert*-butoxycarbonyl derivative **7** (Scheme 2),[16] and then allowed to react with decaborane. Carborane **8**[17] was isolated in 41% yield, after chromatographic purification. The carborane structure was confirmed on the basis of the ^{13}C NMR spectrum. In particular, the signals corresponding to the sp carbons of alkyne **7** centered at 77.16 and 77.25 ppm were shifted to 78.45 and 79.68 ppm in **8**, respectively. All quaternary C resonances were detected by a DEPT experiment.

After the *tert*-butoxycarbonyl deprotection the resulting amino carborane **9** was coupled with palmitic acid, acting as a lipophilic chain, according to the procedure proposed by Kamiński.[18] This affords the palmitamide **10** (64% yield, after chromatographic purification). ^{13}C NMR analysis confirmed the proposed structure, in particular the signals relevant to quaternary carbon atoms of the carborane cage shifted to 78.77 and 78.98 respectively.

At this point it was possible to go on with the functionalisation of the other arm of the *o*-carborane (Scheme 3). The benzylic protecting group was removed by Pd/C-catalysed hydrogenation, and alcohol **11** was readily oxidised to the corresponding carboxylic acid **12** by CrO_3 in acetone-sulfuric acid solution as shown in Scheme 3.[19]

The structure of derivative **12** is supported by the ^{1}H and ^{13}C NMR data. The ^{1}H NMR spectrum shows the disappearance of the signal at 3.84 ppm assigned to the HOCH_2 group whereas the ^{13}C spectrum shows a new signal centered at 170.00 ppm ascribed to the carboxylic group. On the other side, the shift of the signals of the quaternary carboranyl carbon from 78.47 and 78.92 ppm to 74.07 and 78.98 ppm. Carboxylic derivative **12** was subsequently coupled, without purification, to the suitable DOTAMA(*tert*-Bu)$_3$-C_6-NH_2,[20] to produce the desired bifunctionalised *o*-carborane **13**. The structure of the target compound was confirmed by the ESI mass spectrum, which clearly shows the MH^+ peak (1124). After removal of the *tert*-butyl ester group (CF_3CO_2H/CH_2Cl_2) the Gd(III) complex **14** was finally obtained by adding stoichiometric amounts of $GdCl_3$ in MeOH/H_2O.

In spite of the long hydrophobic chain and the neutrality of the coordination cage, the Gd(III) complex **14** showed good water solubility. This observation supports the view that, in aqueous solutions, complex **14** self-assembles to yield micellar aggregates. Size measurements were performed using a dynamic light scattering instrument (DLS) (also known as photon correlation spectroscopy), which measures Brownian motions in solution and relates them to the sizes of the particles. The obtained size distribution diagram for a 0.517 nM solution of complex, showed that one main species present that has a mean diameter of 38 ±10 nm. The measured size appears in the high range values for micelles likely as consequence of the concomitant presence of



Scheme 3 Synthesis of Gd(III)-*C*-(DOTAMA-C_6-amidomethyl)-*C′*-palmitamidomethyl-*o*-carborane complex (**14**). *Reaction conditions and yields*: a) CrO_3, acetone, H_2SO_4 3M, rt (71%); b) CDMT, *N*-methylmorpholine, DOTAMA-C_6-NH_2, CH_2Cl_2, −5 °C→rt (40%); c) CH_2Cl_2, CF_3COOH, rt (99%), d) $GdCl_3$, MeOH/H_2O, r. t. (64%).

two bulky substituents such the DOTA cage and the carborane moiety. As the high paramagnetism of Gd(III) ions prevents the detection of high resolution NMR spectra, the characterisation of the Gd(III) complex has been pursued by investigating its relaxometric properties. The $1/T_1$ water proton NMRD profile has been measured, at 25 °C and pH = 7, over the interval of proton Larmor frequencies from 0.01 to 80 MHz (Fig. 1). The experimental data have been analysed with an iterative least-squares fitting procedure assuming contributions to the relaxivity from inner- and outer-hydration sphere water molecules.[21] In the analysis the following parameters were kept fixed: the hydration number $q = 1$, the distance of closest approach of the outer sphere

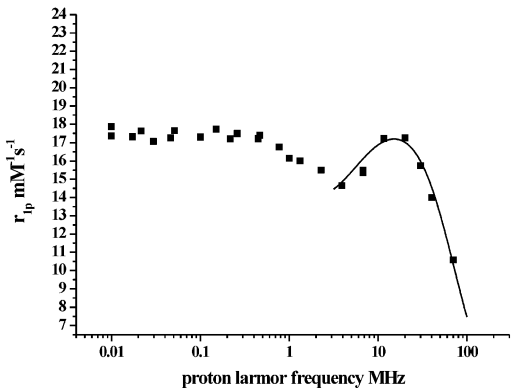


Fig. 1 NMRD profile of a water solution of Gd(III) complex **14** at 25 °C and pH = 7. The solid line indicates the best-fit curve.

solvent proton nuclei to the Gd(III) ion ($a = 3.8$ Å), the relative diffusion coefficient $D = 2.24 \times 10^5$ cm^2 s^{-1} and the distance between the inner sphere water molecule and metal center $r = 3.05$. The other parameters were considered as adjustable within a range of values typical of this class of macrocyclic Gd(III) complexes: reorientational correlation time, $\tau_R \sim 70$ ps to 70 ns; water molecule residence life time, $\tau_M \sim 1$ μs ($\tau_M =$); correlation time characterising the electron spin relaxation, $\tau_V \sim 1$–50 ps; and trace of the square of the transient zero-field splitting tensor, $\Delta^2 \sim 0.4$–50×10^{19} s^{-2}.[22]

The fit between the calculated and experimental values is very good in the high field region. The resulting τ_R (10.5 ns) is definitely much longer than the values shown by molecular complexes of similar size, and indicates the occurrence of large micelles. An attempt to assess the cmc value by measuring the change in relaxivity upon decreasing the concentration of paramagnetic complex failed; no change in slope was observed down to 15 μM, and therefore the actual cmc could be less than this threshold.

The relaxivity value at 0.5 T (20 MHz) and 25 °C is 17.3 mM^{-1} s^{-1}, *i.e.* in the typical range of slowly moving supramolecular adducts involving the neutral Gd(III)-DOTA monoamide moiety. In fact in such systems, the relaxivity is "quenched" by the long exchange lifetime of the coordinated water molecule. From the fitting of the experimental data, a value of 1.16 μs has been obtained for the last parameter, fully consistent with those reported for other related Gd(III)-DOTA monoamide systems.[23]

Conclusions

The bifunctionalised carborane **14** has been obtained in fourteen steps, with the carborane cage being introduced only at the sixth step to reduce waste of the very expensive decaborane. The decaborane-bifunctionalised alkyne insertion reaction in the biphasic system (ionic liquid (bmim)$^+$Cl$^-$ and toluene) is the key step. A very lipophilic palmityl chain has been introduced in order to endow the probe with binding affinity towards LDL, whose transporters are overexpressed on the outer membrane of several tumor cells. On the other side, carborane has been bonded to a Gd(III)-DOTA complex which is a very efficient MRI contrast agent and will allow the quantitative determination of boron in cells. Furthermore, the presence of Gd(III) will improve the NCT properties of this probe. *C*-(2-Benzyloxy)-ethyl-*C′*-*tert*-butoxyamidomethyl-*o*-carborane (**8**) is a versatile intermediate which can be readily functionalised with different biological vectors and MRI contrast agents to build a series of substituted *o*-carboranes. Moreover, thanks to the versatility of metal complexation of DOTA, product **14** could be considered for use in PET or SPECT–BNCT applications. Finally the formation of tightly assembled micelles suggests additional uses of complex **14** in targeting experiments; for example, forming mixed micelles with suitably functionalised amphiphilic molecules.

Experimental

General

Flasks and all equipments used for the generation and reaction of moisture-sensitive compounds were dried by electric heater

under Ar. THF was distilled from benzophenone ketyl, anhydrous Et_2O was distilled from $LiAlH_4$ and anhydrous CH_2Cl_2 from CaH_2 prior to use. BuLi (1.6 M in hexanes) was obtained from Aldrich. $(Bmim)^+Cl^-$ was purchased from Solvent Innovation GmbH. Decaborane was bought from KATCHEM spol. s r. o. All commercially obtained reagents and solvents were used as received. Products were purified by preparative column chromatography on Macherey Nagel silica gel for flash chromatography, 0.04–0.063 mm/230–400 mesh.

Reactions were monitored by TLC using Silica gel on TLC-PET foils Fluka, 2–25 μm, layer thickness 0.2 mm, medium pore diameter 60 Å. Carboranes and their derivatives were visualized on TLC plates using a 5% $PdCl_2$ aqueous solution in HCl. ^1H NMR spectra were recorded at 400 and 200 MHz,[24] ^{13}C NMR spectra at 100.4 and 50.2 MHz. Data were reported as follows: chemical shifts in ppm from tetramethylsilane as internal standard, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = double-doublet, m = multiplet, br = broad), coupling constants (Hz), and assignment. ^{13}C NMR spectra were measured with complete proton decoupling. Chemical shifts were reported in ppm from the residual solvent as an internal standard. GC-MS spectra were obtained on a mass selective detector HP 5970 B instrument operating at an ionizing voltage of 70 eV connected to a HP 5890 GC with a cross linked methyl silicone capillary column (25 m X 0.2 mm X 0.33 μm film thickness). ESI MS spectra were obtained on a Waters micromass ZQ spectrometer equipped with ESI ion source. IR spectra were recorded on a Perkin Elmer BX FT-IR. Benzylbut-2-inylether (**2**) and 5-benzyloxy-pentyn-1-ol (**3**) were synthesised as described in literature and their spectroscopic data corresponded with those reported.[12]

The $1/T_1$ nuclear magnetic relaxation dispersion profiles of water protons were measured over a continuum of magnetic field strengths from 0.00024 to 2.4 T (corresponding to 0.01–80 MHz in proton Larmor frequency) on the fast field-cycling Stelar Spinmaster FFC relaxometer (from 0.01 to 20 MHz) and on the Stelar Spinmaster variable magnetic field instrument (from 20 to 80 MHz). The NMRD profile was acquired on 0.5 ml of an aqueous solution of the complex at 0.5 mM. The exact relaxivity (at 20 MHz and 25 °C was determined after mineralizing a given quantity of the sample with 37% HCl at 120 °C overnight in order to determine the exact concentration of Gd(III) present in the solution. This value is obtained by dividing the relaxation rate (R_1 obs) of the mineralized solution by the relaxivity of the Gd(III) aquaion in acidic solution (13.5 mM^{-1} s^{-1} at 20 MHz and 25 °C). The excess of free Gd(III) eventually present in the solution used for the NMRD measurement was removed by increasing the pH of the solution to 8–9 followed by centrifugation and filtering the basic solution on 0.2 micron syringe filters. Orange Xylenol UV spectrophotometry was used to check for the absence of free Gd(III) ions".[25] Dynamic light scattering measurements, made to determine the size of the micellar system, were performed on the Malvern Zetasizer SZ apparatus. A laser is used as the light source to illuminate the sample particles within the cell.

5-(Benzyloxy)-pent-2-ynyl methanesulfonate (4). 5-benzyloxy-pentyn-1-ol (3) (3.0 mmol, 572 mg) in a 50 mL three necked round bottom flask was dissolved in 25 mL of anhydrous Et_2O and cooled to 0 °C, then Et_3N (1.5 equiv, 4.5 mmol, 0.627 mL) followed by MsCl (1.5 equiv, 4.5 mmol, 0.348 mL) were added. The reaction mixture was stirred for 1 h then quenched with H_2O and extracted with Et_2O (3 × 10 mL). The combined extracts were washed H_2O (2 × 10 mL), dried and evaporated under reduced pressure leaving 0.794 g (98%) of a pale yellow oil which was at once used for the following reaction. Found C, 58.35; H, 5.99; S, 11.98%. Calc. for $C_{13}H_{16}O_4S$: C, 58.19; H, 6.01; S, 11.95%. ν_{max}(neat)/cm^{-1} 3063, 2239, 1367, 1103, 939. δ_H (200 MHz; $CDCl_3$, Me_4Si) 2.55 (2 H, m, $PhCH_2OCH_2CH_2$), 3.02 (3 H, s, $CH_2SO_3CH_3$), 3.59 (2 H, m, $PhCH_2OCH_2CH_2$), 4.52 (2 H, s, $CH_2SO_3CH_3$), 4.81 (2 H, s, $PhCH_2OCH_2CH_2$), 7.33 (5 H, bs, $PhCH_2OCH_2CH_2$); δ_C (50.2 MHz; $CDCl_3$, Me_4Si) 18.0 (1 × t), 36.5 (1 × q), 56.5 (1 × t), 65.6 (1 × t), 70.6 (1 × t), 71.4 (1 × s), 86.1 (1 × s), 125.6 (2 × d), 125.7 (2 × d), 126.3 (1 × d), 136.0 (1 × s). MS (EI, 70 eV): m/z (%) = 268 (0.4) [M^+], 171 (25), 91 (100), 66 (12), 65 (25).

[(5-Azidopent-3-ynyloxy)methyl]benzene (5). A mixture of 5-(benzyloxy)pent-2-ynyl methanesulfonate **4** (5 mmol, 1.36 g) and NaN_3 (2.5 equiv, 12.5 mmol, 0.812 mg) was stirred in 5 mL of DMF at rt overnight. quenched with brine (10 mL) and extracted with Et_2O (3 × 10 mL). The combined extracts were washed with brine (5 × 10 mL), dried and evaporated under reduced pressure to afford 1.00 g (92.5%) of a pale yellow oil which was at once used for the following reaction. Found (C, 67.02; H, 5.99; N, 19.89% Calc. for $C_{12}H_{13}N_3O$: C, 66.96; H, 6.07; N, 19.52%. ν_{max} (neat)/cm^{-1} 3031, 2128, 1248, 1103, 738. δ_H (200 MHz; $CDCl_3$, Me_4Si) 2.61 (2 H, m, $PhCH_2OCH_2CH_2$), 3.63 (2 H, t, J = 6.8 Hz, $PhCH_2OCH_2CH_2$), 3.91 (2 H, s, CH_2N_3), 4.58 (2 H, s, $PhCH_2OCH_2CH_2$), 7.35 (5 H, bs, $PhCH_2OCH_2CH_2$); δ_C (50.2 MHz; $CDCl_3$, Me_4Si) 20.0 (1 × t), 40.0 (1 × t), 68.1 (1 × t), 72.7 (1 × t), 73.1 (1 × s), 85.0 (1 × s), 127.5 (3 × d), 128.3 (2 × d), 138.0 (1 × s). MS (EI, 70 eV): m/z (%) = 161 (13) [M^+ –CN·, –N_2], 107 (19), 91 (100), 79 (39), 77 (26).

5-(Benzyloxy)pent-2-yn-1-amine (6). [(5-Azidopent-3-ynyl-oxy)methyl]benzene **5** (1.7 mmol, 0.36 g) was dissolved in 15 mL of MeOH, then $SnCl_2$ was slowly added (1.5 eq, 2.5 mmol, 0.56 g) the reaction mixture became yellow. The solution was stirred at room temperature overnight. Then the solvent was evaporated under reduced pressure, the residue was dissolved in 10% aqueous NaOH, and this solution was extracted with CH_2Cl_2 (5 × 10 mL). The combined extracts were dried and evaporated under reduced pressure to afford 0.32 g (99%) of a pale yellow oil which was at once used for the following reaction. Found C, 76.30; H, 8.01; N, 7.33% Calc. for $C_{12}H_{15}NO$: C, 76.16; H, 7.99; N, 7.38%. ν_{max} (neat)/cm^{-1} 3367, 1586, 1334, 1099, 738. δ_H (200 MHz; $CDCl_3$, Me_4Si) 1.64 (2 H, bs, CH_2NH_2), 2.49 (2 H, bs, $PhCH_2OCH_2CH_2$), 3.38 (2 H, s, CH_2NH_2), 3.56 (2 H, m, $PhCH_2OCH_2CH_2$), 4.54 (2 H, s, $PhCH_2OCH_2CH_2$), 7.35 (5 H, bs, $PhCH_2OCH_2CH_2$); δ_C (50.2 MHz; $CDCl_3$, Me_4Si) 19.9 (1 × t), 31.4 (1 × t), 68.3 (1 × t), 72.7 (1 × t), 79.0 (1 × t), 81.7 (1 × s), 127.5 (3 × d), 128.2 (2 × d), 137.9 (1 × s). MS (EI, 70 eV): m/z (%) = 189 (0.24) [M^+], 171 (33), 91 (100), 65 (29), 51 (12).

***tert*-Butyl-5-(benzyloxy)pent-2-ynylcarbamate (7).** Di-*tert*-butyl dicarbonate (1.05 equiv, 10.3 mmol, 2.24 g) and sulfamic acid (5% mol, 0.48 mmol, 0.047 g) were mixed at room temperature in a 10 mL round bottom flask with a magnetic stirbar, then 5-(Benzyloxy)pent-2-yn-1-amine **6** was added dropwise (9.7 mmol, 1.83 g). The solution was stirred for 15 min, then the reaction

was quenched with brine, extracted with EtOAc (2 × 10 mL), the combined organic phases were washed with brine (2 × 10 mL) and H_2O (2 × 10 mL). Solvent was evaporated under reduced pressure, leaving 1.81 g (99%) of pale yellow oil which was at once used for the following reaction. Found C, 70.43; H, 8.03; N, 4.85%. Calc. for $C_{17}H_{23}NO_3$: C, 70.56; H, 8.01; N, 4.84%. ν_{max} (neat)/cm^{-1} 3348, 2980, 2933, 1808, 1714. δ_H (200 MHz; $CDCl_3$, Me_4Si) 1.43 (9 H, s, C(C*H*$_3$)$_3$), 2.46 (2 H, m, PhCH$_2$OCH$_2$C*H*$_2$), 3.56 (2 H, bt, J = 6.8 Hz, PhCH$_2$OC*H*$_2$CH$_2$), 3.86 (2 H, m, C*H*$_2$NHCO*t*Bu), 4.51 (2 H, s, PhC*H*$_2$OCH$_2$CH$_2$), 7.27 (6 H, m, *Ph*CH$_2$OCH$_2$CH$_2$ and CH$_2$N*H*CO*t*Bu); δ_C (50.2 MHz; $CDCl_3$, Me_4Si) 19.9 (1 × t), 28.2 (3 × q), 68.1 (1 × t), 72.7 (1 × t), 76.4 (1 × t), 77.2 (1 × s), 77.7 (1 × s), 79.8 (1 × s), 127.5 (3 × d), 128.2 (2 × d), 137.8 (1 × s), 155.1 (1 × s). MS (EI, 70 eV): *m*/*z* (%) = 232 (13) [M$^+$ - *t*Bu], 159 (32), 91 (100), 65 (19), 57 (55).

***C*-(2-Benzyloxy)-ethyl-*C′*-*tert*-butoxyamidomethyl-*o*-carborane (8).** In a dried heavy wall tube containing a stirring bar, 2 mmol of *tert*-Butyl-5-(benzyloxy)pent-2-ynylcarbamate **7** (0.58 g) and decaborane (1.3 mmol, 0.16 g), were reacted under Ar in a biphasic mixture of 0.10 g (bmim)$^+$Cl$^-$ and 3 mL of anhydrous toluene with vigorous stirring at 120 °C for 1 h. After cooling to rt the reaction mixture was filtered on a silica gel column (eluant: CH_2Cl_2). The crude was purified by column chromatography (eluant: CH_2Cl_2) giving 0.33 g (41%) of a white solid. Found C, 49.98; H, 8.30; B, 26.20; N, 3.26%. Calc. for $C_{17}H_{33}B_{10}NO_3$: C, 50.10; H, 8.16; B, 26.53; N, 3.44%. Mp 89–92 °C ν_{max} (neat)/cm^{-1} 2575, 1688, 1537, 1253, 749. δ_H (200 MHz; $CDCl_3$, Me_4Si) 1.46 (9 H, s, C(C*H*$_3$)$_3$), 2.70 (2 H, bt, J = 3.8 Hz, PhCH$_2$OCH$_2$C*H*$_2$), 3.63 (2 H, bt, J = 5.28 Hz, PhCH$_2$OC*H*$_2$CH$_2$), 3.90 (2 H, d, J = 6.6 Hz, C*H*$_2$NHCO*t*Bu), 4.51 (2 H, s, PhC*H*$_2$OCH$_2$CH$_2$), 5.29 (1 H, bt, J = 1.0 Hz, CH$_2$N*H*CO*t*Bu), 7.35 (5 H, s, *Ph*CH$_2$OCH$_2$CH$_2$); δ_C (50.2 MHz; $CDCl_3$, Me_4Si) 28.0 (3 × q), 35.2 (1 × t), 43.0 (1 × t), 68.1 (1 × t), 73.0 (1 × t), 78.4 (1 × s), 79.7 (1 × s), 80.2 (1 × s), 127.6 (3 × d), 128.0 (2 × d), 137.0 (1 × s), 154.8 (1 × s). *m*/*z* (ESI+) 430 [M + Na]$^+$.

***C*-(2-Benzyloxy)-ethyl-*C′*-aminomethyl-*o*-carborane (9).** *C*-(2-Benzyloxy)-ethyl-*C′*-*tert*-butoxyamidomethyl-*o*-carborane **8** (0.6 mmol, 0.29 g) was dissolved in 10 mL of anhydrous CH_2Cl_2, then 10 mL of CF_3COOH were added dropwise. The solution was stirred for 2 h at rt, then quenched with 10 mL of brine, extracted with CH_2Cl_2, the organic phases were washed with brine (10 mL) and dried. The solvent was evaporated under reduced pressure giving 0.17 g (99%) of a pale yellow oil. Found C, 47.01; H, 8.18; N, 4.55%. Calc. for $C_{12}H_{25}B_{10}NO$: C, 46.88; H, 8.20; N, 4.56%. ν_{max} (neat)/cm^{-1} 3401, 3339, 2582, 1106, 738. δ_H (200 MHz; $CDCl_3$, Me_4Si) 1.25 (2 H, bs, N*H*$_2$), 2.51 (2 H, m, PhCH$_2$OCH$_2$C*H*$_2$), 3.34 (2 H, m, C*H*$_2$NH$_2$), 3.62 (2 H, m, PhCH$_2$OC*H*$_2$CH$_2$), 4.44 (2 H, m, PhC*H*$_2$OCH$_2$CH$_2$), 7.34 (5 H, s, *Ph*CH$_2$OCH$_2$CH$_2$); δ_C (50.2 MHz; $CDCl_3$, Me_4Si) 35.0 (1 × t), 46.0 (1 × t), 68.2 (1 × t), 73.2 (1 × t), 77.4 (1 × s), 82.2 (1 × s), 127.8 (2 × d), 127.9 (2 × d), 128.4 (1 × d), 137.0 (1 × s). *m*/*z* (ESI+) 308 [M + H]$^+$.

***C*-(2-Benzyloxy)-ethyl-*C′*-palmitamidomethyl-*o*-carborane (10).** To a stirred solution of CDMT (2-chloro-4,6-dimethoxy-1,3,5-triazine, 0.32 mmol, 57 mg) and palmitic acid (1.02 equiv, 0.37 mmol, 85 mg) in anhydrous CH_2Cl_2, *N*-methylmorpholine was added dropwise (1.02 equiv, 0.332 mmol, 36.5 μL) keeping the temperature at −5 to 0 °C. The reaction was stirred at 0 °C and followed by TLC (petroleum ether/Et_2O 50/50) until the disappereance of CDMT spot (nearly 4 h). To the crude solution above described, a mixture of amino-*o*-carborane **9** (1 equiv, 0.325 mmol, 100 mg) and *N*-methylmorpholine (1 equiv, 0.325 mmol, 36 μL) in CH_2Cl_2 was added, maintaining the temperature at 0 °C for 2 h, then the mixture was left at rt overnight. The solvent was evaporated and the residue was suspended in CH_2Cl_2 (10 mL), washed with H_2O (10 mL), 10% aqueous citric acid (10 mL), saturated $NaHCO_3$ (10 mL) and H_2O (10 mL). The organic layer was dried, the solvent evaporated under reduced pressure. The crude was purified on silica gel (CH_2Cl_2) giving 113 mg (64%) of a white solid. Found C, 61.80; H, 10.02; N, 2.56%. Calc. for $C_{28}H_{54}B_{10}NO_2$: C, 61.72; H, 9.99; N, 2.57%. mp 52–53 °C ν_{max} (neat)/cm^{-1} 3289, 2564, 1655, 1541, 1093, 1073, 700. δ_H (200 MHz; $CDCl_3$, Me_4Si) 0.88 (3 H, bt, J = 7.2 Hz, (CH$_2$)$_{14}$C*H*$_3$), 1.23 (24 H, m, CH$_2$CH$_2$(C*H*$_2$)$_{12}$CH$_3$), 1.51 (2 H, m, CH$_2$C*H*$_2$(CH$_2$)$_{12}$CH$_3$), 1.82 (2 H, m, PhCH$_2$OCH$_2$C*H*$_2$), 2.71 (2 H, bt, J = 5.6 Hz, C*H*$_2$CH$_2$(CH$_2$)$_{12}$CH$_3$), 3.67 (2 H, m, PhCH$_2$OC*H*$_2$CH$_2$), 3.99 (2 H, m, C*H*$_2$NHCO), 4.50 (2 H, m, PhC*H*$_2$O), 6.04 (1 H, m, CH$_2$N*H*CO), 7.34 (5 H, m, *Ph*CH$_2$OCH$_2$CH$_2$); δ_C (50.2 MHz; $CDCl_3$, Me_4Si) 14.0 (1 × q), 22.5 (1 × t), 25.2 (1 × t), 29.0 (1 × t), 29.1 (1 × t), 29.2 (1 × t), 29.3 (3 × t), 29.5 (4 × t), 31.7 (1 × t), 35.4 (1 × t), 35.8 (1 × t), 40.9 (1 × t), 68.5 (1 × t), 73.2 (1 × t), 78.8 (1 × s), 79.0 (1 × s), 127.7 (1 × d), 128.0 (2 × d), 128.5 (2 × d), 136.9 (1 × s) 172.5 (1 × s),. *m*/*z* (ESI+) 546 [M + H]$^+$.

***C*-Palmitamidomethyl-*C′*-2-hydroxyethyl-*o*-carborane (11).** In a 50 mL two necked round bottom flask, *C*-(2-benzyloxy)-ethyl-*C′*-palmitamidomethyl-*o*-carborane **10** (0.3 mmol, 0.16 g) was dissolved in 20 mL of a mixture of MeOH-CH_2Cl_2 (50–50), then Pd/C was wet with few drops of water and added (10%, 0.03 mmol, 17 mg). The reaction mixture was stirred overnight at rt in a H_2 saturated atmosphere, then filtered and the solvent was evaporated under reduced pressure giving 0.13 g (98%) of pale yellow oil. Found C, 55.60; H, 10.61; N, 3.07%. Calc. for $C_{21}H_{49}B_{10}NO_2$: C, 55.47; H, 10.64; N, 3.08%. ν_{max} (neat)/cm^{-1} 3297, 2586, 1655, 1551. δ_H (200 MHz; $CDCl_3$, Me_4Si) 0.85 (3 H, m, C*H*$_3$), 1.25 (24 H, m, CH$_2$CH$_2$(C*H*$_2$)$_{12}$CH$_3$), 1.61 (2 H, m, CH$_2$C*H*$_2$(CH$_2$)$_{12}$CH$_3$), 2.21 (2 H, bt, J = 7.2 Hz, HOCH$_2$C*H*$_2$), 2.64 (2 H, m, C*H*$_2$CH$_2$(CH$_2$)$_{12}$CH$_3$), 2.88 (1 H, bs, O*H*), 3.80 (2 H, m, HOC*H*$_2$CH$_2$), 4.05 (2 H, bd, J = 5.4 Hz, C*H*$_2$NHCO), 6.54 (1 H, bs, CH$_2$N*H*CO); δ_C (50.2 MHz; $CDCl_3$, Me_4Si) 13.9 (1 × q), 22.5 (1 × t), 25.4 (2 × t), 29.1 (2 × t), 29.2 (2 × t), 29.4 (2 × t), 29.5 (2 × t), 31.7 (2 × t), 36.2 (1 × t), 37.6 (1 × t), 41.4 (1 × t), 60.7 (1 × t), 78.5 (1 × s), 78.9 (1 × s), 173.4 (1 × s). *m*/*z* (ESI+) 457 [M + H]$^+$; 495 [M + K]$^+$.

***C*-Carboxymethyl-*C′*-palmitamidomethyl-*o*-carborane (12).** *C*-2-Hydroxyethyl-*C′*-palmitamidomethyl-*o*-carborane **11** (0.37 mmol, 0.17 g) was dissolved in 10 mL of $(CH_3)_2CO$, then a solution of CrO_3 (4 equiv, 1.5 mmol, 0.15 g) in H_2SO_4 3 M was added carefully at 0 °C. The reaction mixture was left overnight at rt, then quenched with H_2O. The solvent was evaporated under reduced pressure and the mixture was extracted with CH_2Cl_2 (5 × 10 mL), the organic layers were washed once with 10 mL of brine, dried and evaporated giving 0.13 g (71%) of a pale yellow oil. Found C, 54.76; H, 10.18; N, 2.89%. Calc. for $C_{21}H_{47}B_{10}NO_3$: C, 53.70; H, 10.09; N, 2.98%. ν_{max} (neat)/cm^{-1} 3292, 2584, 1721, 1548. δ_H (200 MHz; $CDCl_3$, Me_4Si) 0.88 (3 H, m, C*H*$_3$), 1.26 (24

H, m, $CH_2CH_2(CH_2)_{12}CH_3$), 1.63 (2 H, m, $CH_2CH_2(CH_2)_{12}CH_3$), 2.26 (2 H, m, $CH_2CH_2(CH_2)_{12}CH_3$), 3.48 (2 H, s, CH_2COOH), 4.12 (2 H, bd, J = 6.4 Hz, CH_2NHCO), 5.80–6.50 (1 H, bs, $COOH$), 6.49 (1 H, bs, CH_2NHCO); δ_C (50.2 MHz; $CDCl_3$, Me_4Si) 13.9 (1 × q), 22.5 (1 × t), 25.3 (1 × t), 29.0 (1 × t), 29.1 (1 × t), 29.2 (1 × t), 29.3 (3 × t), 29.5 (3 × t), 31.7 (1 × t), 36.1 (1 × t), 40.6 (1 × t), 41.4 (1 × t), 41.7 (1 × t), 74.1 (1 × s), 79.0 (1 × s), 170.0 (1 × s), 173.9 (1 × s); m/z (ESI+) 493 $[M + Na]^+$.

***C*-(*tert*-ButylDOTAMA-C_6-amidomethyl)-*C′*-palmitamidomethyl-*o*-carborane (13).** Method for the preparation of **10** was used, derivative **12** (0.527 mmol, 0.255 g), CMDT (0.517 mmol, 0.91 g) and *N*-methylmorpholine (0.527 mmol, 60 μL) were dissolved in 5 mL of in anhydrous CH_2Cl_2 at 0 °C. After 4 h *N*-*tert*-ButDOTAMA-C_6-NH_2 (0.517 mmol, 0.347 g), *N*-methylmorpholine (0.517 mmol, 57 μL) in 10 mL of anhydrous CH_2Cl_2 were added. The solution was stirred for 60 h, then treated as described above. A pale yellow solid was obtained and purified by chromatography (CH_2Cl_2-MeOH 96–4, then CH_2Cl_2-MeOH 80–20) affording 237 mg of a viscous colorless oil (40%). Found C, 59.00; H, 9.94; N, 8.75% Calc. for $C_{55}H_{111}B_{10}N_7O_9$: C, 58.84; H, 9.97; N, 8.76%. ν_{max} (neat)/cm^{-1} 3437, 2581, 1732, 1670. δ_H (200 MHz; $CDCl_3$, Me_4Si) 0.86 (3 H, m, CH_3), 1.23 (24 H, m, $CH_2CH_2(CH_2)_{12}CH_3$), 1.44 (27 H, s, $COOtBu$), 1.00–2.00 (12 H, m, $CH_2CH_2(CH_2)_{12}CH_3$, CH_2CH_2NH), 2.00–3.00 (22 H, m, $CH_2NCOOtBu$, CH_2CONH, CH_2NH), 3.00–4.20 (10 H, m, $CH_2COOtBu$), 8.10 (1 H, bs, J = 6.4 Hz, $NHCH_2CO$), 8.80 (2 H, bs, CH_2NHCO); δ_C (50.2 MHz; $CDCl_3$, Me_4Si) 13.9 (1 × q), 25.1 (1 × t), 25.3 (2 × t), 25.5 (2 × t), 27.3 (9 × q), 28.2 (2 × t), 28.4 (2 × t), 29.1 (3 × t), 29.3 (2 × t), 29.5 (2 × t), 31.7 (1 × t), 36.0 (1 × t), 38.0 (1 × t), 38.4 (1 × t), 41.1 (1 × t), 41.4 (1 × t), 48.0–56.0 (8 × t), 55.3 (2 × t), 55.5 (1 × t), 55.9 (1 × t), 75.8 (1 × s), 80.8 (1 × s), 81.6 (2 × s), 81.7 (1 × s), 166.3 (1 × s), 171.0 (1 × s), 171.9 (1 × s), 172.2 (2 × s), 173.6 (1 × s); m/z (ESI+) 1124 $[M + H]^+$.

Gd(III)-*C*-(DOTAMA-C_6-amidomethyl)-*C′*-palmitamidomethyl-*o*-carborane complex (14). In a 50 mL round bottom flask, 140 mg (0.12 mmol) of product **13** were cooled to 0 °C, dissolved in 5 mL of a mixture of CF_3COOH-CH_2Cl_2 (50–50) and stirred for 4 h at rt. After evaporation of CF_3COOH-CH_2Cl_2 115 mg of viscous colorless oil were obtained (99%). Found C, 54.28; H, 9.16; N, 10.24%. Calc. for $C_{43}H_{87}B_{10}N_7O_9$: C, 54.12; H, 9.19; N, 10.27%. ν_{max} (neat)/cm^{-1} 3323, 2922, 2585, 1682. δ_H (200 MHz; MeOD, Me_4Si) 0.87 (3 H, m, CH_3), 1.29 (24 H, m, $CH_2CH_2(CH_2)_{12}CH_3$), 1.00–2.00 (14 H, m, $CH_2CH_2(CH_2)_{12}CH_3$, CH_2CH_2NH, CH_2CH_2CO), 2.25 (2 H, bt, J = 6.8 Hz $(CH_2)_{12}CH_2CO$), 3.00–4.30 (28 H, m, CH_2NCOOH, CH_2CONH, CH_2NH), 7.20 (3 H, bs, $NHCH_2CO$, CH_2NHCO); δ_C (50.2 MHz; $CDCl_3$, Me_4Si) 12.9 (1 × q), 22.1 (1 × t), 25.2 (1 × t), 25.6 (1 × t), 28.4 (1 × t), 28.7 (2 × t), 28.8 (3 × t), 28.9 (5 × t), 29.2 (3 × t), 31.4 (2 × t), 35.1 (1 × t), 38.9 (1 × t), 41.3 (1 × t), 52.5 (2 × t), 52.6 (1 × t), 53.9 (1 × t), 76.1 (1 × s), 80.1 (1 × s), 159.8 (1 × s), 160.5 (1 × s), 166.8 (1 × s), 174.5 (3 × s);[26] m/z (ESI+) 956 $[M + H]^+$. In a 10 mL round bottom flask, 110 mg of deprotected intermediate (0.11 mmol) and 1 equivalent of $GdCl_3$ were dissolved in a 50:50 mixture of water and MeOH at rt. The pH solution was checked and maintained to 6.5 by 1 M NaOH aqueous solution. The solution was stirred overnight, then the pH was adjusted to 8.5 by 1 M NaOH aqueous solution and the mixture was stirred for 2 h, then filtered over 0.2 μm syringe filter, the pH was adjusted to 7 by a 1 M HCl aqueous solution and the solvent evaporated. Inorganic salts were removed by gel filtration on Sephadex® G10 column using a 50:50 mixture of water and MeOH as eluent. The solvent was removed affording 80 mg of complex **15** (0.07 mmol, 64%). Found C, 46.61; H, 7.65; N, 8.83%. Calc. for $C_{43}H_{84}B_{10}GdN_7O_9$: C, 46.59; H, 7.64; N, 8.84%. ν_{max} (neat)/cm_{-1} 3447, 2926, 2589, 1683, 1626, m/z (ESI+) 1131 $[M + Na]^+$.

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