DOI: 10.1002/ejoc.201000213

# Bis-Carbaborane-Bridged Bis-Glycophosphonates as Boron-Rich Delivery Agents for BNCT

Sven Stadlbauer,[a] Peter Lönnecke,[a] Peter Welzel,[b][‡] and Evamarie Hey-Hawkins*[a]

**Keywords:** Boron / Antitumor agents / Medicinal chemistry / Phosphorus / Cluster compounds

The synthesis and properties of boron-rich bis(*meta*-carbaborane) derivatives containing glycophosphonate and glycophosphonothioate moieties are reported. All compounds are water-soluble; however, the tetragalactosylated compounds show lower solubility than their disodium salts.

## Introduction

To date, the treatment of malign tumors has always been 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 the preferential incorporation of $^{10}$B-containing compounds into tumor cells followed by irradiation of the tumor by 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 of $^{10}$B per gram of 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 first phosphorus-containing boron cluster compounds bearing phosphate and pyrophosphate moieties were synthesized by Bechtold and Kaczmarczyk in 1975 and their bioactivities were studied.[3] However, these compounds turned out to be highly toxic. Some simple carbaboranediyl bis-phosphonates were found to possess high skeletal affinity and were proposed for the treatment of calcifying tumors, for example, osteosarcoma.[4] Oligomeric phosphate diesters that contain *closo*- or *nido*-carbaboranes show high accumulation in tumor tissue in BALB/c mice bearing EMT6 tumors.[5] However, comprehensive biological assessments of boron-containing phosphonates as potential tumor-targeting agents in BNCT are still rare.[6]

Endogenous lectins are located on the surface of normal and malignant cells and serve as specific receptors for mediating the endocytosis of glycoconjugates.[7] The 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.[8] Monosaccharides, for example, galactose, also have the potential to target tumors. A galactosyl derivative of mercaptoundecahydro-*closo*-dodecaborate [$(B_{12}H_{11}SH)^{2-}$, BSH] has been reported to show the highest boron uptake in a mouse tumor model compared with glucosyl and mannosyl derivatives.[9] We have therefore devised efficient syntheses of boron compounds that 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.[10] The 6-position of galactose is usually involved in recognition in lectins, but for proof of our general synthetic principle[11] we synthesized galactosyl derivatives that are connected with the phosphonate through the 6-position. For BNCT to be successful a very high $^{10}$B concentration must be achieved and the neutron capture reaction is more effective if the molecule contains a high number of boron atoms. To fulfill this requirement, we have synthesized compounds with two boron clusters bearing glycophosphonate groups[10] as the carbaborane derivatives.

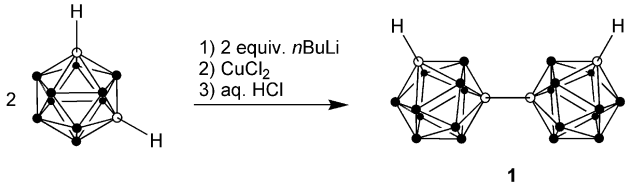
## Results and Discussion

To synthesize compounds containing two carbaborane clusters, we started from bis(*meta*-carbaborane). In 1973 Zakharkin and Kovredov published a general synthesis of *ortho*-, *meta*-, and *para*-bis(carbaboranes), which they achieved by coupling the corresponding monolithiated species using copper(I) or copper(II) chloride,[12] but without reporting any experimental details. Copper(II) chloride mediated coupling has also been reported for the synthesis of

[a] Institut für Anorganische Chemie, Universität Leipzig, Johannisallee 29, 04103 Leipzig, Germany
Fax: +49-341-9739319
E-mail: hey@uni-leipzig.de
[b] Institut für Organische Chemie, Universität Leipzig, Johannisallee 29, 04103 Leipzig, Germany
[‡] Professor Peter Welzel deceased in July 2008.

oligomeric *para*-carbaborane rods by Michl and co-workers.[13] Hawthorne and co-workers obtained the bis(*meta*-carbaborane) as a side-product in the synthesis of a tetrameric compound.[14] We were able to prepare the desired bis(*meta*-carbaborane) in good yield according to a modified procedure published for the synthesis of C–C-connected dicarba-*closo*-decaborane(10)[15] in which monolithiated *meta*-carbaborane is coupled by using 1.25 equiv. of copper(II) chloride (see Scheme 1). The reaction was not quantitative and hence unconsumed *meta*-carbaborane was recovered by sublimation and the bis(*meta*-carbaborane) was isolated by column chromatography with *n*-hexane according to the procedure of Hawthorne and co-workers.[14]




Scheme 1. Synthesis of bis(*meta*-carbaborane).

Starting from bis(*meta*-carbaborane), we synthesized *P*-chiral and achiral bis-phosphonite derivatives. Dilithiation of **1** followed by reaction with dimethylamidomethyl chlorophosphite or bis(dimethylamido) chlorophosphite led to *rac*-/*meso*-1,1′-{P(NMe$_2$)(OMe)}$_2$(C$_2$B$_{10}$H$_{10}$)$_2$ (**2**) or 1,1′-{P(NMe$_2$)$_2$}$_2$(C$_2$B$_{10}$H$_{10}$)$_2$ (**3**), respectively (Scheme 2).

Compounds **2** and **3** were both obtained as solids. Recrystallization from *n*-hexane gave single crystals suitable for X-ray crystallography. Separation of the diastereomers of **2** by fractional crystallization was unsuccessful because of their close similarity.

## Spectroscopic Properties of 2 and 3

*P*-Chiral **2** gave only one signal at $\delta$ = 138.7 ppm in the $^{31}$P{$^1$H} NMR spectra because the *rac* and *meso* forms cannot be discriminated by NMR spectroscopy due to the large distance between the two chiral phosphorus atoms. Symmetrically substituted bis-phosphonite **3** exhibits a singlet at $\delta$ = 105.7 ppm. The chemical shifts are similar to those of the corresponding mono-carbaborane derivatives.[11b] In the $^{13}$C{$^1$H} NMR spectra both compounds exhibit a singlet at $\delta$ = 76.2 ppm for the carbon atoms of the C–C bridge and a doublet for the phosphorus-substituted carbon atoms of the cluster [$^1J_{CP}$ = 81.3 (**2**) and 79.5 Hz (**3**)]. The $^{11}$B NMR spectra show four singlets in the ratio 1:1:4:4 for **2** and two singlets in the ratio 1:4 for **3**.

## Molecular Structures of 2 and 3

Compound **3** crystallizes in the triclinic space group $P\bar{1}$ with one molecule in the unit cell, and *P*-chiral compound **2** in the monoclinic space group $P2_1/n$ with two molecules in the unit cell (Figures 1 and 2, Tables 1 and 2). In **2** the presence of both the *rac* and *meso* forms in the crystal results in a disorder of 20% of the phosphonito group. Compound **2** has an inversion center located at the central C–C bond. It is impossible to determine which of the two diastereomers is enriched in the crystals. Achiral compound **3** also has an inversion center located at the center of the

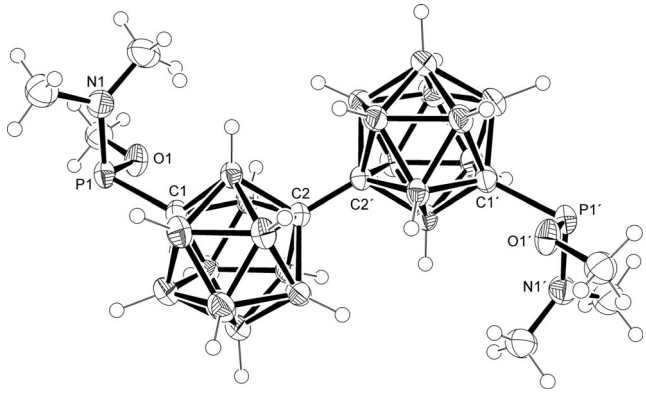



Figure 1. Molecular structure of **2** (ORTEP diagram with atomic labeling scheme; thermal ellipsoids are drawn at the 50% probability level, disorder is not shown).

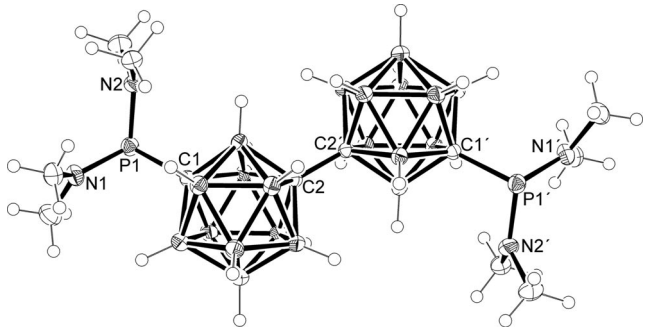
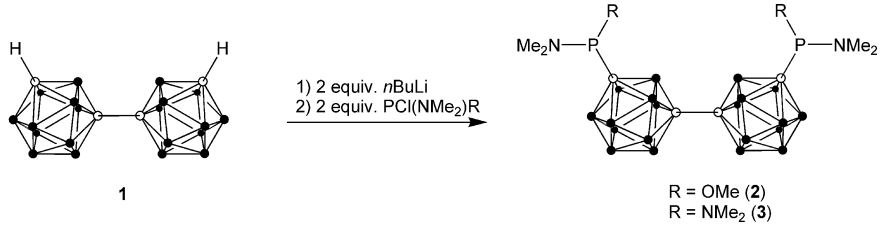



Figure 2. Molecular structure of **3** (ORTEP diagram with atomic labeling scheme; thermal ellipsoids are drawn at the 50% probability level).




Scheme 2. Synthesis of bis-carbaboranediyl bis-phosphonites **2** and **3**.

C–C bond. In both compounds the $C_{carbaborane}$–$C_{carbaborane}$ bond length lies in the range of common C–C bonds and the P–$C_{carbaborane}$ bonds are in the range of those of similar compounds.[11b,16]

Table 1. Bond lengths and angles of **2**.

| Bond lengths [pm] | | Bond angles [°] | |
|---|---|---|---|
| P1–O1 | 162.5(2) | O1–P1–N1 | 102.3(2) |
| P1–N1 | 165.6(3) | O1–P1–C1 | 94.6(2) |
| P1–C1 | 190.2(3) | N1–P1–C1 | 106.7(2) |
| C2–C2′ | 153.0(4) | | |

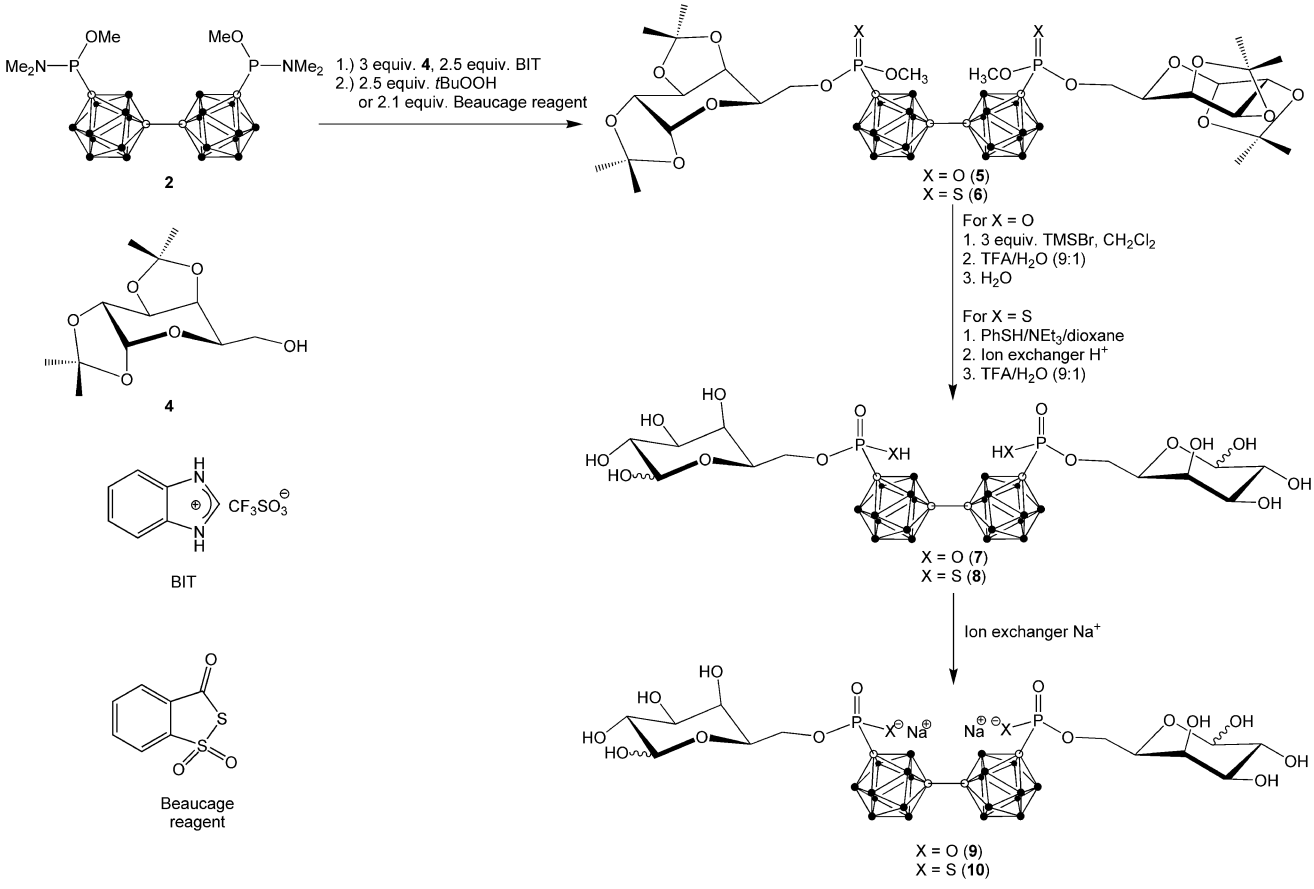
Table 2. Bond lengths and angles of **3**.

| Bond length [pm] | | Bond angles [°] | |
|---|---|---|---|
| P1–N1 | 167.3(1) | N1–P1–N2 | 109.87(6) |
| P1–N2 | 167.4(1) | N1–P1–C1 | 101.14(6) |
| P1–C1 | 190.6(1) | N2–P1–C1 | 103.87(6) |
| C2–C2′ | 152.7(2) | | |

## Synthesis of Bis-Galactosylated Bis-Carbaboranediyl Bis-Phosphonates

Bis-phosphonate **5** and bis-phosphonothioate **6** were prepared from *rac*/*meso*-**2** and protected galactose **4** with benzimidazolium triflate (BIT)[17] as the activator. The reaction was monitored by $^{31}P\{^1H\}$ NMR spectroscopy and was complete after 3 hours, as indicated by two signals at $\delta$ = 161 ppm. Owing to the presence of two chiral phosphorus atoms and two chiral sugar units, four stereoisomers, and thus four signals, were expected. However, because of the large distance between the two phosphorus atoms, the two stereoisomers are so similar that NMR cannot discriminate between them. The final products **5** and **6** were obtained by oxidation with *tert*-butyl hydroperoxide (TBHP) or by sulfurization with 3*H*-1,2-benzodithiol-3-one 1,1-dioxide (Beaucage reagent)[18] (Scheme 3). Purification of the compounds was laborious and required repeated separation by column chromatography resulting in low yields (49 and 41% for **5** and **6**, respectively).

Compounds **5** and **6** were deprotected according to the conditions reported for mono-carbaborane derivatives[11b] (see Scheme 3). Demethylation of the phosphonate moieties with thiophenol/triethylamine in 1,4-dioxane[19] followed by passing through an $H^+$ ion exchanger and subsequent deprotection of the galactosyl moieties with aqueous trifluoroacetic acid yielded bis-hydroxyphosphonate **7** and bis-phosphonothioate **8**. Both compounds were purified by preparative HPLC with gradient elution on a ProntoSIL® column. In the last step ion exchange yielded disodium salts **9** and **10**, which were obtained as white powders after




Scheme 3. Synthesis of **5** and **6** according to the phosphoramidite methodology followed by deprotection of the phosphonate and galactosyl moieties.

lyophilization in 61 (**10**) and 20% (**9**) yields. The reason for the low yield of bis-phosphonate **9** can be traced back to several problems. One problem is that the ammonium salts formed by demethylation cannot be removed by $H^+$ ion exchange. Thus, triethylammonium trifluoroacetate, which is formed after the addition of trifluoroacetic acid, can only be removed by repeated extraction with ethyl acetate, which, however, also partly dissolves the product, as shown by $^{31}P\{^1H\}$ NMR spectroscopy.

Therefore, **5** was deprotected by using trimethylsilyl bromide.[20] The subsequent hydrolysis in water was accompanied by problems relating to the low solubility of the product. Heating of the aqueous reaction mixture to 60 °C for several hours increased the yield because the partial deprotection of the galactosyl moieties that occurred under these conditions resulted in better water solubility and therefore improved conditions for hydrolysis of the trimethylsilyl ester. For further optimization of the reaction, the isopropylidene protecting groups were removed with 90% trifluoroacetic acid directly after transesterification. Hydrolysis of the trimethylsilyl ester also occurred in part. For complete hydrolysis, the reaction mixture was evaporated to dryness and then diluted with water and stirred for a further 24 hours to give the fully deprotected compound **7**, as shown by $^{31}P\{^1H\}$ NMR spectroscopy. The product **9** was obtained in a remarkably improved yield of 49% after purification by HPLC and ion exchange.

As was also observed for the analogous mono-carbaborane derivatives,[11b] a high-field shift of the signals is observed in the $^{31}P\{^1H\}$ NMR spectra after deprotection. In accordance with a thione–thiole rearrangement, two signals are observed for bis-phosphonothioate **10** at $\delta$ = 60.6 ppm, whereas a signal with a shoulder was observed for the corresponding bis-phosphonate **9** at 4.3 ppm. In **10** the two phosphorus atoms remain chiral after deprotection and therefore the compound is obtained as a mixture of a maximum of 16 possible diastereomers. Interestingly, two (hardly separated) signals were also observed for **9** despite the fact that the chirality at the phosphorus atoms is lost after deprotection. The same observation was made for a bis-phosphonato-substituted *meta*-carbaborane cluster.[11b] To examine whether micelles are formed, a dilute solution of **9** ($c = 3 \times 10^{-4}$ M) was prepared to achieve a concentration that was supposed to be below the critical micelle concentration (c.m.c.) at which the compound should occur in the nonaggregated form. However, no change in the signal ratio in the $^{31}P\{^1H\}$ NMR spectrum was observed. Even if the c.m.c. was not reached, a significant change in the ratio of the signals would be expected. Thus, this result indicates that no micelles are formed. For the bis(*meta*-carbaborane) moiety, two conformers are conceivable: A "*cis*" conformation with both phosphonate groups on the same side with respect to the C–C bond and a "*trans*" conformation with the two phosphonate groups in an opposite arrangement, of which the latter should be favored for steric reasons. A high-temperature $^{31}P\{^1H\}$ NMR spectrum at 55 °C showed no coalescence of the signals, that is, either the energy barrier for the free rotation around the C–C bond is markedly higher or this assumption is not applicable. For technical reasons, measurements at higher temperatures were not possible.

The $^1H$ NMR spectra of **9** and **10** show a very broad multiplet for the 20 protons of the bis(*meta*-carbaborane) unit. Due to overlap of the multiplets of the sugar units, their assignment was not possible with any certainty. Only the anomeric protons of the α (at $\delta$ = 5.24 ppm) and β (at $\delta$ = 4.63 ppm) forms could be assigned without problems. These signals appear as multiplets in the $^1H$ NMR spectrum of **10** due to the possible formation of 16 stereoisomers. Interestingly, in **9**, in contrast to the $^{31}P\{^1H\}$ NMR spectra, no doubling of the signals occurred, as would be expected if two conformers were present.

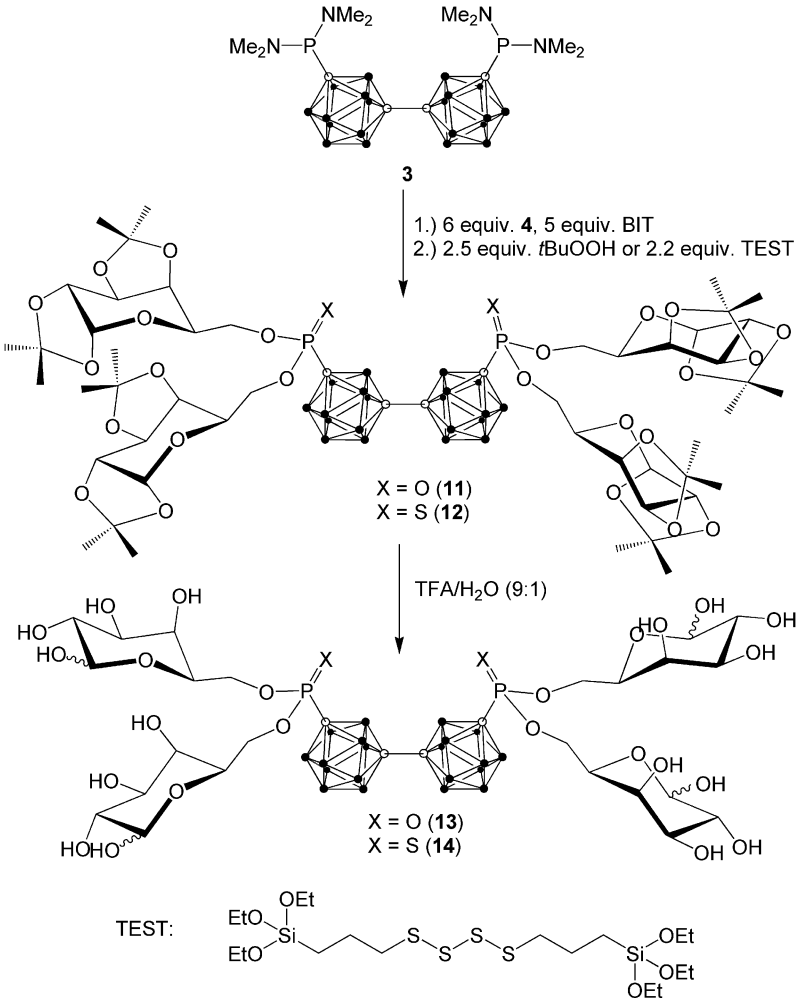
The $^{13}C\{^1H\}$ NMR spectra are dominated by signals of the galactosyl moieties. Also, no doubling of the signals of the carbohydrate moiety was observed in **9**. However, the signals of the carbon atoms of the carbaboranes appear as multiplets. Two singlets are observed at $\delta$ = 76.5 ppm for the C–C atoms and two doublets at $\delta$ = 70.9 ppm for the C–P atoms with C–P coupling constants of 153.3 and 154.0 Hz, respectively, which could be indicative of the presence of two conformers. In **10**, multiplication of the signals was observed for all carbon atoms. For the C–P carbon atoms of the bis-carbaborane unit the C–P coupling constant of 106.7 Hz is about 45 Hz smaller than in **9**. This phenomenon has previously been observed for the mono-carbaborane analogues[11b] and is common for thiophosphonates. Komarov et al. tried to explain this phenomenon of a smaller $^1J_{CP}$ coupling constant in thiophosphoryl compounds in comparison with phosphoryl compounds by theoretical calculations, but failed.[21]

Because of the anomerization of the galactosyl moieties, the $^{13}C\{^1H\}$ and $^1H$ NMR spectra of **9** and **10** exhibit signals for the α and β forms, but only for the pyranosyl form of galactose. The ratio of the α and β forms was determined by integration of the signals of C-1α and C-1β in the $^{13}C\{^1H\}$ NMR spectra because their chemical shifts are significantly different. First, the relaxation time $T_1$ of the anomeric carbon atoms was determined to be 372 ± 10 ms for both compounds and is therefore relatively short. On this basis an inverse-gated $^1H$-decoupling experiment was performed.[22] The α:β ratio is 34:66 for **9** and 33:67 for **10**. Within the margin of error this ratio is identical to that of free galactose (sum of the α vs. β forms of pyranoses and furanoses).[23] The $^{11}B$ NMR spectra show only one broad signal between +20 and –35 ppm, as expected for **9** and **10**.

### Tetra-D-Galactosylated Bis-Carbaboranediyl Bis-Phosphonate

Starting from tetraamido-substituted bis-phosphonite **3** the corresponding tetragalactosyl esters were prepared by using the phosphoramidite method described above. The reaction proceeds much more slowly than for the above-mentioned bis-galactosyl esters. When **3** was dissolved in acetonitrile by heating at reflux and the reaction continued at




Scheme 4. Synthesis of tetragalactosylated bis(*meta*-carbaboranediyl) bis-phosphonates **13** and **14**.

room temperature, complete conversion was observed after 48 h. Performing the reaction in a microwave oven at the reflux temperature of acetonitrile resulted in complete conversion after 180 min. However, the $^{31}P\{^{1}H\}$ NMR spectra showed the formation of a significant amount of side-products. Subsequent oxidation with TBHP or sulfurization with the Beaucage reagent gave bis-phosphonate **11** or bis-phosphonothioate **12** (see Scheme 4). After purification by column chromatography and preparative HPLC the compounds were obtained in 29 (**11**) and 8% (**12**) yields. Use of the liquid sulfurization agent bis[3-(triethoxysilyl)-*n*-propyl] tetrasulfide (TEST)[24] instead of the Beaucage reagent gave an improved yield of 28% of the isolated product; this is in contrast to our previous findings that a tetragalactosylated single-carbaborane analogue shows the same low yield as with the Beaucage reagent.[11b] TEST was reported by Hayakawa and co-workers[24] to exhibit similar rates of reaction as the Beaucage reagent, but has the advantage that no oxidizing reagent is formed during the sulfurization process. Subsequent deprotection of the galactopyranosyl moieties was accomplished by using 90% trifluoroacetic acid. The crude products were purified by preparative HPLC followed by repeated lyophilization. Compounds **13** and **14** were obtained as white, cotton-wool-like solids. Their partial flocculation in aqueous solution indicates reduced water solubility due to the bis-carbaborane unit.

## Spectroscopic Properties of the Diastereomeric Mixtures of 13 and 14

The $^{31}P\{^{1}H\}$ NMR spectrum of compound **13** exhibits several overlapping signals at 9.7 ppm, whereas compound **14** shows only one very broad signal at $\delta$ = 78.2 ppm with a full width at half-maximum of 0.8 ppm. As a result of the anomerization of the galactosyl moieties 16 stereoisomers can in theory be expected, which causes the multiplication of signals in the $^{31}P\{^{1}H\}$ and $^{1}H$ NMR spectra. The anomeric protons in the $^{1}H$ NMR spectrum can be assigned on the basis of their typical chemical shifts of 4.54 (1β-H) and 5.21 ppm (1α-H) in **13** and 4.58 (1β-H) and 5.26 ppm (1α-H) in **14**. The $^{13}C\{^{1}H\}$ NMR spectra are similar to those of bis-galactosyl derivatives **11** and **12**. The $^{1}J_{CP}$ coupling constant of the P–$C_{carbaborane}$ bond is 181.4 Hz for **13** and 108.3 Hz for **14**. The anomeric ratio was determined according to the $^{13}C$ NMR experiment described above; the

relaxation times are 478 ± 10 ms for both compounds and the α:β ratio is about 34:66 for **13** and **14**. Taking the margin of error into account, the values are in the same range as those of free galactose.[23] Surprisingly, the $^{11}$B NMR spectra show three signals between –5 und –17 ppm instead of one broad signal, that is, the symmetry of the electron-density distribution is disturbed to a lesser extent in comparison with the bis-carbaborane moiety in **9** and **10** despite the fact that four instead of two sugar units are present.

### Water Solubility

The water solubilities of all the glycophosphonate derivatives reported herein were determined and compared with that of D-galactose (Table 3). Due to the small amounts available, the values could not be determined with very high precision: the margin of error is 20 g/L. In general, the same trend as for the analogous mono-carbaborane derivatives was observed.[11b] The disodium salts exhibit the highest water solubility of these compounds of 700 (**9**) and 600 g/L (**10**). These absolute values are in the same range as D-galactose (650 g/L).[25] However, the molar solubilities of 0.83 (**9**) and 0.71 mol/L (**10**) are significantly lower than that of D-galactose (3.6 mol/L). As expected, the neutral tetragalactosyl-substituted compounds **13** and **14** are much less water soluble and the thio derivatives show lower solubility than their phosphonate counterparts. In general, the introduction of the bis-carbaborane unit remarkably increases the hydrophobicity of these molecules compared with the mono-carbaborane species. Therefore the cytotoxicity of these compounds is increased compared with the mono-carbaborane derivatives. A detailed report on the biological properties of the above-mentioned compounds and their mono-carbaborane counterparts will be given elsewhere.[26] Based on the biological studies, these boron-rich compounds may serve as model compounds for the synthesis of, for example, lactosylphosphonate derivatives for potential applications in BNCT.

Table 3. Water solubility of bis-carbaborane derivatives.

| Compound | Water solubility[a] | |
|---|---|---|
| | g/L | mol/L |
| **9** | 700 | 0.83 |
| **10** | 600 | 0.71 |
| **13** | 480 | 0.44 |
| **14** | 370 | 0.33 |
| D-Galactose | 650 | 3.6 |

[a] The margin of error is ±20 g/L.

## Conclusions

We have developed a facile synthesis of bis(*meta*-carbaborane)-containing bis-glycophosphonates with one (**9** and **10**) or two galactosyl moieties (**13** and **14**) at each phosphorus atom. These compounds are soluble in water, but to a lesser extent than their corresponding mono-carbaborane analogues. In particular, the tetragalactosylated compounds **13** and **14** show relatively low water solubility. Cytotoxicity and further biological studies will now be undertaken to show whether these compounds are suitable candidates for 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 mass spectra were recorded with a Bruker Daltonics 7 Tesla APEX II (ESI) or Finnigan MAT MAT8200 (EI) spectrometer. The reported masses refer to the most intense peak of the isotopic 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 with a Knauer ProntoSIL® 120-10 C8 ace-EPS column at a flow rate of 25 mL/min. Elemental analyses were performed with a Heraeus VARIO EL instrument. Microwave reactions were performed at normal pressure in a microwave oven from Mikrowellen Labor Systeme GmbH (Leutkirch, Germany).

The solvents were dried and saturated with nitrogen. 1,7-Dicarba-*closo*-dodecaborane(12) is commercially available from Katchem (Prague, Cech Republic). 1,2:3,4-Di-*O*-isopropylidene-α-D-galactose (**4**) 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. Benzimidazolium triflate was synthesized according to a modified literature procedure:[17a] 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 product was isolated by filtration, washed with dichloromethane, and dried in high vacuum at 50 °C overnight; m.p. 216–217 °C (lit.:[17a] 188–190 °C).

**1,1′-Bis[1,7-dicarba-*closo*-dodecaborane(12)] (1):** *n*BuLi (3.38 mL, 8 mmol, 2.37 M) in *n*-hexane was added slowly to an ice-bath-cooled solution of *meta*-carbaborane (1.15 g, 8 mmol) in diethyl ether (75 mL). The resulting suspension was stirred at room temperature for 1 h. Then a suspension of anhydrous copper(II) chloride (1.34 g, 10 mmol) in diethyl ether (50 mL) was added, which immediately gave a green suspension. The reaction mixture was stirred for another 1 h and then heated at reflux for 20 min. After cooling to room temperature, hydrochloric acid (40 mL, 2.5 M) was added and stirring was continued until two clear phases had formed. The phases were separated and the organic layer was dried with $MgSO_4$ and then concentrated. Purification was performed by column chromatography on silica gel with *n*-hexane. Appropriate product fractions were collected, evaporated to dryness and then heated in vacuo at a bath temperature of 50 °C to sublime the remaining *meta*-carbaborane; yield 0.57 g (50%). $R_f$ (*n*-hexane) = 0.36. $^1$H NMR ($C_6D_6$): $\delta$ = 3.73 (s, 2 H, $HCB_{10}H_{10}C$-$CB_{10}H_{10}CH$), 3.7–1.8 (br. m, 20 H, 2 $C_2B_{10}H_{10}$) ppm. $^{13}$C{$^1$H} NMR ($C_6D_6$): $\delta$ = 74.5 (s, $HCB_{10}H_{10}C$-$CB_{10}H_{10}CH$), 54.4 (s, $HCB_{10}H_{10}C$-

$CB_{10}H_{10}CH$) ppm. $^{11}B\{^1H\}$ NMR ($C_6D_6$): $\delta$ = –3.8 (br. s, 2 B), –7.8 (s, 2 B), –11.2 (s, 4 B), –13.9 (s, 4 B), –14.3 (s, 4 B), –16.8 (s, 4 B) ppm.

**Dimethylamidomethyl Chlorophosphite:** (Dimethylamido)trimethylsilane (12.1 mL, 75.0 mmol) was slowly added to a solution of methyl dichlorophosphite (7.3 mL, 75.6 mmol) in dichloromethane (50 mL) at 0 °C. After complete addition, stirring was continued at room temperature for 2 h. All volatile compounds were removed in vacuo. The residue was distilled in a vacuum at 17 mbar and 51–52 °C; yield 9.43 g (88%), colorless product. $^1H$ NMR ($C_6D_6$): $\delta$ = 2.60 [d, $^3J_{HP}$ = 12.0 Hz, 6 H, $N(CH_3)_2$], 3.13 (d, $^3J_{HP}$ = 13.6 Hz, 3 H, $OCH_3$) ppm. $^{31}P\{^1H\}$ NMR ($C_6D_6$): $\delta$ = 179.5 (s) ppm.

**7,7′-Bis[dimethylamido-*O*-methylphosphonito]-1,1′-bis[1,7-dicarba-*closo*-dodecaborane(12)] (2):** *n*BuLi (1.85 mL, 4.38 mmol, 2.37 M) in *n*-hexane was added to an ice-bath-cooled solution of 1,1′-bis-(*meta*-carbaborane) (0.57 g, 1.99 mmol) in diethyl ether (20 mL). The resulting suspension was stirred at room temperature for 2 h. The dilithiobis(*meta*-carbaborane) slurry was added slowly through a cannula to an ice-bath-cooled solution of dimethylamidomethyl chlorophosphite (0.52 mL, 4.38 mmol) in diethyl ether (10 mL). After complete addition the mixture was stirred for 30 min in an ice bath and then at room temperature overnight. The reaction mixture was filtered through silica gel, the filtrate concentrated in vacuo, and the residue was dissolved in *n*-hexane. Cooling to –25 °C yielded the crystalline product as a mixture of the *rac* and *meso* form; yield 0.60 g (60%); m.p. 116–118 °C. $^1H$ NMR ($C_6D_6$): $\delta$ = 3.8–1.8 (br. m, 20 H, 2 $C_2B_{10}H_{10}$), 3.42 (d, $^3J_{HP}$ = 13.6 Hz, 6 H, $OCH_3$), 2.31 [d, $^3J_{HP}$ = 8.4 Hz, 12 H, $N(CH_3)_2$] ppm. $^{13}C\{^1H\}$ NMR ($C_6D_6$): $\delta$ = 80.1 (d, $^1J_{CP}$ = 81.3 Hz, P*C*$B_{10}H_{10}$C-$CB_{10}H_{10}$*C*P), 76.3 (s, $CB_{10}H_{10}$*C*-*C*$B_{10}H_{10}$C), 54.4 (d, $^2J_{CP}$ = 20.8 Hz, O*C*$H_3$), 36.0 [br. s, N(*C*$H_3$)$_2$] ppm. $^{31}P\{^1H\}$ NMR ($C_6D_6$): $\delta$ = 138.7 (s) ppm. $^{11}B$ NMR ($C_6D_6$): $\delta$ = –3.2 (br. s, $^1J_{BH}$ n.d., 2 B), –5.7 (br. s, $^1J_{BH}$ n.d., 2 B), –9.8 (d, $^1J_{BH}$ = 150.7 Hz, 8 B), –12.5 (d, $^1J_{BH}$ = n.d., 8 B) ppm. IR (KBr): $\tilde{\nu}$ = 2975 (w), 2932 (w), 2895 (w), 2843 (w), 2833 (w), 2801 (w, C–H), 2665 (w), 2652 (w), 2615 (s), 2598 (s), 2579 (s), 1648 (w), 1482 (w), 1463 (w), 1449 (m), 1410 (w), 1288 (m), 1262 (w), 1190 (s), 1140 (w), 1083 (s), 1064 (m), 1028 (s), 975 (s), 934 (w), 906 (w), 894 (w), 860 (w), 836 (w), 812 (m), 765 (w), 748 (m), 728 (w), 678 (m), 629 (w), 604 (w), 514 (w), 494 (w), 456 (w), 433 (w) cm$^{-1}$. MS (EI positive, 70 eV): *m*/*z* = 496.5 (100) $[M]^+$, 465.5 (28) $[M - OMe]^+$. $C_{10}H_{38}B_{20}N_2O_2P_2$ (496.59): calcd. C 24.19, H 7.71, N 5.64; found C 25.13, H 7.89, N 5.04.

**Bis(dimethylamido) Chlorophosphite:** (Dimethylamido)trimethylsilane (14 mL, 87.1 mmol) was slowly added to a solution of dimethylamido dichlorophosphite (10 mL, 87.1 mmol) in dichloromethane (50 mL) at 0 °C. After complete addition, stirring was continued at room temperature for 2 h. All volatile compounds were removed in vacuo. The residue was distilled in a vacuum at 11 mbar and 57 °C; yield 10.51 g (78%), colorless product. $^1H$ NMR ($C_6D_6$): $\delta$ = 2.47 [d, $^3J_{HP}$ = 12.4 Hz, 12 H, $N(CH_3)_2$] ppm. $^{31}P\{^1H\}$ NMR ($C_6D_6$): $\delta$ = 159.1 (s) ppm.

**7,7′-Bis[bis(dimethylamido)phosphonito]-1,1′-bis[1,7-dicarba-*closo*-dodecaborane(12)] (3):** *n*BuLi (1.85 mL, 4.38 mmol, 2.37 M) in *n*-hexane was added to an ice-bath-cooled solution of 1,1′-bis(*meta*-carbaborane) (0.57 g, 1.99 mmol) in diethyl ether (20 mL). The resulting suspension was stirred at room temperature for 2 h. The dilithiobis(*meta*-carbaborane) slurry was added slowly through a cannula to an ice-bath-cooled solution of bis(dimethylamido) chlorophosphite (0.58 mL, 4.39 mmol) in diethyl ether (10 mL). After complete addition the mixture was stirred for 30 min in an ice bath and then at room temperature overnight. The reaction mixture was filtered through silica gel, the filtrate concentrated in vacuo, and the residue dissolved in *n*-hexane. Cooling to –25 °C yielded the product as a white crystalline solid; yield 0.65 g (62%); m.p. 162–164 °C. $^1H$ NMR ($C_6D_6$): $\delta$ = 3.8–1.8 (br. m, 20 H, 2 $C_2B_{10}H_{10}$), 2.47 [d, $^3J_{HP}$ = 9.60 Hz, 24 H, $N(CH_3)_2$] ppm. $^{13}C\{^1H\}$ NMR ($C_6D_6$): $\delta$ = 80.1 (d, $^1J_{CP}$ = 79.5 Hz, P*C*$B_{10}H_{10}$C-$CB_{10}H_{10}$*C*P), 76.2 (s, $CB_{10}H_{10}$*C*-*C*$B_{10}H_{10}$C), 41.3 [d, $^2J_{CP}$ = 22.1 Hz, $N(CH_3)_2$] ppm. $^{31}P\{^1H\}$ NMR ($C_6D_6$): $\delta$ = 105.7 (s) ppm. $^{11}B$ NMR ($C_6D_6$): $\delta$ = –4.0 (br. s, $^1J_{BH}$ n.d., 4 B), –9.8 (d, $^1J_{BH}$ = 140.2 Hz, 16 B) ppm. IR (KBr): $\tilde{\nu}$ = 3021 (w), 2975 (w), 2887 (s), 2840 (s) 2793 (w, C–H) 2653 (w), 2605 (s), 2574 (s, B–H), 1628 (w) 1449 (m), 1409 (w), 1272 (s), 1189 (s), 1136 (w), 1080 (s), 1058 (m), 968 (s), 856 (w), 831 (m), 796 (w), 744 (m), 730 (m), 684 (m), 647 (m), 606 (w), 579 (w), 488 (w), 419 (w) cm$^{-1}$. MS (ESI positive in THF/$CH_3CN$): *m*/*z* = 523.5 $[M]^+$. $C_{12}H_{44}B_{20}N_4P_2$ (522.67): calcd. C 27.58, H 8.49, N 10.72; found C 28.14, H 8.56, N 10.11.

**($R_{P1}$,$S_{P1}$:$R_{P2}$,$S_{P2}$)-*O*,*O*′′-Bis(1,2:3,4-di-*O*-isopropylidene-6-deoxy-α-D-galactopyranos-6-yl)-*O*′,*O*′′′-dimethyl-{1,1′-bi[1,7-dicarba-*closo*-dodecaborane(12)]-7,7′-diyl}bis(phosphonate) (5):** Compound **2** (0.33 g, 0.66 mmol) was suspended in acetonitrile (5 mL). Then a solution of 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose in acetonitrile (2.5 mL, 2.0 mmol, 0.8 M) and benzimidazolium triflate (0.45 g, 1.68 mmol) were added. The reaction mixture was heated at reflux until the solid had dissolved and then stirred for 3 h at room temperature. Then a 70% solution of *tert*-butyl hydroperoxide in water (0.22 mL, 1.45 mmol) was added and the mixture stirred for 40 min at room temperature. The reaction mixture was diluted with ethyl acetate (20 mL) and washed three times with brine. The organic layer was dried with $MgSO_4$ and then concentrated. The residue was purified twice by column chromatography with a 2:3 mixture of acetone/*n*-hexane to give the product as a white foam after treatment with diethyl ether; yield 236 mg (37%). $R_f$ (acetone/*n*-hexane, 2:3) = 0.54. Due to the presence of diastereomers, all signals occur twice in the NMR spectra. $^1H$ NMR ($CDCl_3$): $\delta$ = 5.53 (m, 2 H, 1-H), 4.61 (m, 2 H, 3-H), 4.32 (m, 2 H, 2-H), 4.22 (m, 2 H, 4-H), 4.13 (m, 2 H, 5-H), 4.0 (m, 4 H, $CH_2O$), 3.77 (d, $^3J_{HP}$ = 11.2 Hz, 6 H, $POCH_3$), 3.6–1.5 (m, 20 H, 2 $C_2B_{10}H_{10}$), 1.47 (s, 6 H, $CH_3$), 1.38 (s, 6 H, $CH_3$), 1.26 (s, 12 H, $CH_3$) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$): $\delta$ = 109.8–108.8 ($C_{quat}$ of isopropylidene), 96.3 (C-1), 75.0 (s, $CB_{10}H_{10}$*C*-*C*$B_{10}H_{10}$C), 70.7 ($^3J_{CP}$ = 6.8 Hz, C-5), 70.6 and 70.5 (C-3 and C-4), 70.4 (C-2), 67.1 ($^2J_{CP}$ = 4.1 Hz, C-6), 66.6 (d, $^1J_{CP}$ = 176.2 Hz, P*C*$B_{10}H_{10}$C-$CB_{10}H_{10}$*C*P), 54.7 (d, $^2J_{CP}$ = 6.9 Hz, $OCH_3$), 26.1–24.4 ($CH_3$) ppm. $^{31}P\{^1H\}$ NMR ($CDCl_3$): $\delta$ = 10.5 (s), 10.0 (s) (diastereomers) ppm. $^{11}B$ NMR ($CDCl_3$): $\delta$ = –10.2 (br. s, $^1J_{BH}$ n.d., 20 B) ppm. IR (KBr): $\tilde{\nu}$ = 2990 (m, CH), 2621 (BH) 1638 (m), 1458 (m), 1384 (w), 1277 (w), 1259 (w), 1138 (m), 1091 (w), 1040 (w), 870 (w), 813 (w), 771 (w), 729 (w), 650 (w), 617 (w), 462 (w), 419 (w) cm$^{-1}$. MS (ESI positive in $CH_3CN$): *m*/*z* = 982.5 $[M + Na]^+$. $C_{30}H_{64}B_{20}O_{16}P_2 \cdot 2H_2O$ (995.02): calcd. C 36.21, H 6.89; found C 35.72, H 6.19.

**Disodium *O*,*O*′′-Bis(6-deoxy-D-galactopyranos-6-yl)-{1,1′-bi[1,7-dicarba-*closo*-dodecaborane(12)]-7,7′-diyl}bis(phosphonate) (9)**

**Deprotection with Trimethylsilyl Bromide:** Under nitrogen, compound **5** (300 mg, 0.31 mmol) was dissolved in dichloromethane (3 mL). Then trimethylsilyl bromide (125 μL, 0.95 mmol) was added and the resulting reaction mixture stirred for 24 h at room temperature. All volatile compounds were removed in vacuo. A 90% solution of TFA (4 mL) was added to the residue and the mixture stirred for 2 h at room temperature. Then the trifluoroacetic acid was removed under reduced pressure, water (10 mL) was added and stirring was continued for a further 24 h. The mixture was concentrated and purified by preparative HPLC on a Pron-

toSIL® phase (gradient $CH_3CN/H_2O$, 80:20 over 30 min to $CH_3CN/H_2O$, 0:100; $t_R$ = 8.9 min). Appropriate fractions were collected and the solvent evaporated. The remaining white solid was dissolved in water (15 mL) and stirred with Amberlite IR-120 ion-exchange resin ($Na^+$ form, 15 mL). The resin was filtered off and washed three times with water. The aqueous solution was lyophilized to yield the product as a pale-yellow powder; yield 125.6 mg (49%). $^1H$ NMR ($D_2O$): $\delta$ = 5.20 (m, 2×0.33 H, 1α-H), 4.55 (m, $^3J_{HH}$ = 7.5 Hz, 2×0.67 H, 1β-H), 4.14 (s, 2×0.33 H, 5α-H), 3.97 (m, 4 H, $CH_2O$, α + β form), 3.90 (s, 2 H, 2α-H + 4β-H), 3.82 (m, 4×0.33 H, 3α-H and 4α-H), 3.74 (m, 2×0.67 H, 5β-H), 3.60 (d, $^3J_{HH}$ = 8.5 Hz, 2×0.67 H, 3β-H), 3.42 (m, 2×0.67 H, 2β-H), 3.4–1.6 (br. m, 20 H, 2 $C_2B_{10}H_{10}$) ppm. $^{13}C\{^1H\}$ NMR ($D_2O$): $\delta$ = 96.5 (C-1β), 92.4 (C-1α), 76.5 (s, $CB_{10}H_{10}$*C*-*C*$B_{10}H_{10}$C), 73.6 ($^3J_{CP}$ = 7.6 Hz, C-5β), 72.6 (C-3β), 71.8 (C-2β), 70.9 (d, $^1J_{CP}$ = 153.3 Hz, P*C*$B_{10}H_{10}$C-$CB_{10}H_{10}$*C*P), 69.2 ($^3J_{CP}$ = 7.2 Hz, C-5α), 69.0 and 68.9 (C-3α and C-4α), 68.3 (C-4β), 68.2 (C-2α), 65.5 ($^2J_{CP}$ = 6.1 Hz, C-6α), 64.8 ($^2J_{CP}$ = 5.7 Hz, C-6β) ppm. $^{31}P\{^1H\}$ NMR ($D_2O$): $\delta$ = 4.3 (s), 4.2 (s) ppm. $^{11}B$ NMR ($D_2O$): $\delta$ = –11.2 (br. s, $^1J_{BH}$ n.d., 20 B) ppm. IR (KBr): $\tilde{\nu}$ = 3424 (s, OH), 2924 (w), 2857 (w, CH), 2620 (BH), 1686 (m), 1636 (w), 1444 (w), 1384 (w), 1210 (s), 1145 (m), 1088 (m), 1042 (w), 880 (w), 840 (w), 804 (w), 726 (w), 636 (w), 607 (w), 547 (m) $cm^{-1}$. MS (ESI positive in $H_2O/CH_3OH$): *m*/*z* = 837.37 $[M + Na]^+$, 854.34 $[M + K]^+$, 869.32 $[M + CH_3OH + Na]^+$. $C_{16}H_{42}B_{20}Na_2O_{16}P_2$ (814.64): calcd. C 23.59, H 5.20; found C 22.98, H 4.99.

**Deprotection with Thiophenol/Triethylamine:** Triethylamine (0.5 mL, 3.6 mmol) and thiophenol (0.25 mL, 2.4 mmol) were added to a stirred solution of **5** (327 mg, 0.34 mmol) in 1,4-dioxane (1 mL). The reaction mixture was stirred for 1 h at room temperature. Then all the volatile materials were evaporated and ethyl acetate was added to the resulting residue to remove thiophenol (can be distilled azeotropically with ethyl acetate). The residue was 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 preparative HPLC on a ProntoSIL® column (gradient $CH_3CN/H_2O$, 80:20 over 30 min to $CH_3CN/H_2O$, 0:100; $t_R$ = 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-exchange resin ($Na^+$ form, 10 mL) for 48 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 (55.2 mg, 20%). The analytical data are identical to the data mentioned above.

**($R_{P1}$,$S_{P1}$:$R_{P2}$,$S_{P2}$)-*O*,*O*′′-Bis(1,2:3,4-di-*O*-isopropylidene-6-deoxy-α-D-galactopyranos-6-yl)-*O*′,*O*′′′-dimethyl-{1,1′-bi[1,7-dicarba-*closo*-dodecaborane(12)]-7,7′-diyl}bis(phosphonothioate) (6):** Compound **2** (0.27 g, 0.54 mmol) was suspended in acetonitrile (7 mL). Then 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**2**) in acetonitrile (2.0 mL, 1.60 mmol, 0.8 M) and benzimidazolium triflate (0.36 g, 1.35 mmol) were added. The reaction mixture was heated at reflux until the solid had dissolved and then stirred for 3 h at room temperature. Conversion was monitored by $^{31}P\{^1H\}$ NMR spectroscopy. Then powdered Beaucage reagent (0.22 g, 1.10 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 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 (0.22 g, 41%) after treatment with diethyl ether. $R_f$ (ethyl acetate/cyclohexane, 1:2) = 0.49. Due to the diastereomeric mixture all signals in the $^1H$ and $^{13}C\{^1H\}$ NMR occur twice. $^1H$ NMR ($CDCl_3$): $\delta$ = 5.53 (m, 2 H, 1-H), 4.61 (m, 2 H, 3-H), 4.32 (m, 2 H, 2-H), 4.22 (m, 2 H, 4-H), 4.13 (m, 2 H, 5-H), 4.0 (m, 4 H, $CH_2O$), 3.70 (d, $^3J_{HP}$ = 14.2 Hz, 6 H, $POCH_3$), 3.4–1.9 (m, 20 H, 2 $C_2B_{10}H_{10}$), 1.49 (br. s, 2 H, $CH_3$), 1.47 (br. s, 3 H, $CH_3$), 1.38 (br. s, 4 H, $CH_3$), 1.36 (br. s, 6 H, $CH_3$), 1.26 (br. s, 9 H, $CH_3$) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$): $\delta$ = 109.6–108.8 ($C_{quat}$ of isopropylidene), 96.2 (C-1), 75.2 (s, $CB_{10}H_{10}$*C*-*C*$B_{10}H_{10}$C), 70.7–70.4 (m, C-2, C-3, and C-4), 67.5 (d, $^3J_{CP}$ = 6.5 Hz, C-5), 67.0 (d, $^2J_{CP}$ = 8.2 Hz, C-6), 66.7 (d, $^1J_{CP}$ = 132.3 Hz, P*C*$B_{10}H_{10}$C-$CB_{10}H_{10}$*C*P), 54.7 (d, $^2J_{CP}$ = 6.5 Hz, $OCH_3$), 26.1–24.4 ($CH_3$) ppm. $^{31}P\{^1H\}$ NMR ($CDCl_3$): $\delta$ = 79.2 (s), 79.0 (s) (diastereomers) ppm. $^{11}B$ NMR ($CDCl_3$): $\delta$ = –10.6 (br. s, $^1J_{BH}$ n.d., 20 B) ppm. IR (KBr): $\tilde{\nu}$ = 2989 (m), 2937 (m, C–H), 2621 (s, B–H), 1860 (w), 1456 (w), 1382 (m), 1306 (w), 1256 (m), 1213 (w), 1171 (m), 1146 (w), 1072 (w), 1029 (w), 1006 (w), 905 (w), 888 (w), 838 (m), 768 (w), 730 (w), 691 (w), 665 (w), 608 (w), 570 (w), 512 (w), 492 (w) $cm^{-1}$. MS (ESI positive in $CH_3CN$): *m*/*z* = 1014.6 $[M + Na]^+$. $C_{30}H_{64}B_{20}O_{14}P_2S_2{\cdot}3H_2O$ (1045.17): calcd. C 34.48, H 6.75; found C 33.64, H 7.00.

**Diastereomeric Mixture of Disodium *O*,*O*′′-Bis(6-deoxy-D-galactopyranos-6-yl)-{1,1′-bi[1,7-dicarba-*closo*-dodecaborane(12)]-7,7′-diyl}bis(phosphonothioate) (10):** Triethylamine (0.5 mL, 3.6 mmol) and thiophenol (0.25 mL, 2.4 mmol) were added to a stirred solution of **6** (312 mg, 0.31 mmol) in 1,4-dioxane (1 mL). The reaction mixture was stirred for 1 h at room temperature. Then all volatiles were evaporated and ethyl acetate was added several times (5 mL each time) 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-exchange resin ($H^+$ 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, trifluoroacetic acid (4 mL, 90% in water) was added, and stirring was continued for 40 min at room temperature. The solvent was evaporated and the residue extracted several times with ethyl acetate (5 mL each time). Purification was performed by preparative HPLC on a ProntoSIL® column (gradient $CH_3CN/H_2O$, 80:20 over 30 min to $CH_3CN/H_2O$, 0:100; $t_R$ = 15.0 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-exchange resin ($Na^+$ form, 10 mL) for 48 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 (162.2 mg, 61%). Due to the formation of diastereomers all NMR signals occur manifold. The signals of the protons and carbon atoms of the galactopyranosyl moieties could not be assigned with certainty. $^1H$ NMR ($D_2O$): $\delta$ = 5.24 (m, 2×0.33 H, 1α-H), 4.63 (m, $^3J_{HH}$ n.d., 2×0.67 H, 1β-H), 4.22 (s, 2×0.33 H, 5α-H), 4.10 (m, 4 H, $CH_2O$, α + β form), 4.00 (s, 2 H, 2α-H + 4β-H), 3.88–3.77 (m, 2.66 H, 4α-H, 3α-H, 5β-H), 3.71 (d, $^3J_{HH}$ = 8.5 Hz, 2×0.67 H, 3β-H), 3.46 (m, 2×0.67 H, 2β-H), 3.4–1.6 (br. m, 20 H, 2 $C_2B_{10}H_{10}$) ppm. $^{13}C\{^1H\}$ NMR ($D_2O$): $\delta$ = 96.5 (C-1β), 92.4 (C-1α), 77.5 (d, $^1J_{CP}$ = 106.7 Hz, P*C*$B_{10}H_{10}$C-$CB_{10}H_{10}$*C*P), 75.0 (s, $CB_{10}H_{10}$*C*-*C*$B_{10}H_{10}$C), 73.6 ($^3J_{CP}$ = 8.9 Hz, C-5β), 72.6 (C-3β), 71.9 (C-2β), 69.1 (m, $^3J_{CP}$ n.d., C-5α), 68.5 and 68.4 (C-3α + C-4α), 68.2 (C-2α + C-4β), 65.1 ($^2J_{CP}$ n.d., C-6α), 64.0 (m, $^2J_{CP}$ n.d., C-6β) ppm. $^{31}P\{^1H\}$ NMR ($D_2O$): $\delta$ = 60.5 (s), 60.6 (s) (diastereomers) ppm. $^{11}B$ NMR ($D_2O$): $\delta$ = –10.9 (br. s, $^1J_{BH}$ n.d., 20 B) ppm. IR (KBr): $\tilde{\nu}$ = 3416 (s, O–H), 2928 (w, C–H), 2617 (B–H), 1637 (m), 1407 (m), 1368 (w), 1206 (w), 1138 (m), 1091 (w), 1040 (w), 870 (w), 813 (w), 771 (w), 729 (w), 650 (w), 617 (w), 462 (w), 419 (w) $cm^{-1}$. MS (ESI positive in

$H_2O/CH_3OH$): *m*/*z* = 826.3 [M – Na + 2H]$^+$, 848.2 [M + H]$^+$, 870.2 [M + Na]$^+$. $C_{16}H_{42}B_{20}Na_2O_{14}P_2S_2{\cdot}3H_2O$ (900.82): calcd. C 21.33, H 5.37; found C 21.22, H 5.44.

**Tetrakis(1,2:3,4-di-*O*-isopropylidene-6-deoxy-α-D-galactopyranos-6-yl)-1,1′-bi[1,7-dicarba-*closo*-dodecaborane(12)-7,7′-diyl]bis(phosphonate) (11):** Compound **3** (0.30 g, 0.57 mmol) was suspended in acetonitrile (5 mL). Then a solution of 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**4**) in acetonitrile (3.6 mL, 2.88 mmol, 0.8 M) and benzimidazolium triflate (0.77 g, 2.87 mmol) were added. The reaction mixture was heated in a microwave oven for 3 h at 81 °C. After complete conversion a 70% solution of *tert*-butyl hydroperoxide (0.23 mL, 1.68 mmol) in water was added and the mixture stirred for 40 min at room temperature. The reaction mixture was diluted with ethyl acetate (30 mL) and washed three times with brine (3 × 30 mL). The organic layer was dried with $MgSO_4$ and then concentrated. The honey-like residue was purified by column chromatography with a 1:1 mixture of ethyl acetate/*n*-hexane and then with a 1:1 mixture of ethyl acetate/cyclohexane to give the product as a white foam after treatment with diethyl ether; yield 230 mg (29%). $R_f$ (ethyl acetate/cyclohexane, 1:1) = 0.46. $^1$H NMR ($CDCl_3$): $\delta$ = 5.53 (m, 4 H, 1-H), 4.61 (m, 4 H, 3-H), 4.32 (m, 4 H, 2-H), 4.22 (m, 4 H, 4-H), 4.13 (m, 4 H, 5-H), 4.0 (m, 8 H, $CH_2O$), 3.4–1.9 (m, 20 H, 2 $C_2B_{10}H_{10}$), 1.54 (s, 12 H, $CH_3$), 1.43 (s, 12 H, $CH_3$), 1.33 (s, 24 H, $CH_3$) ppm. $^{13}$C{$^1$H} NMR ($CDCl_3$): $\delta$ = 109.6–108.8 ($C_{quat}$ of isopropylidene), 96.2 (C-1), 75.2 (s, $CB_{10}H_{10}C$-$C$$B_{10}H_{10}C$), 70.7–70.4 (m, C-2, C-3, C-4, and C-5), 67.0 (C-6), 66.7 (d, $^1J_{CP}$ = 176.9 Hz, P$C$$B_{10}H_{10}C$-$CB_{10}H_{10}C$P), 26.1–24.4 ($CH_3$) ppm. $^{31}$P{$^1$H} NMR ($CDCl_3$): $\delta$ = 9.3 (s) ppm. $^{11}$B NMR ($CDCl_3$): $\delta$ = –10.2 (br. s, $^1J_{BH}$ n.d., 20 B) ppm. IR (KBr): $\tilde{\nu}$ = 2988, 2936 (C–H), 2621 (B–H), 2250 (w), 1630 (w), 1457 (w), 1382 (m), 1257 (s), 1213 (s), 1170 (m), 1146 (w), 1115 (w), 1073 (s), 1006 (s), 905 (w), 862 (w), 806 (w), 764 (w), 731 (w), 689 (w), 645 (w), 554 (w), 512 (w), 478 (w) cm$^{-1}$. MS (ESI positive in $CH_3CN$): *m*/*z* = 1438.76 [M + Na]$^+$. $C_{52}H_{96}B_{20}O_{26}P_2$ (1415.47): calcd. C 44.12, H 6.84; found C 44.06, H 6.83.

**Diastereomeric Mixture of Tetrakis(6-deoxy-D-galactopyranos-6-yl)-1,1′-bi[1,7-dicarba-*closo*-dodecaborane(12)-7,7′-diyl]bis(phosphonate) (13):** Compound **11** (200 mg, 0.14 mmol) was dissolved in trifluoroacetic acid (4 mL, 90% in water) and the solution stirred at room temperature for 1 h. The trifluoroacetic acid was removed under reduced pressure and the resulting residue dissolved in water, filtered, and 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; $t_R$ = 5.8 min). Appropriate fractions were collected and concentrated in vacuo. The residue was lyophilized several times to yield the product as a white powder (140 mg, 87.4%). Due to the formation of diastereomers all NMR signals occur manifold. The signals of the protons and carbon atoms of the galactopyranosyl moieties could not be assigned with certainty. $^1$H NMR ($D_2O$): $\delta$ = 5.21 (m, 4 × 0.33 H, 1α-H), 4.54 (m, $^3J_{HH}$ n.d., 4 × 0.67 H, 1β-H), 4.27 (m, 9.32 H, $CH_2O$, α + β form, 5α-H), 4.00–3.70 (m, 9.32 H, 3α-H + 4α-H, 2α-H + 4β-H, 5β-H), 3.58 (m, 4 × 0.67 H, 3β-H), 3.45 (m, 4 × 0.67 H, 2β-H), 3.4–1.6 (br. m, 20 H, 2 $C_2B_{10}H_{10}$) ppm. $^{13}$C{$^1$H} NMR ($D_2O$): $\delta$ = 96.5 (C-1β), 92.4 (C-1α), 75.5 (s, $CB_{10}H_{10}C$-$C$$B_{10}H_{10}C$), 73.2 (m, $^3J_{CP}$ n.d., C-5β), 72.8 (C-3β), 71.9 (C-2β), 69.2 ($^3J_{CP}$ n.d., C-5α), 68.6 (m, C-3α and C-4α), 68.4 (m, C-2α + C-4β), 67.9 (m, $^2J_{CP}$ n.d., C-6α + C-6β), 66.0 (d, $^1J_{CP}$ = 181.4 Hz, P$C$$B_{10}H_{10}C$-$CB_{10}H_{10}C$P) ppm. $^{31}$P{$^1$H} NMR ($D_2O$): several singlets between $\delta$ = 9.5 and 9.9 ppm (diastereomers). $^{11}$B NMR ($D_2O$): $\delta$ = –5.6 (br. s, $^1J_{BH}$ n.d., 2 B), –12.3 (br. s, $^1J_{BH}$ n.d., 10 B), –16.1 (br. s, $^1J_{BH}$ n.d., 8 B) ppm. IR (KBr): $\tilde{\nu}$ = 3404 (s, O–H), 2925 (m, C–H), 2621 (m, B–H), 1676 (m), 1638 (m), 1401 (m), 1247 (s), 1155 (s), 1077 (s), 896 (w), 804 (w), 727 (w), 639 (w), 555 (w), 504 (w) cm$^{-1}$. MS (ESI positive in $CH_3CN$): *m*/*z* = 1118.51 [M + Na]$^+$, 1095.53 [M + H]$^+$. $C_{28}H_{64}B_{20}O_{26}P_2$ (1094.96): calcd. C 30.71, H 5.89; found C 30.61, H 5.87.

***O*,*O*′,*O*′′,*O*′′′-Tetrakis(1,2:3,4-di-*O*-isopropylidene-6-deoxy-α-D-galactopyranos-6-yl)-1,1′-bi[1,7-dicarba-*closo*-dodecaborane(12)-7,7′-diyl]bis(phosphonothioate) (12)**

**Sulfurization with the Beaucage Reagent:** Compound **3** (0.41 g, 0.78 mmol) was suspended in acetonitrile (7 mL). Then a solution of 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**4**) in acetonitrile (5.90 mL, 4.72 mmol, 0.8 M) and benzimidazolium triflate (1.05 g, 4.72 mmol) were added. The reaction mixture was heated in a microwave oven for 3 h at 81 °C. Then powdered Beaucage reagent (0.33 g, 1.65 mmol) was added and stirring was continued for 2 h at room temperature. The reaction mixture was diluted with ethyl acetate (20 mL) and washed three times with brine (3 × 20 mL). The organic layer was dried with $MgSO_4$ and then concentrated. The residue was purified by chromatography on silica gel with ethyl acetate/cyclohexane (1:2) to give the product as a white foam after treatment with diethyl ether; yield 100 mg (9%). $R_f$ (ethyl acetate/cyclohexane, 1:2) = 0.49. $^1$H NMR ($CDCl_3$): $\delta$ = 5.53 (m, 4 H, 1-H), 4.61 (m, 4 H, 3-H), 4.32 (m, 4 H, 2-H), 4.22 (m, 4 H, 4-H), 4.13 (m, 4 H, 5-H), 4.0 (m, 8 H, $CH_2O$), 3.4–1.9 (m, 20 H, 2 $C_2B_{10}H_{10}$), 1.54 (s, 12 H, $CH_3$), 1.43 (s, 12 H, $CH_3$), 1.33 (s, 24 H, $CH_3$) ppm. $^{13}$C{$^1$H} NMR ($CDCl_3$): $\delta$ = 109.6–108.8 ($C_{quat}$ of isopropylidene), 96.2 (C-1), 75.2 (s, $CB_{10}H_{10}C$-$C$$B_{10}H_{10}C$), 70.7 (C-5), 70.4 and 70.5 (C-3 and C-4), 70.3 (C-2), 67.0 (C-6), 66.7 (d, $^1J_{CP}$ = 135.0 Hz, P$C$$B_{10}H_{10}C$-$CB_{10}H_{10}C$P), 26.0–24.3 ($CH_3$) ppm. $^{31}$P{$^1$H} NMR ($CDCl_3$): $\delta$ = 77.4 (s) ppm. $^{11}$B NMR ($CDCl_3$): $\delta$ = –10.2 (br. s, $^1J_{BH}$ n.d., 20 B) ppm. IR (KBr): $\tilde{\nu}$ = 2989 (m), 2933 (m, C–H), 2621 (m, B–H), 1735 (w), 1637 (w), 1458 (m), 1383 (s), 1257 (s), 1213 (s), 1168 (s), 1117 (m), 1073 (s), 1006 (s), 968 (w), 906 (w), 889 (w), 858 (w), 770 (w), 671 (w), 513 (w), 465 (w) cm$^{-1}$. MS (ESI positive in $CH_3CN$): *m*/*z* = 1470.72 [M + Na]$^+$, 1466.75 [M + $NH_4$]$^+$. $C_{52}H_{96}B_{20}O_{24}P_2S_2$ (1447.60): calcd. C 43.14, H 6.68; found C 42.95, H 6.65.

**Sulfurization with Bis[3-(triethoxysilyl)propyl] Tetrasulfide (TEST):** Compound **3** (0.20 g, 0.38 mmol) was suspended in acetonitrile (5 mL). Then a solution of 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**4**) in acetonitrile (2.87 mL, 2.3 mmol, 0.8 M) and benzimidazolium triflate (0.51 g, 1.96 mmol) were added. The reaction mixture was heated in a microwave oven for 3 h at 81 °C. Then TEST (0.41 mL, 0.82 mmol) and *N*-methylimidazole (0.43 mL, 5.40 mmol) were added and the mixture was stirred for 1 h at room temperature. The reaction mixture was diluted with ethyl acetate (20 mL) and washed with a saturated aqueous $NaHCO_3$ solution (20 mL) and then three times with brine (3 × 20 mL). The organic layer was dried with $MgSO_4$ and then concentrated. The residue was purified twice by column chromatography (a 1:2 mixture of ethyl acetate/cyclohexane and a 1:3 mixture of ethyl acetate/*n*-hexane) to give the product as a white foam after treatment with diethyl ether; yield 158 mg (28%). The analytical data are identical with the data mentioned above.

**Diastereomeric Mixture of *O*,*O*′,*O*′′,*O*′′′-Tetrakis(6-deoxy-D-galactopyranos-6-yl)-1,1′-bi[1,7-dicarba-*closo*-dodecaborane(12)-7,7′-diyl]bis(phosphonothioate) (14):** Compound **12** (128 mg, 0.09 mmol) was dissolved in a 90% aqueous solution of trifluoroacetic acid (4 mL) and stirred for 1 h at room temperature. The trifluoroacetic acid was removed under reduced pressure and the resulting residue dissolved in water, filtered, and 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; $t_R$ = 5.5 min). Appropriate fractions were collected and concentrated in vacuo. The residue was lyophilized

several times to yield the product as a white powder (83.4 mg, 84%). Due to the formation of diastereomers all NMR signals occur manifold. The signals of the protons and carbon atoms of the galactopyranosyl moieties could not be assigned with certainty. $^1$H NMR ($D_2O$): $\delta$ = 5.26 (m, 4×0.33 H, 1α-H), 4.58 (m, $^3J_{HH}$ n.d., 4×0.67 H, 1β-H), 4.48–4.05 (m, 9.32 H, $CH_2O$, α + β form, 5α-H), 4.05–3.72 (m, 9.32 H, 3α-H, 4α-H, 2α-H + 4β-H, 5β-H), 3.64 (m, 4×0.67 H, 3β-H), 3.48 (m, 4×0.67 H, 2β-H), 3.4–1.6 (br. m, 20 H, 2 $C_2B_{10}H_{10}$) ppm. $^{13}$C{$^1$H} NMR ($D_2O$): $\delta$ = 92.4 (m, C-1α), 96.7 (m, C-1β), 75.3 (s, $CB_{10}H_{10}C$-$CB_{10}H_{10}C$), 74.4 (d, $^1J_{CP}$ = 108.3 Hz, P$CB_{10}H_{10}C$-$CB_{10}H_{10}C$P), 73.5 (m, $^3J_{CP}$ n.d., C-5β), 72.8 (C-3β), 71.9 (C-2β), 69.0 ($^3J_{CP}$ n.d., C-5α), 68.6–67.5 (m, C-2α + C-4β, C-3α and C-4α), 65.6 (C-6β), 64.1 (C-6α) ppm. $^{31}$P{$^1$H} NMR ($D_2O$): $\delta$ = 78.2 (s, vbr) (diastereomers) ppm. $^{11}$B NMR ($D_2O$): $\delta$ = –6.2 (br. s, $^1J_{BH}$ n.d., 2 B), –12.9 (br. s, $^1J_{BH}$ n.d., 10 B), –16.2 (br. s, $^1J_{BH}$ n.d., 8 B) ppm. IR (KBr): $\tilde{\nu}$ = 3420 (vs, O–H), 2921 (w, C–H), 2622 (w, B–H), 1635 (w), 1401 (w), 1147 (w), 1064 (s), 853 (w), 660 (w), 495 (w) cm$^{-1}$. MS (ESI positive in $CH_3CN$): $m/z$ = 1145.51 $[M + NH_4]^+$, 1150.46 $[M + Na]^+$. $C_{28}H_{64}B_{20}O_{24}P_2S_2$ (1127.09): calcd. C 29.84, H 5.72; found C 29.87, H 5.62.

**Structure Determination of 2 and 3:** The X-ray crystallographic analysis was performed with an Oxford Diffraction CCD Xcalibur-S diffractometer (data reduction with CrysAlis Pro[27] with the program SCALE3 ABSPACK[28] used for empirical absorption correction) using Mo-$K_\alpha$ radiation ($\lambda$ = 71.073 pm) and $\omega$-scan rotation (Table 4). The structures were solved by direct methods and refinement of all non-hydrogen atoms was performed by using SHELXL-97.[29] Hydrogen atoms were located on difference Fourier maps calculated at the final stage of the structure refinement. The structures of **2** and **3** were generated with ORTEP.[30]

Table 4. Crystallographic data of **2** and **3**.

| | **2** | **3** |
|---|---|---|
| Empirical formula | $C_{10}H_{38}O_2N_2P_2B_{20}$ | $C_{12}H_{44}N_4P_2B_{20}$ |
| Formula mass | 496.56 | 522.65 |
| $T$ [K] | 130(2) | 130(2) |
| Crystal system | monoclinic | triclinic |
| Space group | $P2_1/n$ | $P\bar{1}$ |
| $a$ [pm] | 995.54(2) | 786.80(2) |
| $b$ [pm] | 1290.52(2) | 920.24(3) |
| $c$ [pm] | 1126.91(2) | 1096.14(5) |
| $\alpha$ [°] | 90 | 102.496(3) |
| $\beta$ [°] | 107.231(2) | 102.599(3) |
| $\gamma$ [°] | 90 | 101.266(3) |
| $V$ [nm$^3$] | 1.38283(4) | 0.73128(5) |
| $Z$ | 2 | 1 |
| $\rho_{calcd}$ [Mg m$^{-3}$] | 1.193 | 1.187 |
| $\mu(Mo_{K\alpha})$ [mm$^{-1}$] | 0.173 | 0.164 |
| $F(000)$ | 516 | 274 |
| Number of reflections collected | 26913 | 19806 |
| $R1/wR2$ [$I > 2\sigma(I)$] | 0.0579/0.1418 | 0.0382/0.0923 |
| $R1/wR2$ (all data) | 0.0831/0.1542 | 0.0671/0.1014 |

CCDC-743275 (for **2**) and -743274 (for **3**) 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.

**General Procedure for the Determination of Water Solubility:** Depending on the amount available, 10–20 mg of compound **9**, **10**, **13**, or **14** was placed in an Eppendorf tube. Then water (2 μL) was added and the mixture shaken manually. This procedure was repeated until the substance was completely dissolved.

## Acknowledgments

We thank Dr. Karl-Heinz Hellwich from the Beilstein Institute, Frankfurt/Main, Germany, for assigning systematic names to the carbohydrate-containing compounds. We thank Prof. Dr. Stefan Berger, Dr. Matthias Findeisen, and Dr. Lothar Hennig for their help with the NMR spectra, especially with the integratable $^{13}$C NMR spectra.

[1] a) M. F. Hawthorne, *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 950–984; b) A. H. Soloway, W. Tjarks, B. A. Barnum, F.-G. Rong, R. F. Barth, I. M. Codogni, J. G. Wilson, *Chem. Rev.* **1998**, *98*, 1515–1562; c) J. F. Valliant, K. J. Guenther, A. S. King, P. Morel, P. Schaffer, O. O. Sogbein, K. A. Stephenson, *Coord. Chem. Rev.* **2002**, *232*, 173–230.
[2] M. F. Hawthorne, M. W. Lee, *J. Neurooncol.* **2003**, *62*, 33–45.
[3] R. A. Bechtold, A. Kaczmarczyk, *J. Med. Chem.* **1975**, *18*, 371–376.
[4] J. J. Benedict, EP 0068584 A1, **1981**.
[5] M. W. Lee, K. Shelly, R. R. Kane, M. F. Hawthorne, *Advances in Neutron Capture Therapy 2006*, *Proceedings of ICNCT-12, Chemistry and Pharmacy* (Eds.: Y. Nakagawa, T. Kobayashi, H. Fukuda), **2006**, pp. 234–236.
[6] W. Tjarks, R. F. Barth, J. H. Rotaru, D. M. Adams, W. Yang, R. G. Kultyshev, J. Forrester, B. A. Barnum, A. H. Soloway, S. G. Shore, *Anticancer Res.* **2001**, *21*, 841–846.
[7] a) M. S. Wadhwa, K. G. Rice, *J. Drug Target.* **1995**, *3*, 111–127; b) H. Lis, N. Sharon, *Chem. Rev.* **1998**, *98*, 637–674; c) N. Yamazaki, S. Kojima, N. V. Bovin, S. André, S. Gabius, H.-J. Gabius, *Adv. Drug Delivery Rev.* **2000**, *43*, 225–244.
[8] B. Dean, H. Oguchi, S. Cai, E. Otsuji, K. Tashiro, S. Hakomori, T. Toyokuni, *Carbohydr. Res.* **1993**, *245*, 175–192.
[9] T. Peymann, D. Preusse, D. Gabel, in: *Advances in Neutron Capture Therapy*, vol. II, *Chemistry and Biology* (Eds.: B. Larsson, J. Crawford, R. Weinreich), **1997**, pp. 35–38.
[10] S. Stadlbauer, E. Hey-Hawkins, WO2009021978 (A2), **2009**.
[11] a) S. Stadlbauer, P. Welzel, E. Hey-Hawkins, *Inorg. Chem.* **2009**, *48*, 5005–5010; b) S. Stadlbauer, P. Lönnecke, P. Welzel, E. Hey-Hawkins, *Eur. J. Org. Chem.* **2009**, 6301–6310.
[12] L. I. Zakharkin, A. I. Kovredov, *Izv. Akad. Nauk SSSR, Ser. Khim.* **1973**, 1428.
[13] J. Müller, K. Base, T. F. Magnera, J. Michl, *J. Am. Chem. Soc.* **1992**, *114*, 9721–9722.
[14] X. Yang, W. Jiang, C. B. Knobler, M. D. Mortimer, M. F. Hawthorne, *Inorg. Chim. Acta* **1995**, *240*, 371–378.
[15] L. I. Zakharkin, A. I. Kovredov, *Zh. Obshch. Khim.* **1974**, *44*, 1840–1841.
[16] S. Stadlbauer, R. Frank, I. Maulana, P. Lönnecke, B. Kirchner, E. Hey-Hawkins, *Inorg. Chem.* **2009**, *48*, 6072–6082.
[17] a) Y. Hayakawa, M. Kataoka, R. Noyori, *J. Org. Chem.* **1996**, *61*, 7996–7997; b) Y. Hayakawa, R. Kawai, A. Hirata, J.-I. Sugimoto, M. Kataoka, A. Sakakura, M. Hirose, R. Noyori, *J. Am. Chem. Soc.* **2001**, *123*, 8165–8176.
[18] a) R. P. Iyer, L. R. Philipps, W. Egan, J. B. Regan, S. L. Beaucage, *J. Org. Chem.* **1990**, *55*, 4693–4696; b) R. P. Iyer, L. R. Philipps, W. Egan, J. B. Regan, S. L. Beaucage, *J. Am. Chem. Soc.* **1990**, *112*, 1253–1254.
[19] G. W. Daub, E. E. van Tamelen, *J. Am. Chem. Soc.* **1977**, *99*, 3526–3528.
[20] C. E. McKenna, M. T. Higa, N. H. Cheung, M.-C. McKenna, *Tetrahedron Lett.* **1977**, *2*, 155–158.
[21] V. Ya. Komarov, V. I. Zakharov, Yu. V. Belov, B. I. Ionin, *Zh. Obshch. Khim.* **1980**, *50*, 1262–1269.
[22] S. Berger, S. Braun, *200 and more NMR experiments*, Wiley-VCH, Weinheim **2004**.
[23] Y. Zhu, J. Zajicek, A. S. Serianni, *J. Org. Chem.* **2001**, *66*, 6244–6251.
[24] M. Hyodo, Y. Sato, S. Yamashita, A. Hattori, E. Kambe, M. Kataoka, Y. Hayakawa, *Tetrahedron* **2005**, *61*, 965–970.

[25] S. Budavari (Ed.), *The Merck Index*, 11th ed., Merck & Co. Inc., **1989**, p. 4238.
[26] S. Stadlbauer, P. Welzel, A. G. Beck-Sickinger, D. Gabel, E. Hey-Hawkins, unpublished results.
[27] *CrysAlis Pro*, data collection and data reduction software package, version 1.171.32.4 (release 27-04-2006 CrysAlis171.NET), Oxford Diffraction Ltd., Oxford.
[28] *SCALE3 ABSPACK*, Empirical absorption correction using spherical harmonics, included in CrysAlis Pro software; version 1.171.32.4 (release 27-04-2006 CrysAlis171.NET).
[29] *SHELX97* [includes SHELXS97, SHELXL97]: G. M. Sheldrick, *SHELX97*, *Programs for Crystal Structure Analysis* (release 97-2), University of Göttingen, Göttingen, **1997**.
[30] ORTEP3 for Windows: L. J. Farrugia, *J. Appl. Crystallogr.* **1997**, *30*, 565.

Received: February 16, 2010
Published Online: April 23, 2010