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Highly Water-Soluble Carbaborane-Bridged Bis(glycophosphonates)

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A facile synthesis of carbaboranediyl-bis(glycophosphonates) and corresponding phosphonothioates is presented. These compounds show extraordinarily high water solubility and low cytotoxicity.

Introduction

To date, the treatment of malignant tumors is always accompanied by extremely negative side effects. One potentially useful approach for the selective destruction of tumor cells is boron neutron capture therapy (BNCT), a powerful form of radiotherapy involving preferential incorporation of ^{10}B-containing compounds into tumor cells, followed by irradiation of the tumor with thermal neutrons.[1] The high-energy fission products that are formed on absorption of a neutron allow selective destruction of the tumor cells without affecting the surrounding healthy tissue. High and selective accumulation in tumor cells is one important requirement for a BNCT agent. For successful treatment, a concentration of 30 µg ^{10}B per gram tumor must be achieved. The main problem to date is the availability of boron compounds that exhibit the necessary high selectivity, water solubility, and low toxicity in high concentrations.[2]

The synthesis and bioactivity studies of the first phosphorus-containing boron cluster compounds bearing phosphate and pyrophosphate moieties were reported by Kaczmarczyk and Bechtold in 1975.[3] However, these compounds turned out to be highly toxic. Interestingly, some simple carbaboranyl bis(phosphonates) exhibit high tumor selectivity and can be used in the treatment of calcifying tumors. Oligomeric phosphate diesters which contain *closo-* or *nido*-carbaboranes show high accumulation in tumor tissue in BALB/c mice bearing EMT6 tumors.[4] However, comprehensive biological assessments of boron-containing phosphonates as potential tumor-targeting agents in BNCT are still rare.[5]

Endogenous lectins are located on the surface of normal and malignant cells and serve as specific receptors for mediating endocytosis of glycoconjugates.[6] Transformation of normal to malignant cells is often accompanied by modification of the lectin composition and overexpression of certain lectins. For example, lactose-binding lectin (LBL) plays an important role in the metastatic growth of tumors.[7] We have therefore devised efficient syntheses for boron compounds which provide a combination of tumor-targeting systems: The use of phosphonato groups as phosphate mimics and galactosyl groups for binding to lectins at the surface of a tumor cell.[8] The 6-position of the galactose is usually involved in recognition in lectins, but for proof of our general synthetic principle[9] we synthesized galactosyl derivatives connected via the 6-position to the phosphonate.

Results and Discussion

Carbaboranediyl-bis(glycophosphonates) were synthesized according to the phosphoramidite method from a *meta-* or *para*-carbaboranyl bis(phosphonite) and protected galactose **2** and benzimidazolium triflate (BIT) as promoter.

Synthesis of disodium salts **5** and **6** starts from *meta*-carbaboranediyl bis(phosphonite) **1**,[9] which acts as a phosphoramidite analogue. Galactosylation of **1** with a slight excess of protected galactose **2** and benzimidazolium triflate led to the desired glycophosphonite derivative. Oxidation of this intermediate with *tert*-butyl hydroperoxide (TBHP) yielded target bis(phosphonate) **3** which was previously reported[9] to exhibit four signals in the ^{31}P{^{1}H} NMR spectrum at δ = 10.4 ppm corresponding to the four possible stereomers. The phosphonate groups were deprotected either with thiophenol/triethylamine/dioxane according to the method developed by van Tamelen and Daub[10] or by using Me_3SiBr[11] followed by aqueous hydrolysis. In our hands the first method was found to be better, as it gave

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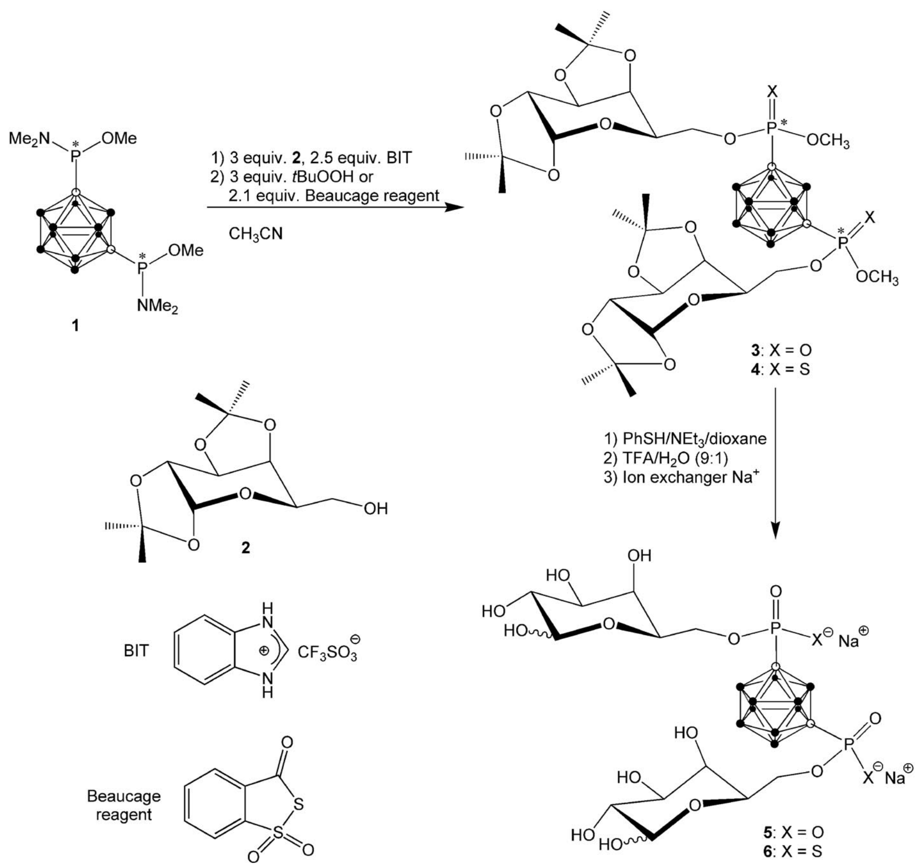


Scheme 1. Synthesis of the carbaborandiyl-bis(phosphonate) **5** and -bis(phosphonothioate) **6**.

higher yields of **5**. After phosphonate deprotection, the isopropylidene groups at the galactose moieties were cleaved with trifluoroacetic acid/water (9:1).[12] After purification by preparative HPLC, the bis(hydroxyphosphonate) was converted into the desired disodium salt **5** by ion exchange (see Scheme 1).

Phosphonates are usually stabilized against attack of phosphatases.[13] However, there are also phosphonate esterases known that are able to cleave phosphonates.[14] Therefore, we synthesized the bis(phosphonothioate) derivative **6**. Galactosylation was performed as described for the bis(phosphonate) **5**.

Instead of TBHP a sulfurization agent is used in the oxidation step. Elemental sulfur in combination with an amine base is a simple and widely used reagent for this purpose,[15] but in the case of carbaboranediyl-bis(phosphonites) this led to excessive decomposition (^{31}P NMR spectroscopic proof). Instead, 3*H*-1,2-benzodithiol-3-one 1,1-dioxide, the so-called Beaucage reagent,[16] is the sulfurization agent of choice, because it leads smoothly to the bis(phosphonothioate) derivative **4**. The product exhibits four signals around $\delta = 79.6$ ppm in the ^{31}P NMR spectrum. Separation of the stereomers was not possible. Deprotection of the diastereomeric mixture was performed in analogy to the corresponding bis(phosphonate) **5**. Subsequent ion exchange led to highly water-soluble compound **6**.

Spectroscopic Properties of 5 and 6

Both phosphorus atoms in **5** are nonchiral, because the negative charge is delocalized. Therefore, one signal is expected in the ^{31}P NMR spectrum. Interestingly, two signals are observed at 4.9 ppm. One reason might be formation of micelles, as was observed for a lactosyl and a bis(glucosyloxomethyl) carbaborane.[17] To prove the existence of micelles, a dilute solution of **5** ($c = 3 \times 10^{-4}$ M) was prepared to achieve a concentration below the critical micelle concentration (CMC), at which the compound should occur in the nonaggregated form. However, the ^{31}P{^{1}H} NMR spectrum indicated no change in the ratio of the two signals. Even if the CMC was not reached, a significant change in the ratio of the signals would be expected. Thus, this result indicates that no micelles are formed. Another possibility is that the cluster may act as a conformational anchor, which would allow formation of two possible arrangements of the two phosphonate groups. While a high-temperature ^{31}P{^{1}H} NMR spectrum of a solution of **5** shows only one broad signal at 50 °C, this result does not definitively support the theory of the two conformers, as the line width also increases at elevated temperature.

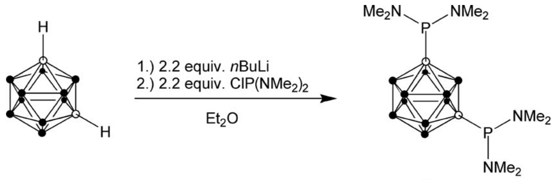
In the case of compound **6** cleavage of the methyl ester led to a high field shift of about 18 ppm due to a thione-thiol rearrangement. Because both phosphorus atoms in disodium salt **6** are chiral, in contrast to **5**, the $^{31}P\{^1H\}$ NMR spectrum exhibits two signals, at δ_P = 61.2 ppm. Due to anomerization of the galactose moieties, a maximum of 16 possible stereomers would be expected theoretically. The observation of only two signals is probably due to only small magnetic differences between the epimers. For the carbon atoms of the carbaborane core the ^{13}C NMR spectrum shows a doublet with a $^1J_{CP}$ coupling constant of 110.5 Hz, which is about 20 Hz smaller than in the corresponding bis(phosphonate) **5**. This is a general observation for thiophosphonates. Komarov et al. tried to explain the phenomenon of a smaller $^1J_{CP}$ coupling constant in thiophosphoryl compounds in comparison with phosphoryl compounds by theoretical calculations, but failed.[18]

Because of the anomerization of the galactosyl moieties, the ^{13}C and ^1H NMR spectra of **5** and **6** exhibit signals for the α and β forms, but only for the pyranosyl form of galactose. The ratio between α and β forms was determined with the integrateable ^{13}C NMR method, because the chemical shifts of C-1α and C-1β are significantly different. Measurement of the anomeric ratio by optical rotation angle was impossible due to the small amounts of the substances available. In the first step of the ^{13}C NMR method, the relaxation time T_1 of the anomeric carbon atoms was determined to 375 ms and is therefore relatively short. On this basis an inverse gated ^1H-decoupling experiment was performed.[19] The ratio of α to β forms amounts is 33:67. In galactose the α/β ratio (sum of the α vs. β forms of pyranoses and furanoses) is 33.5:66.4.[20] Taking the error margin into account, the anomeric ratio in **5** is identical with that in galactose.

The ^{11}B NMR spectra only show one very broad signal at δ = –10.1 ppm. For a similar compound, namely, 1,2-bis[(β-D-galactopyranosyl)-(1→4)-(β-D-glucopyranosyl)methyl]-1,2-dicarba-*closo*-dodecaborane(12), two signals and for a β-lactosyl-*closo*-*ortho*-carbaborane five signals, were reported.[17] Disubstitution, especially by sterically demanding groups like carbohydrate units, interrupts the symmetry of the electron density distribution of the cluster and results in a broad signal.

Tetra-D-galactosylated Carbaboranediyl Bis(phosphonates)

To examine whether two sodium monogalactosyl phosphonate groups or two digalactosyl phosphonate moieties are better for accumulation in tumor cells, the latter compounds were also synthesized according to the protocol for **3** and **4**. Therefore, a carbaboranediyl bis(phosphonite) precursor with four dimethylamido groups was needed. A two-step synthesis of **7** was reported by Alexander and Schroeder[21] in 1966 starting from a bis(dichlorophosphanyl)-*meta*-carbaborane, which led to **7** after amination with dimethylamine gas in nearly 30% total yield. The synthesis of the analogous *ortho*-carbaborane derivative was reported by Hill et al. in 1978 starting from dilithiated carbaborane and bis(diamido)chlorophosphite.[22] In a slightly modified procedure of the latter, the desired compound **7** can be obtained in 60% yield (see Scheme 2), which is an improved yield and easier access than the two-step synthesis of Alexander and Schroeder.



7

Scheme 2. Synthesis of **7**.

Molecular Structure of 7

Compound **7** crystallizes in the triclinic space group $P\bar{1}$ with four molecules in the unit cell. Only one of the two molecules of **7** in the asymmetric unit is shown in Figure 1. Selected bond lengths and angles are presented in Table 1.

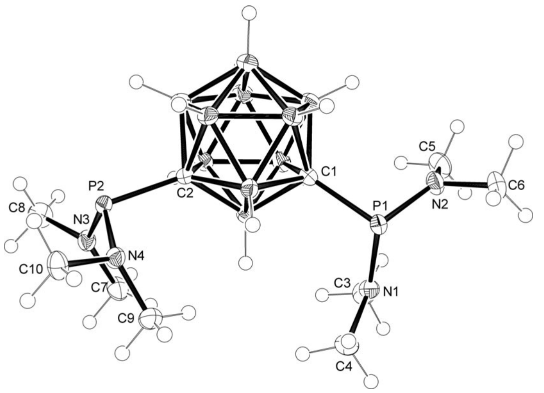


Figure 1. Molecular structure of **7** (only one of the two independent molecules is shown).

Table 1. Selected bond lengths and angles of **7** (data are shown for only one of the two independent molecules).

Bond lengths [pm]		Bond angles [°]	
P(1)–N(1)	167.3(1)	N(2)–P(1)–N(1)	109.55(6)
P(1)–N(2)	167.8(1)	N(2)–P(1)–C(1)	101.62(6)
P(1)–C(1)	189.7(1)	N(1)–P(1)–C(1)	104.72(6)
P(2)–N(3)	167.1(1)	N(3)–P(2)–N(4)	110.63(6)
P(2)–N(4)	168.6(1)	N(3)–P(2)–C(2)	103.98(5)
P(2)–C(2)	188.6(1)	N(4)–P(2)–C(2)	101.31(5)

The P(1)–C(1) and P(2)–C(2) bond lengths are in the range observed for similar *ortho*-carbaborane derivatives.[23] Both phosphorus atoms have a pyramidal environment, and the four nitrogen atoms are surrounded in a trigonal-planar fashion by the methyl groups and the phosphorus atom.

Galactosylation of 7

Compound **7** was treated with an excess of six equivalents of protected galactose **2** (i.e., 1.5 equiv. per amido group) and five equivalents of BIT according to the procedure described above. Galactosylation proceeds very slowly at room temperature, because of substitution at the phosphorus atom with two highly sterically demanding carbohydrate moieties and was completed only after five days. Due to the low reaction rate, the intermediate steps could be monitored by $^{31}P\{^{1}H\}$ NMR spectroscopy (Figure 2).

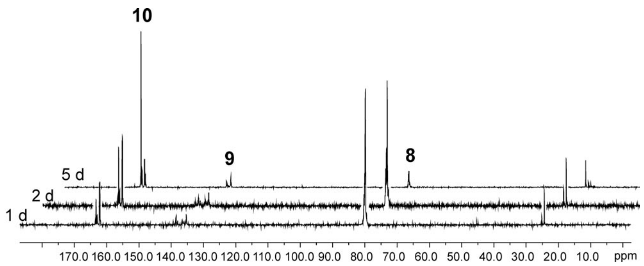
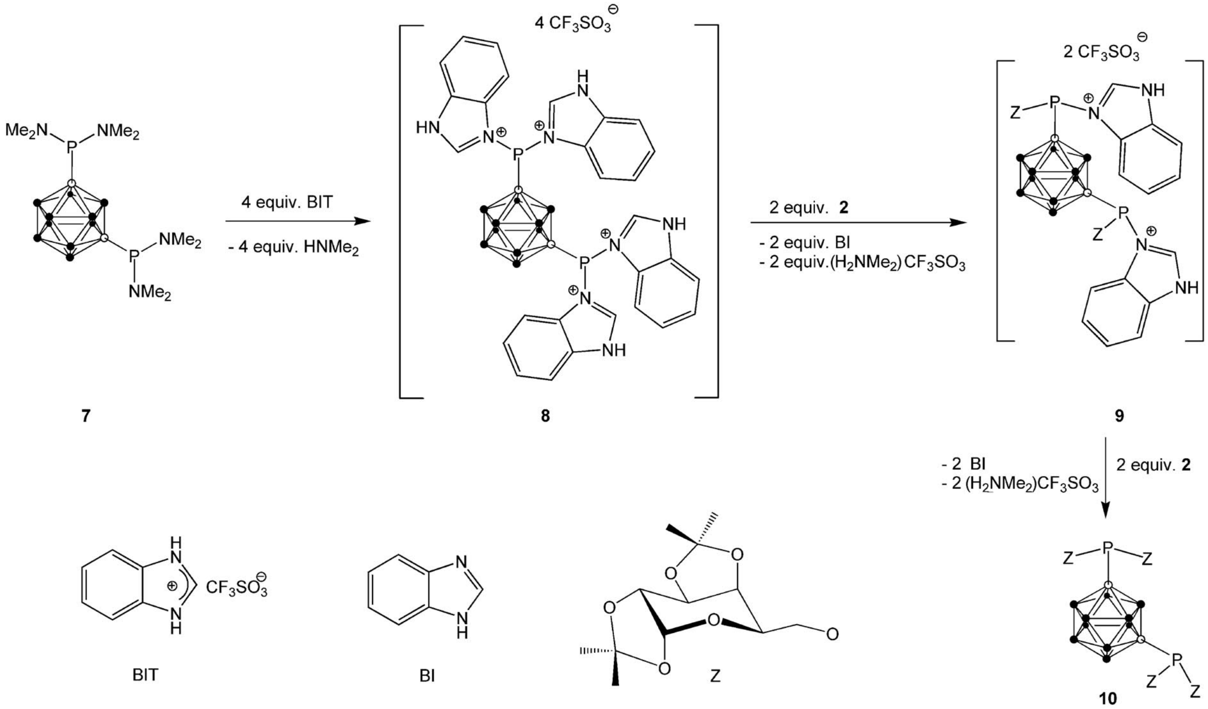


Figure 2. $^{31}P\{^{1}H\}$ NMR spectra of the reaction mixture after 1, 2, and 5 d (in CH_3CN).

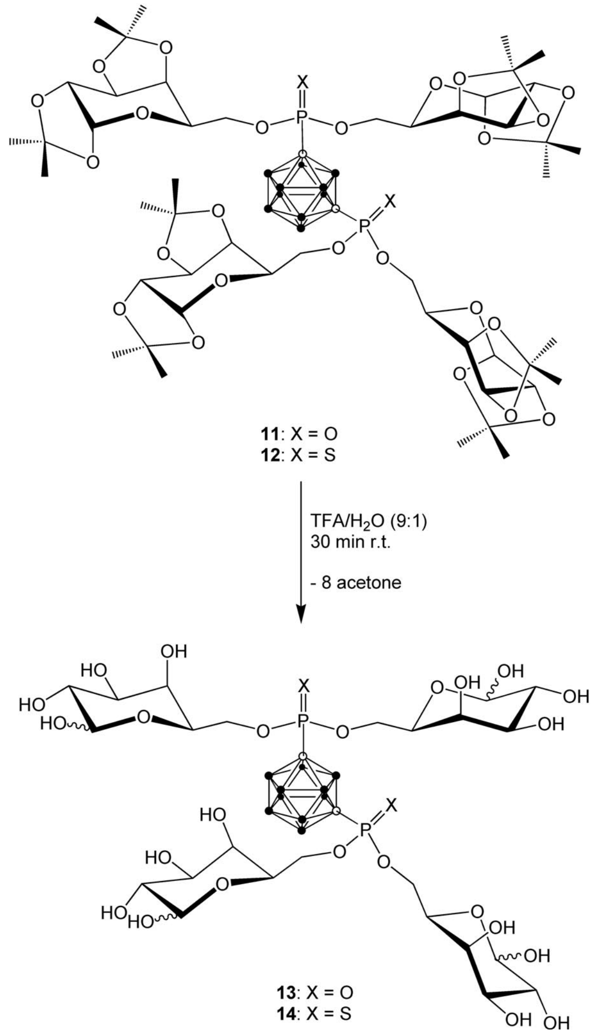
After one day an intense signal at δ_P = 80 ppm was observed, which can be assigned according to the reaction mechanism proposed by Noyori et al.[24] to the tetraammonium salt of **8** (Scheme 3). Noyori et al. reported that an azolium complex such as **8**, in the presence of a nucleophile (e.g., a free OH group of a nucleoside) cannot be observed in the $^{31}P\{^{1}H\}$ NMR spectrum, and instead the signal of the resulting product is seen. They postulated that conversion of this azolium complex is faster than its formation. If **7** and an excess of BIT are dissolved in CD_3CN, a signal at δ_P = 79 ppm results, which can be assigned to tetrabenzimidazolium-substituted carbaboranediyl bis(phosphonite) **8** in accordance with the ^{1}H NMR spectrum. We assume that the observation of **8** also in the presence of a nucleophile can only be explained by its much lower reactivity, in contrast to phosphoramidites used in oligonucleotide chemistry. Due to steric hindrance, monogalactosylated product **9** is formed, which gives rise to low-intensity signals at δ_P = 137 ppm. The very low concentration of **9** indicates that it rapidly transforms into tetragalactosylated compound **10** (δ_P = 163 ppm).

After five days at room temperature the reaction was complete, but a significant amount of side products was formed. The reaction time could be reduced to three hours by irradiation in a microwave oven. Oxidation with TBHP and sulfurization with the Beaucage reagent led to bis(phosphonate) **11** in 30% yield and to bis(phosphonothioate) **12** in 13% yield, respectively. The yield of **12** is very low even though ^{31}P NMR spectra of the reaction mixture show prevailing formation of the bis(phosphonothioate) together with a small amount of oxidized species **11**. Additionally, a mixed oxo/thiophosphonate derivative could be isolated in 9% yield by column chromatography. It was previously reported that the reaction product of the Beaucage reagent is a strong oxidizing agent.[16] We assume that this compound reacts faster with the sterically constrained phosphorus atoms than the sulfurization agent. Therefore, we used bis[3-(triethoxysilyl)-*n*-propyl] tetrasulfide (TEST), which was reported by Hayakawa et al.[25] in 2005 as an alternative to the Beaucage reagent, because it exhibits similar rates but does not produce any oxidation reagent during the sulfurization process. Unexpectedly, performing the reaction



Scheme 3. Synthesis of tetragalactosylated compound **10**.

with TEST led to a yield of only 13%, too. Deprotection of the galactosyl moieties in **11** and **12** with trifluoroacetic acid at room temperature led to the highly water-soluble compounds **13** and **14** (Scheme 4).



Scheme 4. Deprotection of **11** and **12**.

Spectroscopic Properties of 13 and 14

Cleavage of the isopropylidene moieties led to an equilibrium between α and β forms of the galactosyl groups. The four carbohydrate units can theoretically form 16 stereoisomers. Anomerization induces chirality at the phosphorus atoms, which results in the observation of several signals in the $^{31}P\{^1H\}$ NMR spectra, in contrast to the protected compounds **11** and **12**. For **13** three signals at δ = 10.1 ppm and for bis(phosphonothioate) **14** three signals at δ = 78.4 ppm are observed (Figure 3). The ^1H NMR spectra show a characteristic multitude of multiplets. Only the anomeric protons can be assigned with certainty. The anomeric protons of bis(phosphonate) **13** exhibit a multiplet for the β anomer at δ = 4.56 ppm and a doublet at δ = 5.24 ppm for the α anomer. The corresponding thio derivative **14** exhibits a very similar signal pattern. The detailed assignment of the signals in the $^{13}C\{^1H\}$ NMR spectra was possible only in part, as the occurrence of stereomers led to strong overlap of multiple signals. The carbon atoms of the boron cluster can be identified due to their large coupling constant to the phosphorus atoms ($^1J_{CP}$ is 136.4 Hz for **14** and 182.5 Hz for **13**). The $^1J_{CP}$ coupling constant of the bis(phosphonothioate) is about 46 Hz smaller than in the corresponding bis(phosphonate). The anomeric carbon atoms exhibit two signals in both compounds. Integration of the signal intensity yields α:β ratios of 34:66 for **14** and 37:63 for **13**. Considering the measurement error, the ratio is similar to that of galactose. The ^{11}B NMR spectra show in both cases only one very broad signal.

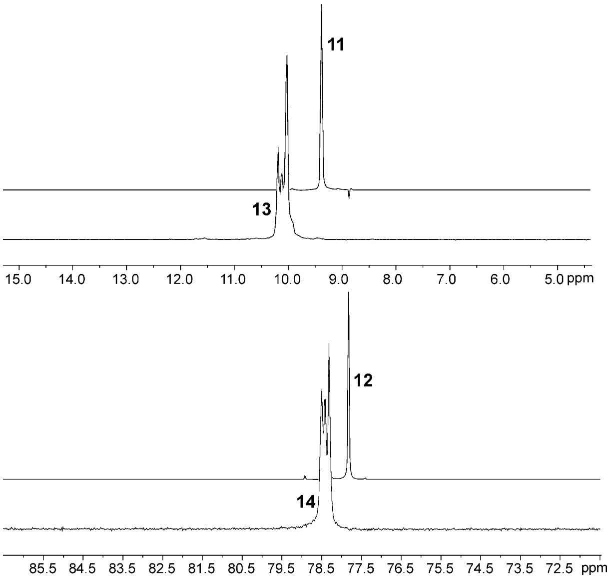


Figure 3. $^{31}P\{^1H\}$ NMR spectra of the protected compounds **11** and **12** in $CDCl_3$ and the deprotected compounds **13** and **14** in D_2O.

para-Carbaborane-Containing Bis(glycophosphonate)

For future studies on the influence of the isomeric carbaborane core on the biological activity, the *para*-carbaborane analogue of **7** was synthesized according to the procedure described for **7**. Compound **15** was obtained as a crystalline solid in 55% yield. The compound crystallizes in the monoclinic space group $P2_1/n$ with two molecules in the unit cell. The crystal structure is shown in Figure 4, selected bond lengths and angles are presented in Table 2.

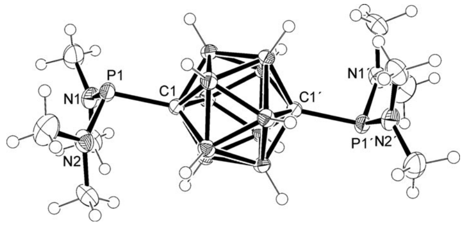


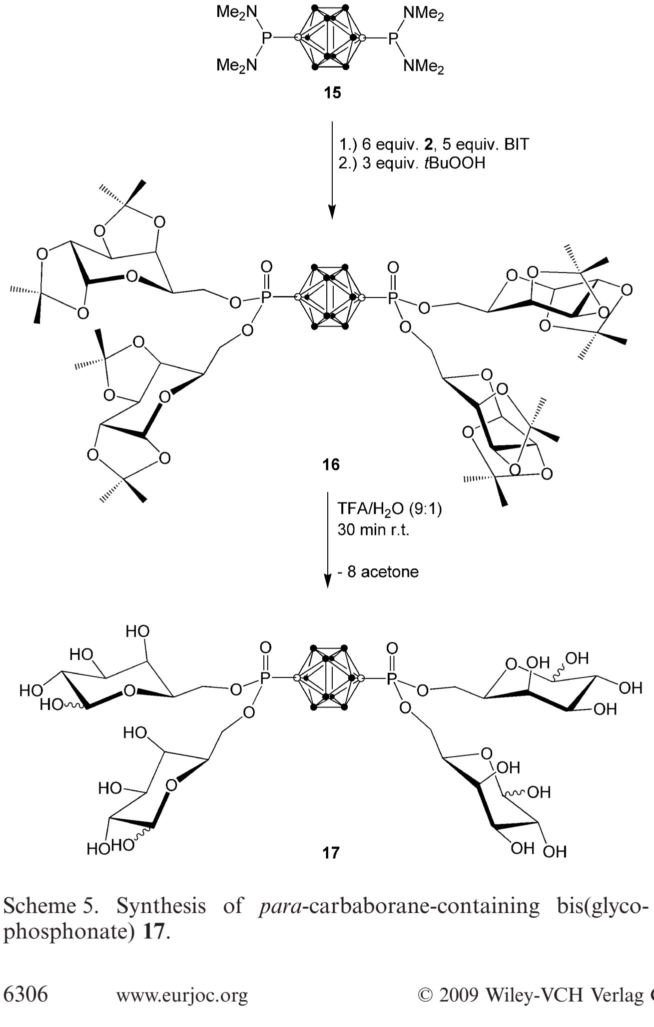
Figure 4. Molecular structure of **15**.

Table 2. Selected bond lengths and angles of **15**.

Bond lengths [pm]		Bond angles [°]	
P(1)–N(1)	166.8(1)	N(1)–P(1)–N(2)	110.29(5)
P(1)–N(2)	167.1(1)	N(1)–P(1)–C(1)	101.65(6)
P(1)–C(1)	189.0(1)	N(2)–P(1)–C(1)	103.26(5)

The molecule lies on an inversion center. The P(1)–C(1) and the P(2)–C(2) bond lengths are in the same range as in the *meta*-carbaborane derivative **7** and similar *ortho*-carbaborane derivatives.[23]

Compound **15** was treated with an excess of protected galactose **2** under microwave conditions. Interestingly, the reaction proceeds faster than with *meta*-carbaborane analogue **7**. We suppose that this is mainly due to the lesser steric interaction of the four galactosyl moieties than in the *meta*-carbaborane derivative. Additionally, the less pronounced electron-withdrawing character in comparison with the *ortho*- and *meta*-carbaboranes may also play a role. To support this hypothesis, theoretical calculations on this phenomenon are underway and will be presented elsewhere. After oxidation and isolation, the galactosyl moieties of intermediate compound **16** were deprotected with 90% trifluoroacetic acid to yield highly water-soluble target compound **17** in 33% yield (Scheme 5). In general the NMR spectra show no differences in comparison to the spectra of **13** with the exception of the ^{11}B NMR spectrum, which shows a sharp doublet with a $^{1}J_{BH}$ coupling constant of 151.2 Hz.



Scheme 5. Synthesis of *para*-carbaborane-containing bis(glycophosphonate) **17**.

Water Solubility of the Bis(glycophosphonates)

The water solubility of all compounds reported herein was determined and found to be high in comparison with D-galactose. The values for the glycophosphonate derivatives are shown in Table 3. Due to the relatively small amounts available, the values could not be determined with precision and are therefore rounded. The disodium salts exhibit the highest water solubility among these compounds of 910 (**5**) and 830 g/L (**6**). These absolute values are higher than for D-galactose (650 g/L). However, the molar solubilities of about 1.35 (**5**) and about 1.18 mol/L (**6**) are lower than that of galactose (3.6 mol/L). Due to the missing ionic part of the molecules, tetragalactosyl-substituted compounds **13** and **14** are less water-soluble. In general, all thio derivatives show lower solubility than their phosphonate counterparts. This is especially the case for the tetragalactosyl compounds, whereby bis(phosphonothioate) **14** exhibits only half the water solubility of corresponding bis(phosphonate) **13**. The *para*-carbaborane unit was reported to be the most lipophilic in the series of carbaborane isomers.[26] Therefore, lower water solubility of **17** was expected. Interestingly, the *para*-carbaborane cage seems to have little influence on the water solubility when **17** is compared with *meta*-carbaborane analogue **13**. It can be concluded that in general the combination of an ionic phosphonato group and carbohydrate moieties provides high water solubility of the extremely hydrophobic carbaborane moieties, which is crucial for a proposed application in BNCT.

Table 3. Water solubility of **5**, **6**, **13**, **14**, **17**.

Compound	Water solubility[a]	
	g/L	mol/L
5	910	1.35
6	830	1.18
13	790	0.83
14	380	0.39
17	780	0.81
D-galactose	650	3.6

[a] Values for the carbaborane derivatives could not be precisely determined and are rounded. The error margin is ca. ±10 g/L.

A detailed report on the biological properties will be given elsewhere.

Conclusions

We have developed a facile synthesis of *meta*- and *para*-carbaborane-containing bis(glycophosphonates) with one and two galactosyl moieties at the phosphorus atoms. These compounds exhibit high water solubility in comparison with D-galactose and, as will be reported elsewhere, low cytotoxicity even in millimolar concentrations, and they are therefore excellent candidates for further biological studies with potential applications in BNCT.

Experimental Section

General: Standard Schlenk and vacuum-line techniques were employed for all manipulations of air- and moisture-sensitive compounds. The NMR spectra were recorded with a Bruker AVANCE DRX 400 spectrometer: ^{1}H NMR (400.13 MHz): internal standard solvent, external standard TMS in the case of organic solvents and DSS [$Na(Me_3SiCH_2CH_2CH_2SO_3)$] in the case of water. ^{31}P NMR (161.98 MHz): external standard 85% H_3PO_4. ^{13}C NMR (100.16 MHz): internal standard solvent, external standard TMS in the case of organic solvents or DSS for water, ^{11}B NMR (128.38 MHz): external standard $BF_3{\cdot}OEt_2$. The solvents were dried and saturated with nitrogen. 1,2:3,4-di-*O*-isopropylidene-α-D-galactose (**2**) is commercially available from Sigma–Aldrich and was dried under vacuum for several hours before preparing a stock solution in dry acetonitrile. 3*H*-1,2-Benzodithiol-3-one 1,1-dioxide was purchased from Alfa Aesar. The syntheses of **1** and **3** were recently reported.[9] Benzimidazolium triflate was synthesized according to a modified literature procedure:[27] benzimidazole was dissolved in dichloromethane and cooled to 0 °C. An equimolar amount of trifluoromethanesulfonic acid (distilled prior to use) was added slowly under vigorous stirring. After complete addition, the purple salt was isolated by filtration, washed with dichloromethane, and dried in high vacuum at 50 °C overnight; m.p. 216–217 °C (ref.[27] 188–190 °C).

The mass spectra were recorded with a Bruker Daltonics 7 Tesla APEX II spectrometer (ESI) or on a Finnigan MAT MAT8200 spectrometer (EI). The reported masses refer to the most intense peak of the isotopic boron pattern. Column chromatography was performed on silica gel 60 (230 ± 400 mesh). For detection of carbohydrates a 1:10 mixture of concentrated phosphoric acid in ethanol was used. Visualization of boron compounds was achieved with a 2% solution of $PdCl_2$ in methanol. Preparative HPLC was performed on a ProntoSIL® 120–10 C8 ace-EPS column (Knauer) with a flow rate of 25 mL/min. Elemental analyses were performed with a VARIO EL (Heraeus). Microwave reactions were performed in a microwave oven from Mikrowellen Labor Systeme GmbH at normal pressure.

The data for X-ray crystallographic analysis (Table 4) were collected with an Oxford Diffraction CCD Xcalibur-S diffractometer (data reduction with CrysAlis Pro[28] including the program SCALE3 ABSPACK[29] for empirical absorption correction) using Mo-K_α radiation (λ = 71.073 pm) and ω-scan rotation. The structures were solved by direct methods, and the refinement of all non-hydrogen atoms was performed with SHELXL-97.[30] H atoms were located on difference Fourier maps calculated at the final stage of the structure refinement. Structure figures were generated with ORTEP.[31]

CCDC-724122 (for **7**) and -724123 (for **15**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Disodium Bis(6-deoxy-D-galactopyranos-6-yl) [1,7-Dicarba-*closo*-dodecaborane(12)-1,7-diyl]bis(phosphonate) (5): Thiophenol (0.25 mL, 2.4 mmol) and triethylamine (0.5 mL, 3.6 mmol) were added to a stirred solution of **3** (213 mg, 0.26 mmol) in dioxane (1 mL). The reaction mixture was stirred at room temperature for 1 h, then the solvent was evaporated and a 1:1 (v/v) mixture of ethyl acetate and water was added to the residue. The phases were separated and the aqueous solution stirred with Amberlite IR-120 ion exchanger (H$^+$ form, 20 mL) for 50 min. The resin was filtered off and washed three times with 20 mL of water. The combined extracts were evaporated to dryness, and then 90% trifluoroacetic acid (2 mL) was added and the resulting solution stirred for 40 min at room temperature. The mixture was evaporated to dryness and the residue purified by preparative HPLC on a ProntoSIL® column (gradient CH_3CN/H_2O, 80:20 in 30 min to CH_3CN/H_2O, 0:100; t_R = 8.2 min). Appropriate fractions were collected and the solvents evaporated to dryness and the remaining aqueous solution was concentrated and then lyophilized several times. The white powder was dissolved in water (15 mL) and stirred with Amberlite IR-120 ion exchanger (Na$^+$ form, 10 mL) for 48 h. The resin was removed by filtration and washed with water. Lyophilization yielded the product (136 mg, 77.8%) as a pale yellow powder. ^{1}H NMR (D_2O): δ = 1.6–3.4 (br. m, 10 H, $B_{10}H_{10}$), 3.33 (m, 2 × 0.67 H, 2β-H), 3.51 (d, $^{3}J_{HH}$ = 9.4 Hz, 2 × 0.67 H, 3β-H), 3.67 (m, 2 × 0.67 H, 5β-H), 3.72 (m, 4 × 0.33 H, 3α-H and 4α-H), 3.82 (m, 2 H, 2α-H + 4β-H), 3.88 (m, 4 H, CH_2-O, α + β form), 4.04 (s, 2 × 0.33 H, 5α-H), 4.45 (d, $^{3}J_{HH}$ = 8.0 Hz, 2 × 0.67 H, 1β-H), 5.11 (s, 2 × 0.33 H, 1α-H) ppm. ^{13}C{^{1}H} NMR (D_2O): δ = 64.7 ($^{2}J_{CP}$ = 6.4 Hz, *C*-6β), 65.2 ($^{2}J_{CP}$ = 6.0 Hz, *C*-6α), 68.1 (*C*-2α), 68.2 (*C*-4β), 68.7 and 68.9 (*C*-3α and *C*-4α), 69.3 ($^{3}J_{CP}$ = 6.8 Hz, *C*-5α), 71.7 (*C*-2β), 71.8 (d, $^{1}J_{CP}$ = 154.6 Hz, $C_2B_{10}H_{10}$), 72.5 (*C*-3β), 73.6 ($^{3}J_{CP}$ = 7.0 Hz, *C*-5β), 92.4 (*C*-1α), 96.5 (*C*-1β) ppm. ^{31}P{^{1}H} NMR (D_2O): δ = 4.9 (s) ppm. ^{11}B NMR (D_2O): δ = –10.0 (br. s, 10 B, $C_2B_{10}H_{10}$, $^{1}J_{BH}$ n.d.) ppm. IR (KBr): $\tilde{\nu}$ = 3426 (vs) (OH), 2919 (w) (CH), 2610 (m) (BH) cm^{-1}. MS (ESI positive, CH_3CN): *m*/*z* = 695.1 [M + Na]$^+$, 674.1 [M + H]$^+$. $C_{14}H_{32}B_{10}Na_2O_{16}P_2{\cdot}2H_2O$ (708.46): calcd. C 23.73, H 5.12; found C 23.33, H 5.10.

Table 4. Crystallographic data of **7** and **15**.

	7	**15**
Empirical formula	$C_{10}H_{34}B_{10}N_4P_2$	$C_{10}H_{34}B_{10}N_4P_2$
Formula weight	380.45	380.45
T [K]	130(2)	130(2)
Crystal system	triclinic	monoclinic
Space group	$P\bar{1}$	$P2_1/n$
a [pm]	1047.5(1)	1177.64(3)
b [pm]	1450.0(4)	788.73(1)
c [pm]	1592.4(2)	1237.09(2)
α [°]	112.52(2)	90
β [°]	90.03(1)	107.608(2)
γ [°]	103.52(2)	90
V [nm^3]	2.1614(7)	1.09522(4)
Z	4	2
ρ_{calcd} [Mg m^{-3}]	1.169	1.154
μ(Mo-K_α) [mm^{-1}]	0.204	0.201
F(000)	808	404
No. of reflns. collected	64811	15874
*R*1/*wR*2 [$I > 2\sigma(I)$]	0.0349/0.0772	0.0335/0.0935
*R*1/*wR*2 (all data)	0.0621/0.0879	0.0468/0.0984

***O*,*O*′′-Bis(1,2:3,4-di-*O*-isopropylidene-6-deoxy-α-D-galactopyranos-6-yl)-*O*′,*O*′′′-Dimethyl (R_{P1},S_{P1}:R_{P2},S_{P2})-[1,7-Dicarba-*closo*-dodecaborane(12)-1,7-diyl]bis(phosphonothioate) (4):** Compound **2** (8.0 mL, 6.40 mmol, 0.8 M solution in acetonitrile) and benzimidazolium triflate (1.42 g, 5.30 mmol) were added to a solution of **1** (0.75 g, 2.12 mmol) in acetonitrile (20 mL). The reaction mixture was stirred for 3 h at room temperature. Conversion was monitored by ^{31}P NMR spectroscopy. Then powdered Beaucage reagent (0.90 g, 4.49 mmol) was added and stirring was continued for 2 h at room temperature. The reaction mixture was diluted with ethyl acetate (30 mL) and extracted with brine (3 × 30 mL). The organic layer was dried with anhydrous $MgSO_4$, and the solvent removed under reduced pressure. The honey-like residue was purified by chromatography on silica gel with ethyl acetate/cyclohexane (1:2). The product was obtained as a white foam (0.88 g, 48.9%). R_f (ethyl acetate/cyclohexane, 1:2) = 0.63. Due to the diastereomeric mixture all signals in the ^1H and $^{13}C\{^1H\}$ NMR appear twice. ^1H NMR ($CDCl_3$): δ = 1.33 (s, 12 H, CH_3), 1.43 (s, 6 H, CH_3), 1.54 (s, 6 H, CH_3), 1.6–3.5 (br. m, 10 H, $B_{10}H_{10}$), 3.77 (d, $^3J_{HP}$ = 14.4 Hz, 6 H, $POCH_3$), 4.0 (m, 4 H, CH_2O), 4.11 (m, 2 H, 5-H), 4.20 (m, 2 H, 4-H), 4.31 (m, 2 H, 2-H), 4.62 (m, 2 H, 3-H), 5.53 (m, 2 H, 1-H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ = 24.4–26.9 (CH_3), 54.8 (d, $^2J_{CP}$ = 6.5 Hz, OCH_3), 67.3 (OCH_2, $^2J_{CP}$ n.d.), 70.3 (C-2), 70.5 and 70.7 (C-3 and C-4), 70.8 (C-5, $^3J_{CP}$ n.d.), 73.9 (d, $^1J_{CP}$ = 132.4 Hz, $C_2B_{10}H_{10}$), 70.3–70.8 (OCH), 96.2 (C-1α), 108.5–109.6 (C_{quart} from isopropylidene) ppm. $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ = 79.46 (s), 79.52 (s), 79.75 (s), 79.83 (s), (4 stereomers) ppm. ^{11}B NMR ($CDCl_3$): δ = –2.8 (br. s, 2 B, $C_2B_{10}H_{10}$, $^1J_{BH}$ n.d.), –9.9 (br. s, 8 B, $C_2B_{10}H_{10}$, $^1J_{BH}$ n.d.) ppm. IR (KBr): $\tilde{\nu}$ = 2989 (m), 2936 (w) (C–H), 2620 (m) (B–H) cm^{-1}. MS (ESI positive in CH_3CN): *m*/*z* = 872.33 $[M + Na]^+$. $C_{28}H_{54}B_{10}O_{14}P_2S_2$ (848.91): calcd. C 39.62, H 6.41; found C 38.04, H 6.21.

Diastereomeric Mixture of Disodium *O*,*O*′′-Bis(6-deoxy-D-galactopyranos-6-yl) [1,7-Dicarba-*closo*-dodecaborane(12)-1,7-diyl]bis(phosphonothioate) (6): Triethylamine (1 mL, 7.2 mmol) and thiophenol (0.5 mL, 4.9 mmol) were added to a stirred solution of **4** (846 mg, 1 mmol) in dioxane (2 mL). The reaction mixture was stirred at room temperature for 1 h. Then all volatile materials were evaporated, and ethyl acetate was added to the resulting residue to remove thiophenol (evaporates azeotropically with ethyl acetate). The oily residue was dissolved in dichloromethane (50 mL) and stirred with Amberlite IR-120 ion exchanger (H^+ form, 50 mL) for 50 min. The resin was filtered off and washed three times with dichloromethane (50 mL). The combined extracts were evaporated to dryness and the remaining residue dissolved in trifluoroacetic acid (4 mL, 90% in water) and stirred for 40 min at room temperature. The reaction mixture was evaporated to dryness and the residue purified by prparative HPLC on a ProntoSIL® column (gradient CH_3CN/H_2O, 80:20 in 30 min to CH_3CN/H_2O, 0:100; t_R = 11.0 min). Appropriate fractions were collected and concentrated in vacuo. The residue was lyophilized several times. The resulting white powder was dissolved in water (15 mL) and stirred with Amberlite IR-120 ion exchanger (Na^+ form, 10 mL) for 36 h. The resin was filtered off and washed three times with water (10 mL). The aqueous solution was lyophilized to yield the product as a pale yellow powder (260 mg, 36.9%). ^1H NMR (D_2O): δ = 1.6–3.4 (br. m, 10 H, $B_{10}H_{10}$), 3.48 (m, 2 × 0.67 H, 2β-H), 3.67 (m, 2 × 0.67 H, 3β-H), 3.79 (m, 2 × 0.67 H, 5β-H), 3.86 (m, 4 × 0.33 H, 3α-H and 4α-H), 3.88 (m, 2 H, 2α-H + 4β-H), 3.99–4.14 (m, 6 H, CH_2O, α + β form, 5α-H), 4.61 (d, $^3J_{HH}$ = 8.0 Hz, 2 × 0.67 H, 1β-H), 5.25 (m, 2 × 0.33 H, 1α-H) ppm. $^{13}C\{^1H\}$ NMR (D_2O): δ = 64.5 ($^2J_{CP}$ = 6 Hz, C-6β), 65.1 ($^2J_{CP}$ = 5.7 Hz, C-6α), 68.3 (C-2α), 68.4 (C-4β), 68.9 and 69.1 (C-3α and C-4α), 69.3 ($^3J_{CP}$ = 6.7 Hz, C-5α), 71.9 (C-2β), 72.7 (C-3β), 73.6 ($^3J_{CP}$ = 8.3 Hz, C-5β), 78.2 (d, $^1J_{CP}$ = 110.5 Hz, $C_2B_{10}H_{10}$), 92.4 (C-1α), 96.5 (C-1β) ppm. $^{31}P\{^1H\}$ NMR (D_2O): δ = 61.2 (s), 61.3 (s), (stereomers) ppm. ^{11}B NMR (D_2O): δ = –10.2 (br. s, $^1J_{BH}$ n.d., 10 B, $C_2B_{10}H_{10}$) ppm. IR (KBr): $\tilde{\nu}$ = 3424 (vs) (O–H), 2611 (m) (B–H) cm^{-1}. MS (ESI positive in CH_3CN): *m*/*z* = 728.1 $[M + Na]^+$. $C_{14}H_{32}B_{10}Na_2O_{14}P_2S_2$ (704.56): calcd. C 23.87, H 4.58; found C 23.21, H 4.58.

1,7-Bis[bis(dimethylamidophosphonito)]-1,7-dicarba-*closo*-dodecaborane(12) (7): *n*BuLi (7.0 mL, 14.0 mmol, 2.0 M solution in *n*-hexane) was added to a cooled solution (ice bath) of *meta*-carbaborane (1.0 g, 6.94 mmol) in diethyl ether (25 mL). The solution was warmed to room temperature and stirred for 2 h. The dilithiocarbaborane suspension was slowly added with a cannula to a cooled solution (ice bath) of bis(dimethylamido)chlorophosphite (2.16 g, 14.02 mmol) in diethyl ether (15 mL). The reaction mixture was stirred for 30 min at 0 °C and at room temperature overnight. Lithium chloride was filtered off and the diethyl ether was removed under reduced pressure. The residue was extracted with *n*-hexane (50 mL) and the extract stored at –18 °C. The product was obtained as colorless crystals (1.58 g, 60%); m.p. 77–79 °C. ^1H NMR ($CDCl_3$): δ = 2.56 [d, $^3J_{HP}$ = 9.6 Hz, 24 H, $N(CH_3)_2$], 2.0–4.3 (br. m, 10 H, $B_{10}H_{10}$) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ = 41.8 [d, $^2J_{CP}$ = 21.2 Hz, $N(CH_3)_2$], 80.5 (d, $^1J_{CP}$ = 73.3 Hz, $C_2B_{10}H_{10}$) ppm. $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ = 105.4 (s) ppm. ^{11}B NMR ($CDCl_3$): δ = –1.0 (br. d, $^1J_{BH}$ = 144.0 Hz, 2 B, $C_2B_{10}H_{10}$), –6.3 (d, $^1J_{BH}$ = 132.2 Hz, 3 B, $C_2B_{10}H_{10}$), –7.0 (d, $^1J_{BH}$ = 112.3 Hz, 3 B, $C_2B_{10}H_{10}$), –10.1 (d, $^1J_{BH}$ = 173.0 Hz, 2 B, $C_2B_{10}H_{10}$) ppm. IR (KBr): $\tilde{\nu}$ = 2999 (w), 2974 (w), 2886 (s), 2837 (m), 2792 (m) (C–H), 2635 (w), 2603 (s), 2576 (s) (B–H), 1477 (m), 1448 (m) (C–H) cm^{-1}. MS (EI positive, 14 eV): *m*/*z* (%) = 380.1 (100) $[M]^+$, 336.1 (15) $[M - NMe_2]^+$, 294.1 (1.7) $[M - 2\ NMe_2]^+$, 119.0 (12) $[P(NMe_2)_2]^+$.

1,12-Bis[bis(dimethylamidophosphonito)]-1,12-dicarba-*closo*-dodecaborane(12) (15): *n*BuLi (2.9 mL, 6.96 mmol, 2.4 M solution in *n*-hexane) was added to a cooled solution (ice bath) of *para*-carbaborane (0.5 g, 3.47 mmol) in diethyl ether (15 mL). The solution was warmed to room temperature and stirred for 2 h. The dilithiocarbaborane suspension was slowly added with a cannula to a cooled solution (ice bath) of bis(dimethylamido)chlorophosphite (0.92 mL, 6.96 mmol) in diethyl ether (15 mL). The reaction mixture was stirred for 30 min at 0 °C and at room temperature overnight. Lithium chloride was filtered off and the diethyl ether was removed under reduced pressure. The remaining residue was extracted with *n*-hexane (25 mL) and the extract was stored at –18 °C. The product was obtained as colorless crystals (0.72 g, 55%); m.p. 155–156 °C. ^1H NMR ($CDCl_3$): δ = 2.50 [d, $^3J_{HP}$ = 9.6 Hz, 24 H, $N(CH_3)_2$], 2.0–3.7 (br. m, 10 H, $B_{10}H_{10}$) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ = 41.4 [d, $^2J_{CP}$ = 21.9 Hz, $N(CH_3)_2$], 88.9 (d, $^1J_{CP}$ = 74.6 Hz, $C_2B_{10}H_{10}$) ppm. $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ = 107.1 (s) ppm. ^{11}B NMR ($CDCl_3$): δ = –11.7 (d, $^1J_{BH}$ = 161.0 Hz, 10 B, $C_2B_{10}H_{10}$) ppm. IR (KBr): $\tilde{\nu}$ = 3018 (w), 2972 (w), 2883 (s), 2835 (m), 2798 (m) (C–H), 2604 (s), 2582 (s) (B–H) cm^{-1}. MS (ESI positive, CH_3CN): *m*/*z* (%) = 381.3 $[M + H]^+$. $C_{10}H_{34}B_{10}N_4P_2$ (380.46): calcd. C 31.56, H 9.00; found C 31.29, H 9.06.

Tetrakis(1,2:3,4-di-*O*-isopropylidene-6-deoxy-α-D-galactopyranos-6-yl) [1,7-Dicarba-*closo*-dodecaborane(12)-1,7-diyl]bis(phosphonate) (11): Compound **2** (15.9 mL, 12.72 mmol, 0.8 M solution in acetonitrile) and benzimidazolium triflate (2.84 g, 10.60 mmol) were added to a solution of **7** (0.75 g, 2.12 mmol) in acetonitrile (20 mL). The reaction mixture was heated in a microwave oven at 81 °C for 3 h. Then *tert*-butyl hydroperoxide (0.87 mL, 6.36 mmol, 70% in water) was added and stirring was continued for 30 min at room temperature. The reaction mixture was diluted with ethyl acetate (30 mL) and extracted with brine (3 × 30 mL). The organic layer was dried with anhydrous $MgSO_4$, and the solvent was removed under reduced pressure. The honey-like residue was purified by chromatography on silica gel with ethyl acetate/cyclohexane (1:1). The product was obtained as a white foam (1.88 g, 70.0%). R_f (ethyl acetate/cyclohexane, 1:1) = 0.35. ^1H NMR ($CDCl_3$): δ = 1.16–1.46 (m, 48 H, CH_3), 2.0–3.4 (m, 10 H, $C_2B_{10}H_{10}$), 3.64 (m, 8 H, CH_2O), 3.79 (m, 4 H, 5-H), 4.20 (m, 4 H, 4-H), 4.25 (m, 4 H, 2-H), 4.54 (m, 4 H, 3-H), 5.47 (m, 4 H, 1-H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ = 24.9–25.9 (CH_3), 66.9 (O-CH_2, $^2J_{CP}$ n.d.), 70.3 (C-2), 70.5 and 70.6 (C-3 and C-4), 71.3 ($^3J_{CP}$ n.d., C-5), 70.0 (d, $^1J_{CP}$ =

185.2 Hz, $C_2B_{10}H_{10}$), 96.1 (*C*-1α), 108.5–109.4 (C_{quart} of isopropylidene) ppm. ^{31}P NMR ($CDCl_3$): δ = 9.3 (s) ppm. ^{11}B NMR ($CDCl_3$): δ = –9.3 (br. s, $^1J_{BH}$ n.d., 10 B, $C_2B_{10}H_{10}$) ppm. IR (KBr): ṽ = 2988 (m), 2936 (m) (C–H), 2618 (m) (B–H) cm^{-1}. MS (ESI positive in CH_3CN): *m/z* = 1296.57 [M + Na]$^+$. $C_{50}H_{86}B_{10}O_{26}P_2$ (1273.26): calcd. C 47.17, H 6.81; found C 47.33, H 6.80.

Diastereomeric Mixture of Tetrakis(6-deoxy-D-galactopyranos-6-yl) [1,7-Dicarba-*closo*-dodecaborane(12)-1,7-diyl]bis(phosphonate) (13): Compound **11** (1.62 g, 0.77 mmol) was dissolved in trifluoroacetic acid (4 mL, 90% in water) and stirred at room temperature for 45 min. Then the trifluoroacetic acid was removed under reduced pressure and the resulting residue purified by preparative HPLC on a ProntoSIL® column (gradient CH_3CN/H_2O, 80:20 over 30 min to CH_3CN/H_2O, 0:100; t_R = 4.8 min). Appropriate fractions were collected and concentrated in vacuo. The residue was lyophilized several times to yield the product as a white powder (464 mg, 38%). Due to the formation of stereomers all NMR signals occur manifold. The signals of the proton and carbon atoms of the galactopyranosyl moieties could not be assigned with certainty. ^{1}H NMR (D_2O): δ = 1.6–3.4 (br. m, 10 H, $B_{10}H_{10}$), 3.48 (m, 4 × 0.67 H, 2β-H), 3.67 (m, 4 × 0.67 H, 3β-H), 3.82 (m, 4 × 0.67 H, 5β-H), 3.86–4.0 (m, 8 × 0.33 H + 4 H, 3α-H + 4α-H and 2α-H + 4β-H), 4.30 (m, 12 H, CH_2O, α + β form, 5α-H), 4.56 (m, $^3J_{HH}$ n.d., 4 × 0.67 H, 1β-H), 5.24 (m, 4 × 0.33 H, 1α-H) ppm. ^{13}C{^{1}H} NMR (D_2O): δ = 61.0 ($^2J_{CP}$ n.d., *C*-6β), 61.2 ($^2J_{CP}$ n.d., *C*-6α), 67.0 (d, $^1J_{CP}$ = 182.5 Hz, $C_2B_{10}H_{10}$), 68.2–68.4 (*C*-2α + *C*-4β), 68.8 and 69.0 (*C*-3α and *C*-4α), 69.3 ($^3J_{CP}$ n.d., *C*-5α), 71.9 (*C*-2β), 72.7 (*C*-3β), 73.2 ($^3J_{CP}$ n.d., *C*-5β), 92.4 (*C*-1α), 96.5 (*C*-1β) ppm. ^{31}P{^{1}H} NMR (D_2O): several singlets between δ = 10.0 and 10.2 (stereomers) ppm. ^{11}B NMR (D_2O): δ = –9.7 (br. s, $^1J_{BH}$ n.d., 10 B, $C_2B_{10}H_{10}$) ppm. IR (KBr): ṽ = 3421 (vs) (OH), 2921 (m) (CH), 2617 (m) (BH) cm^{-1}. MS (ESI positive in CH_3CN): *m/z* = 976.3 [M + Na]$^+$, 971.4 [M + NH_4]$^+$. $C_{26}H_{54}B_{10}O_{26}P_2 \cdot H_2O$ (970.76): calcd. C 32.17, H 5.81; found C 32.14, H 5.81.

***O*,*O*′,*O*′′,*O*′′′-Tetrakis(1,2:3,4-di-*O*-isopropylidene-6-deoxy-α-D-galactopyranos-6-yl) [1,7-Dicarba-*closo*-dodecaborane(12)-1,7-diyl]bis(phosphonothioate) (12):** Compound **2** (6.1 mL, 4.88 mmol, 0.8 M solution in acetonitrile) and benzimidazolium triflate (1.09 g, 4.06 mmol) were added to a solution of **7** (0.31 g, 0.81 mmol) in acetonitrile (15 mL). The reaction mixture was heated in a microwave oven at 81 °C for 3 h. Then powdered Beaucage reagent (0.35 g, 1.75 mmol) was added and stirring was continued for 2 h at room temperature. The reaction mixture was diluted with ethyl acetate (20 mL) and extracted with brine (3 × 20 mL). The organic layer was dried with anhydrous $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by chromatography on silica gel with ethyl acetate/cyclohexane (1:2). Further purification was achieved by preparative RP-HPLC (CH_3CN 100%; t_R = 8.7 min). The product was obtained as a white foam (0.14 g, 13%). R_f (ethyl acetate/cyclohexane, 1:2) = 0.29. ^{1}H NMR ($CDCl_3$): δ = 1.12–1.48 (m, 48 H, CH_3), 2.0–3.4 (m, 10 H, $C_2B_{10}H_{10}$), 3.93 (m, 8 H, CH_2O), 4.10 (m, 4 H, 5-H), 4.15 (m, 4 H, 4-H), 4.22 (m, 4 H, 2-H), 4.53 (m, 4 H, 3-H), 5.45 (m, 4 H, 1α-H) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$): δ = 24.3–26.1 (CH_3), 66.0–70.6 (m, *C*-6, 3 × O*C*H), 73.9 (d, $^1J_{CP}$ = 134.2 Hz, $C_2B_{10}H_{10}$), 96.1 (*C*-1α), 108.7–109.4 (C_{quart} of isopropylidene) ppm. ^{31}P{^{1}H} NMR ($CDCl_3$): δ = 77.8 (s, br) ppm. ^{11}B NMR ($CDCl_3$): δ = –9.9 (br. s, $^1J_{BH}$ n.d., 10 B, $C_2B_{10}H_{10}$) ppm. IR (KBr): ṽ = 2989 (m), 2936 (m) (C–H), 2620 (m) (B–H) cm^{-1}. MS (ESI positive in CH_3CN): *m/z* = 1328.53 [M + Na]$^+$. $C_{50}H_{86}B_{10}O_{24}P_2S_2$ (1305.39): calcd. C 46.00, H 6.64; found C 46.42, H 6.66.

Diastereomeric Mixture of *O*,*O*′,*O*′′,*O*′′′-Tetrakis(6-deoxy-D-galactopyranos-6-yl) [1,7-Dicarba-*closo*-dodecaborane(12)-1,7-diyl]bis(phosphonothioate) (14): Compound **12** (460 mg, 0.35 mmol) was dissolved in trifluoroacetic acid (4 mL, 90% in water) and stirred for 45 min at room temperature. Then trifluoroacetic acid was removed under reduced pressure and the resulting residue purified by preparative HPLC on a ProntoSIL® column (gradient CH_3CN/H_2O, 80:20 over 30 min to CH_3CN/H_2O, 0:100; t_R = 4.8 min). Appropriate fractions were collected and concentrated in vacuo. The residue was lyophilized several times to yield the product as a white powder (yield 184 mg, 53%), Due to the formation of stereomers, all NMR signals occur manifold. The signals of the proton and carbon atoms of the galactopyranosyl moieties could not be assigned with certainty. ^{1}H NMR (D_2O): δ = 1.65–3.30 (br. m, 10 H, $B_{10}H_{10}$), 3.37 (m, 4 × 0.67 H, 2β-H), 3.53 (m, 4 × 0.67 H, 3β-H), 3.71 (m, 4 × 0.67 H, 5β-H), 3.75–3.95 (m, 8 × 0.33 H + 4 H, 3α-H + 4α-H and 2α-H + 2β-H), 4.20 (m, 12 H, CH_2O, α + β form, 5α-H), 4.47 (m, $^3J_{HH}$ n.d., 4 × 0.67 H, 1β-H), 5.14 (m, 4 × 0.33 H, 1α-H) ppm. ^{13}C{^{1}H} NMR (D_2O): δ = 65.9 (m, $^2J_{CP}$ n.d., *C*-6β), 67.0 (m, $^2J_{CP}$ n.d., *C*-6α), 67.9–69.3 (m, *C*-5α, *C*-3α, *C*-4α, *C*-2α, *C*-4β), 71.7 (*C*-2β), 72.7 (*C*-3β), 73.3 ($^3J_{CP}$ = 7.4 Hz, *C*-5β), 73.7 (d, $^1J_{CP}$ = 136.4 Hz, $C_2B_{10}H_{10}$), 92.3 (*C*-1α), 96.5 (*C*-1β) ppm. ^{31}P{^{1}H} NMR (D_2O): several singlets between δ = 78.3 and 78.5 (stereomers) ppm. ^{11}B NMR (D_2O): δ = –9.7 (br. s, $^1J_{BH}$ n.d., 10 B, $C_2B_{10}H_{10}$) ppm. IR (KBr): ṽ = 3405 (vs) (OH), 2920 (m) (CH), 2619 (m) (BH) cm^{-1}. MS (ESI positive in H_2O/MeOH): *m/z* = 1008.3 [M + Na]$^+$; 1003.3 [M + NH_4]$^+$. $C_{26}H_{54}B_{10}O_{24}P_2S_2$ (984.88): calcd. C 31.71, H 5.53; found C 31.55, H 5.51.

Tetrakis(1,2:3,4-di-*O*-isopropylidene-6-deoxy-α-D-galactopyranos-6-yl) [1,12-Dicarba-*closo*-dodecaborane(12)-1,12-diyl]bis(phosphonate) (16): Compound **2** (15.9 mL, 12.72 mmol, 0.8 M solution in acetonitrile) and benzimidazolium triflate (2.84 g, 10.6 mmol) were added to a suspension of **15** (0.72 g, 1.98 mmol) in acetonitrile (20 mL). The reaction mixture was heated in a microwave oven for 3 h at 81 °C. Then *tert*-butyl hydroperoxide (0.87 mL, 6.36 mmol, 70% in water) was added and the reaction mixture stirred for 30 min at room temperature. The reaction mixture was diluted with ethyl acetate (30 mL) and extracted with brine (3 × 30 mL). The organic layer was dried with anhydrous $MgSO_4$, and the solvent removed under reduced pressure. The residue was purified by chromatography on silica gel with acetone/*n*-pentane (1:1). Further purification was achieved by preparative HPLC under isocratic conditions (100% CH_3CN, t_R = 8.0 min). Appropriate fractions were combined and the solvent removed under reduced pressure to give the product as a white foam (0.83 g, 34.5%), R_f (ethyl acetate/cyclohexane, 1:1) = 0.35. ^{1}H NMR ($CDCl_3$): δ = 1.16–1.46 (m, 48 H, CH_3), 2.0–3.4 (m, 10 H, $B_{10}H_{10}$), 3.64 (m, 8 H, CH_2O), 3.79 (m, 4 H, 5-H), 4.20 (m, 4 H, 4-H), 4.25 (m, 4 H, 2-H), 4.54 (m, 4 H, 3-H), 5.47 (m, 4 H, 1-H) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$): δ = 24.9–25.9 (CH_3), 66.9 ($^2J_{CP}$ n.d., O-CH_2), 70.3 (*C*-2), 70.5 and 70.6 (*C*-3 and *C*-4), 71.3 ($^3J_{CP}$ n.d., *C*-5), 70.0 (d, $^1J_{CP}$ = 185.2 Hz, $C_2B_{10}H_{10}$), 96.1 (*C*-1α), 108.5–109.4 (C_{quart} of isopropylidene) ppm. ^{31}P NMR ($CDCl_3$): δ = 9.3 (s) ppm. ^{11}B NMR ($CDCl_3$): δ = –12.7 (br. d, $^1J_{BH}$ = 123.4 Hz, 10 B, $C_2B_{10}H_{10}$) ppm. IR (KBr): ṽ = 2988 (m), 2936 (m) (C–H), 2618 (m) (B–H) cm^{-1}. MS (ESI positive in CH_3CN): *m/z* = 1296.57 [M + Na]$^+$. $C_{50}H_{86}B_{10}O_{26}P_2$ (1273.26): calcd. C 47.17, H 6.81; found C 47.21, H 6.79.

Diastereomeric Mixture of Tetrakis(6-deoxy-D-galactopyranos-6-yl) [1,12-Dicarba-*closo*-dodecaborane(12)-1,12-diyl]bis(phosphonate) (17): Compound **16** (0.48 g, 0.31 mmol) was dissolved in trifluoroacetic acid (4 mL, 90% in water) and stirred at room temperature for 45 min. Then trifluoroacetic acid was removed under reduced pressure and the resulting residue purified by preparative HPLC on a ProntoSIL® column (gradient CH_3CN/H_2O, 80:20 over 30 min to CH_3CN/H_2O, 0:100; t_R = 5.1 min). Appropriate fractions were collected and concentrated in vacuo. The residue was lyophilized several times to yield the product as a white powder (98 mg, 33 %). Due to the formation of stereomers, all NMR signals occur manifold. The signals of the proton and carbon atoms of the galactopyranosyl moieties could not be assigned with certainty. ^{1}H NMR (D_2O): δ = 1.6–3.4 (br. m, 10 H, $\mathrm{B}_{10}H_{10}$), 3.45 (m, 4 × 0.67 H, 2β-H), 3.61 (m, 4 × 0.67 H, 3β-H), 3.82 (m, 4 × 0.67 H, 5β-H), 3.88 (s, 8 × 0.33 H, 3α-H + 4α-H), 3.94 (m, 8 × 0.33 H, 2α-H + 4β-H), 4.30 (m, 12 H, $\mathrm{C}H_2\mathrm{O}$, α + β form, 5α-H), 4.54 (d, $^3J_{\mathrm{HH}}$ = 7.45 Hz, 4 × 0.67 H, 1β-H), 5.23 (s, 4 × 0.33 H, 1α-H) ppm. ^{13}C{^{1}H} NMR (D_2O): δ = 67.6 ($^2J_{\mathrm{CP}}$ n.d., *C*-6β), 68.0 ($^2J_{\mathrm{CP}}$ n.d., *C*-6α), 68.19–68.23 (*C*-2α + *C*-4β), 68.5 and 68.8 (*C*-3α and *C*-4α), 69.0 ($^3J_{\mathrm{CP}}$ n.d., *C*-5α), 71.7 (*C*-2β), 72.6 (*C*-3β), 73.1 ($^3J_{\mathrm{CP}}$ n.d., *C*-5β), 76.0 (d, $^1J_{\mathrm{CP}}$ = 182.0 Hz, $C_2\mathrm{B}_{10}\mathrm{H}_{10}$), 92.4 (*C*-1α), 96.5 (*C*-1β) ppm. ^{31}P{^{1}H} NMR (D_2O) several singlets between δ = 10.75 and 10.90 (stereomers) ppm. ^{11}B NMR (D_2O): δ = –12.8 (br. d, $^1J_{\mathrm{BH}}$ = 151.2 Hz, 10 B, $\mathrm{C}_2B_{10}\mathrm{H}_{10}$) ppm. IR (KBr): ṽ = 3418 (vs) (OH), 2918 (m) (CH), 2626 (m) (BH) cm^{-1}. MS (ESI positive in CH_3CN): *m/z* = 975.3 [M + Na]$^+$, 499.2 [M + 2Na]$^{2+}$. $C_{26}H_{54}O_{26}P_2B_{10}\cdot 4H_2O$ (1024.81): calcd. C 30.47, H 6.10; found C 30.10, H 6.12.

General Procedure for Determination of Water Solubility: Depending on the amount available, 10–20 mg of compound **5**, **6**, **13**, **14**, or **17** was placed in an Eppendorf tube. Then, 2 µL of water was added and the mixture shaken manually. This procedure was repeated until the substance was completely dissolved.

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