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Access to Carbaboranyl Glycophosphonates—An Odyssey

Sven Stadlbauer,[†] Peter Welzel,[‡,§] and Evamarie Hey-Hawkins[†,*]

[†]*Institut für Anorganische Chemie,* [‡]*Institut für Organische Chemie, Universität Leipzig, Johannisallee 29, 04103 Leipzig, Germany.* [§] *Deceased in July 2008—he will be missed.*

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Novel bis-phosphonate derivatives of carbaboranes, which might be potential boron-delivery agents for boron neutron capture therapy, are described. Conceivable synthetic routes which failed to give the desired compounds are discussed, and finally, a highly selective route to the target molecules is reported.

Introduction

Currently, the medical treatment of malignant tumors is accompanied by extremely negative side effects and inconvenience for the patient. A more comfortable approach for the selective destruction of tumor tissue is boron neutron capture therapy (BNCT), a powerful form of radiotherapy based on the 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, which are formed on absorption of a neutron by the ^{10}B nucleus, allow selective destruction of the tumor cells without affecting the surrounding healthy tissue. The major problem to date is the availability of boron compounds which exhibit the essentially high selectivity, water solubility, and low toxicity in high concentrations.[2] We have therefore devised efficient syntheses for novel boron compounds which contain phosphonato and galactosyl groups (Figure 1).[3] These compounds might be interesting candidates for future application in BNCT.

Experimental Section

Standard Schlenk and vacuum-line techniques were employed for all manipulations of air- and moisture-sensitive compounds. The NMR spectra were recorded with an AVANCE DRX 400 spectrometer (Bruker): ^{1}H NMR (400.13 MHz), internal standard solvent, external standard TMS; ^{31}P NMR (161.98 MHz), external standard 85% H_3PO_4; ^{13}C NMR (100.16 MHz), internal standard solvent, external standard TMS; ^{11}B NMR (128.38 MHz), external standard $BF_3 \cdot OEt_2$. The solvents were dried and saturated with nitrogen. Diethyl chlorophosphite is commercially available (Sigma Aldrich) and was distilled prior to use. *Ortho*-Carbaborane and *meta*-Carbaborane are commercially available. The mass spectra were recorded on a Bruker Daltonics 7 Tesla APEX II spectrometer (ESI) or on a Finnigan MAT MAT8200 spectrometer (EI). 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 on a VARIO EL (Heraeus).

Compound 2. A total of 5.5 mL (13.9 mmol, 2.52 M) of ^{n}BuLi in *n*-hexane was added slowly to an ice-bath-cooled solution of 1.0 g (13.9 mmol) of *ortho*-carbaborane in 20 mL of diethyl ether. The resulting suspension was stirred at room temperature for 2 h. The dilithiocarbaborane slurry was added slowly through a canula to an ice-bath-cooled solution of 2.2 mL (15.2 mmol) of diethyl chlorophosphite in 20 mL of diethyl ether. After complete addition, the mixture was stirred for 30 min in an ice bath and then at room temperature overnight. Lithium chloride was removed by filtration, and diethyl ether was removed under vacuum conditions. The viscous residue was distilled under vacuum conditions. At a 60 °C bath temperature and 1.8×10^{-2} mbar of pressure, the side products could be removed. The product remained as a yellow oil. Yield of **1**: 2.06 g (77%). ^{1}H NMR (C_6D_6): δ 3.73 (q, 8 H, OCH_2CH_3); 3.5 − 1.8 (m, 10 H, $B_{10}H_{10}$); 1.07 (t, 12 H, OCH_2CH_3). ^{31}P{^{1}H} NMR (C_6D_6): δ 150.3 (s).

Compound 3. A total of 0.35 mL (4.32 mmol) of sulfuryl chloride in 5 mL of *n*-hexane was added slowly to an ice-bath-cooled solution of 0.83 g (2.16 mmol) of **1** in 5 mL of *n*-hexane. After complete addition, the reaction mixture was stirred at room temperature for 2 h. All volatile compounds were removed in a vacuum. The yellow oily residue contains the product at a purity of ca. 96%, according to the ^{31}P{^{1}H} NMR spectrum. Yield of **3**: 0.82 g (96%). Due to the mixture of diastereomers, all signals in the ^{1}H and ^{13}C NMR occur twice. ^{1}H NMR (C_6D_6): δ 3.90 (m, 4 H, OCH_2CH_3); 3.6−1.6 (m, 10 H, $B_{10}H_{10}$); 0.89 (m, 6 H, OCH_2CH_3). ^{13}C{^{1}H} NMR (C_6D_6): δ 76.4 (d, $C_2B_{10}H_{10}$, $^{1}J_{CP}$ = 153.8 Hz); 76.2 (d, $C_2B_{10}H_{10}$, $^{1}J_{CP}$ = 153.2 Hz); 68.0 (d, OCH_2CH_3); 67.7 (d, OCH_2CH_3); 15.2

*To whom correspondence should be addressed. E-mail: hey@uni-leipzig.de.

(1) (a) Hawthorne, M. F. *Angew. Chem., Int. Ed.* **1993**, *32*, 950–984. (b) Soloway, A. H.; Tjarks, W.; Barnum, B. A.; Rong, F.-G.; Barth, R. F.; Codogni, I. M.; Wilson, J. G. *Chem. Rev.* **1998**, *98*, 1515–1562. (c) Valliant, J. F.; Guenther, K. J.; King, A. S.; Morel, P.; Schaffer, P.; Sogbein, O. O.; Stephenson, K. A. *Coord. Chem. Rev.* **2002**, *232*, 173–230.
(2) Hawthorne, M. F.; Lee, M. W. *J. Neurooncol.* **2003**, *62*, 33–45.
(3) Stadlbauer, S.; Hey-Hawkins, E. PCT/EP2008/060649.

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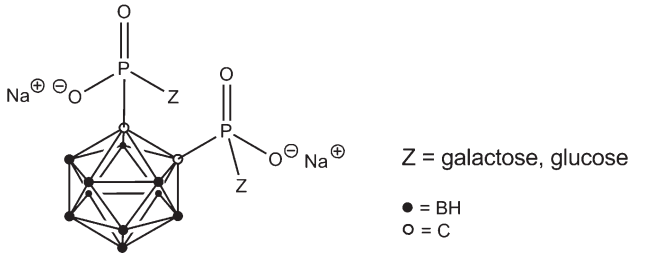


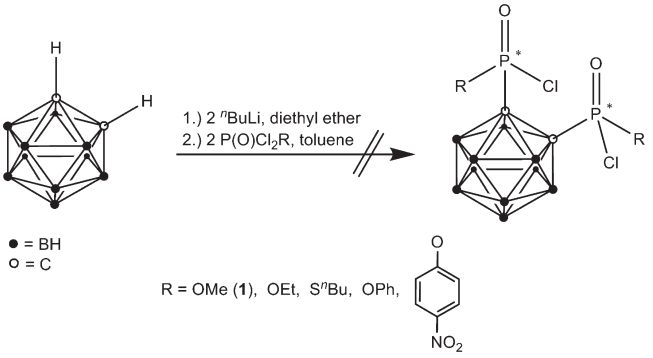
Figure 1. Target molecule.

(m, OCH_2CH_3). $^{31}P\{^1H\}$ NMR (C_6D_6): δ 15.6 (s) and 15.1 (s) (*rac* and *meso* form). ^{11}B NMR (C_6D_6): δ 2.0 (d, br, 2 B, $C_2B_{10}H_{10}$, $^1J_{BH}$ = 153.1 Hz); −7.4 (d, 3 B, $C_2B_{10}H_{10}$, $^1J_{BH}$ = 153.3 Hz); −8.8 (d, br, 5 B, $C_2B_{10}H_{10}$, $^1J_{BH}$ = 156.5 Hz). MS (EI$^+$, 14 eV): *m*/*z* (%) 397.1 (15) $[M]^+$; 396 (15) $[M - H]^+$; 362.1 (57) $[M - Cl]^+$, 334.1 (61) $[M - OEt - H_2O]^+$.

Compound 19. A total of 19.0 mL (45.4 mmol, 2.39 M) of ^{n}BuLi in *n*-hexane was slowly added to an ice-bath-cooled solution of 3.25 g (22.5 mmol) of *meta*-carbaborane in 100 mL of diethyl ether. The suspension was allowed to warm to room temperature and then stirred for 2 h. The dilithiocarbaborane slurry was added slowly through a canula to an ice-bath-cooled solution of 6.45 g (45.6 mmol) of *N*,*N*-dimethylamido methyl chlorophosphite in 60 mL of diethyl ether. After complete addition, the mixture was stirred for 30 min in an ice bath and then at room temperature overnight. Lithium chloride was removed by filtration and diethyl ether removed in a vacuum. The viscous residue was distilled under vacuum conditions. At a bath temperature of 75 °C and 3 × 10^{-3} mbar of pressure, the side products could be removed. The product distilled at 1 × 10^{-6} mbar and a bath temperature of 80 °C as a pale yellow oil. Yield of **19**: 4.0 g (50%). ^1H NMR (C_6D_6): δ 3.5−1.7 (m, 10 H, $B_{10}H_{10}$); 3.13 (d, 6 H, OCH_3, $^3J_{HP}$ = 13.6 Hz); 2.43 (d, 12 H, $N(CH_3)_2$, $^3J_{HP}$ = 8.4 Hz). $^{13}C\{^1H\}$ NMR (C_6D_6): δ 81.0 (d, $C_2B_{10}H_{10}$, $^1J_{CP}$ = 77.8 Hz); 54.4 (d, OCH_3, $^2J_{CP}$ = 20.8 Hz); 36.3 (s, br, $N(CH_3)_2$). $^{31}P\{^1H\}$ NMR (C_6D_6): δ 139.6 (s). ^{11}B NMR (C_6D_6): δ −4.2 (d, 2 B, $C_2B_{10}H_{10}$, $^1J_{BH}$ = 147.1 Hz); −9.0 (d, 3 B, $C_2B_{10}H_{10}$, $^1J_{BH}$ = 165.1 Hz); −10.5 (d, 3 B, $C_2B_{10}H_{10}$, $^1J_{BH}$ = 200.8 Hz); −14.2 (d, 2 B, $C_2B_{10}H_{10}$, $^1J_{BH}$ = 168.7 Hz). MS (EI$^+$, 70 eV): *m*/*z* (%) 354.3 (100) $[M]^+$, 323.3 (10) $[M - OMe]^+$, 310.2 (15) $[M - NMe_2]^+$. IR (KBr, $\tilde{\nu}$ in cm^{-1}): 2929 (s), 2892 (s), 2833 (m), 2801 (m) ν(C−H); 2601 (s) ν(B−H). Elem anal. calcd for $C_8H_{28}N_2O_2P_2B_{10}$: C, 27.11%; H, 7.96%; N, 7.90%. Found: C, 27.37%; H, 7.92%; N, 7.91%.

Compound 20. A total of 0.73 g (2.06 mmol) of **19** was dissolved in 10 mL of acetonitrile. Then, 7.7 mL (6.16 mmol, 0.8 M) of a solution of 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**6**) in acetonitrile and 1.38 g (5.15 mmol) of benzimidazolium triflate were added. The reaction mixture was stirred for 3 h at room temperature. Then, 0.71 mL (6.6 mmol) of a 70% solution of *tert*-butyl hydroperoxide in water was added and the mixture stirred for 30 min at room temperature. The reaction mixture was diluted with 30 mL of ethyl acetate and washed three times with brine. The organic layer was dried with $MgSO_4$ and then concentrated to give a honeylike residue, which was purified by column chromatography on silica gel with a 1:1 mixture of ethyl acetate and *n*-hexane. Further purification was performed by preparative HPLC (CH_3CN 100%; R_t = 8.6 min). Yield of **20**: 0.5 g (29%). ^1H NMR ($CDCl_3$): δ 5.56 (m, 2 H, H-1α); 4.62 (m, 2 H, C*H*CO); 4.33 (m, 2 H, C*H*CO); 4.21 (m, 2 H, C*H*O); 4.15 (m, 2 H, C*H*CO); 4.10 (m, 4 H, CH_2O); 3.72 (d, 6 H, $POCH_3$, $^3J_{HP}$= 11.20 Hz); 3.5−1.8 (m, br, 10 H, $B_{10}H_{10}$); 1.54 (s, 6 H, CH_3); 1.45 (s, 6 H, CH_3); 1.34 (s, 12 H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 108.5−109.6 (C_{quart} of isopropylidene); 96.2 (*C*-1α); 72.2 (*C*-5, $^3J_{CP}$ n.d.); 72.1 and 72.0 (*C*-3 and *C*-4); 71.8 (*C*-2); 68.8 (*C*-6, $^2J_{CP}$ n.d.); 67.6 (d, $C_2B_{10}H_{10}$, $^1J_{CP}$ = 171.6 Hz); 56.3 (d, OCH_3, $^2J_{CP}$ = 6.9 Hz); 27.5−25.8 (CH_3). $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ 10.5 (s); 10.4 (s); 10.0 (s); 9.9 (s) (4 diastereomers). ^{11}B NMR ($CDCl_3$): δ −9.9 (s, br, 10 B, $C_2B_{10}H_{10}$, $^1J_{BH}$ n.d.). MS (ESI positive in CH_3CN): *m*/*z* 839.4 $[M + Na]^+$. IR (KBr, $\tilde{\nu}$ in cm^{-1}): 2990 (s) ν(C−H); 2625 (s) ν(B−H). Elem anal. calcd for $C_{28}H_{54}O_{16}P_2B_{10}$: C, 41.17%; H, 6.66%. Found: C, 40.98%; H, 6.60%.

Scheme 1. Attempted Synthesis of **1** According to ref [6]



Results and Discussion

Although the synthesis of phosphonates is well-established, the route to these target compounds (Figure 1) turned out to be challenging, which may be traced back to the presence of the carbaborane cluster. We herein report approaches toward these compounds which seemed logical at first glance but were found to fail. Finally, we present the successfully established synthetic route.

We attempted the synthesis of sugar-modified carbaboranyl bis-phosphonates starting from the respective chloro derivative and a protected sugar (with one hydroxyl group still available). As a phosphonate protecting group, an alkyl ester, for example, methyl or ethyl ester, is used. The subsequent deprotection of the alkyl ester groups is readily achieved with triethylamine/thiophenol[4] or trimethylsilylbromide.[5] The synthesis of methyl chloro derivative **1** was published in 2003 (Scheme 1).[6] However, following that procedure, we could neither obtain the desired compound nor observe the reported signal at 8.7 ppm in the $^{31}P\{^1H\}$ NMR spectrum; instead, numerous signals were found between +6 and −5 ppm. Due to the two chiral phosphorus centers, two diastereomers are expected and should result in two signals. The isolation of **1**, according to the literature, by aqueous workup of the reaction mixture followed by recrystallization failed. Similar results were obtained with various substituents at the phosphorus atom (Scheme 1).

Due to this unexpected outcome, we chose a different strategy for the synthesis of bis-chlorophosphonates. In 1975, Godovikov et al. published a synthetic route for carbaboranyl halophosphonates starting from a monophosphonite, which can be transformed into the corresponding halophosphonate by using bromine, chlorine, or sulfuryl chloride.[7]

(4) Daub, G. W.; van Tamelen, E. E. *J. Am. Chem. Soc.* **1977**, *99*, 3526–3528.
(5) McKenna, C. E.; Higa, M. T.; Cheung, N. H.; McKenna, M.-C. *Tetrahedron Lett.* **1977**, *2*, 155–158.
(6) Vyakaranam, K.; Rana, G.; Delaney, S.; Ledger, S.; Hosmane, N. S. *Inorg. Chem. Commun.* **2003**, *6*, 654–657.
(7) (a) Godovikov, N. N.; Degtyarev, A. N.; Bregadze, V. I.; Kabachnik, M. I. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1977**, 682–684. (b) Degtyarev, A. N.; Godovikov, N. N.; Bregadze, V. I.; Kabachnik, M. I. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1975**, 2568–2573.

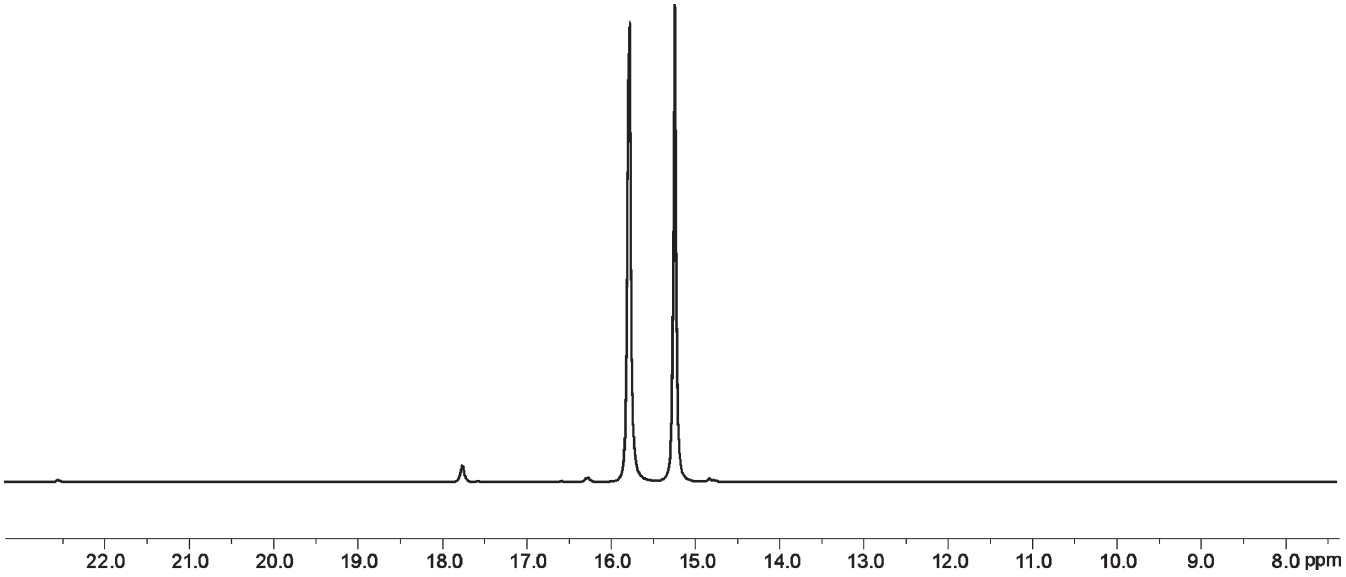
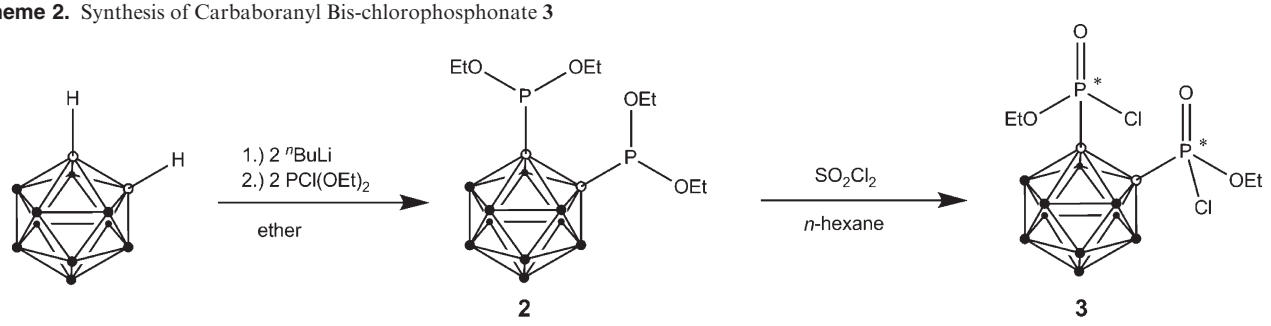
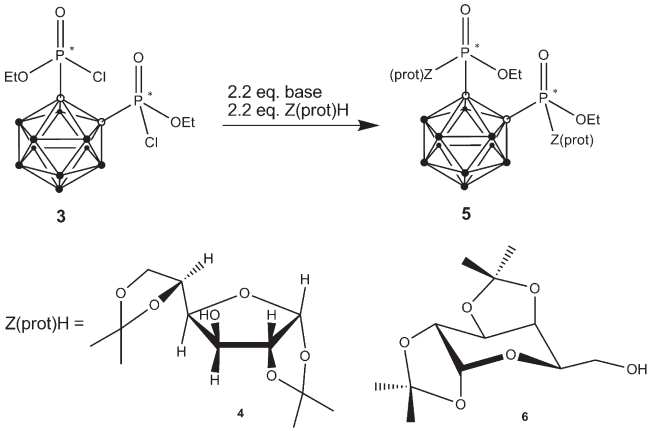


Figure 2. $^{31}P\{^{1}H\}$ NMR spectrum of *rac*/*meso*-1,2-[(Cl)(EtO)(O)P]$_2$C$_2$B$_{10}$H$_{10}$ (**3**) in C_6D_6.

Scheme 2. Synthesis of Carbaboranyl Bis-chlorophosphonate **3**



Scheme 3. Glycosylation of **3** with Protected Glucose **4**



This method was employed for the carbaboranyl bis-phosphonates. In the first step, carbaboranyl bis-phosphonite **2** was prepared according to a slightly modified procedure published by Teixidor et al.[8] In a Michaelis-Arbuzov type reaction, **2** was converted to the corresponding bis-phosphonate **3** by using sulfuryl chloride (Scheme 2).

Compound **3** was obtained at a purity of about 96% as a mixture of *rac* and *meso* isomers. The compound is a pale yellow oil, which decomposes vigorously in water, DMSO, or DMF, in contrast to the previous findings.[6] All further attempts to purify the compound failed due to its high reactivity. Storage at −20 °C for three months resulted in significant decomposition of the compound. Separation of the *rac* and *meso* forms was not possible. Therefore, the compound was used as a mixture of diastereomers for further investigations. Due to the presence of both diastereomers, two signals at δ_P = 15.4 ppm were observed in the $^{31}P\{^{1}H\}$ NMR spectrum (Figure 2). The $^{1}J_{CP}$ coupling constant of 153 Hz for both diastereomers is in the typical range for pentavalent phosphorus compounds.[9] The identity of precursor **3** was additionally proved by mass and IR spectra.

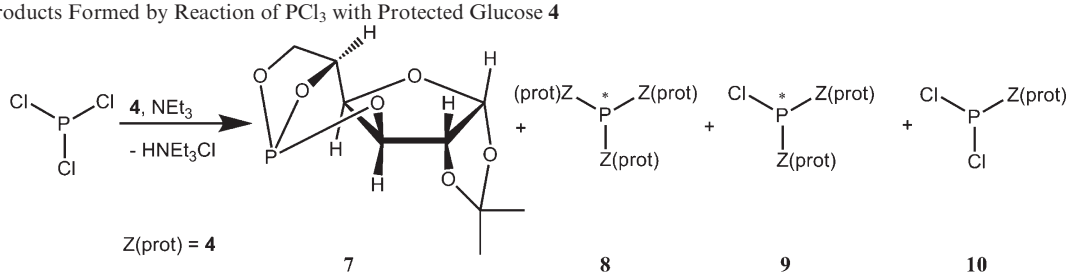
For the subsequent glycosylation of **3**, reactions between the protected glucose **4** and various amine bases were examined (Scheme 3).

Under various conditions (see Table 1), only decomposition was observed. If **3** is mixed with the amine base in the absence of the sugar, the same decomposition products are observed in the $^{31}P\{^{1}H\}$ NMR spectrum. It was concluded that addition of the base immediately leads to decomposition of bis-phosphonate **3**. Thus, glycosylation was attempted in the absence of the base. However, no conversion was detected, even after one week at room temperature, and therefore metalated sugars were used to avoid decomposition. Thus, **3** was treated with the lithium and sodium salts of protected glucose **4** and with the lithium and sodium salts of

(8) Teixidor, F.; Vinas, C.; Abad, M. M.; Nunez, R.; Kivekäs, R.; Sillanpää, R. *J. Organomet. Chem.* **1995**, *503*, 193–203.

(9) Berger, S.; Braun, S.; Kalinowski, H.-O. In *NMR-Spektroskopie von Nichtmetallen, Band 3: 31P-NMR-Spektroskopie*; Thieme: Stuttgart, 1993.

Scheme 4. Products Formed by Reaction of PCl_3 with Protected Glucose **4**



Scheme 5. Synthesis of Carbaboranyl Bis-phosphonites **11** and **12**

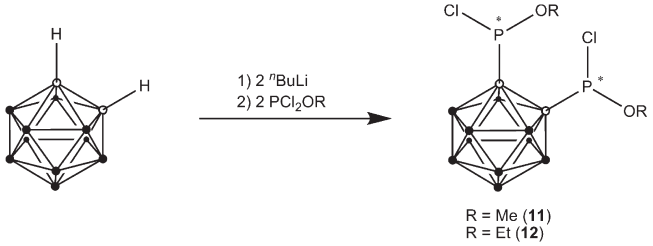


Table 1. Amine Bases and Solvents Used for the Attempted Glycosylation Reaction[a]

amine base	additive	solvent	temperature
triethylamine		Et_2O	−80 °C
triethylamine		THF	0 °C
triethylamine	4-DMAP	DCM	0 °C
triethylamine	1*H*-1,2,4-triazole	DCM	0 °C
4-DMAP		DCM	0 °C
1*H*-1,2,4-triazole		DCM	0 °C
N,*N* diisopropyl ethylamine		THF	0 °C
1,8-diazabicyclo [5.4.0]undec-7-ene		THF	−60 °C

[a] 4-DMAP = 4-dimethylaminopyridine, DCM = dichloromethane.

protected galactose **6**. Again, numerous decomposition products were observed in the $^{31}P\{^1H\}$ NMR spectrum. Our findings indicate that pentavalent phosphorus derivatives of carbaboranes are not suitable for glycosylation, although chlorophosphonates are well-known to undergo smooth substitution with O nucleophiles. We assume that the carbaborane moiety is responsible for this behavior.

An alternative strategy included the use of the more reactive trivalent phosphorus compounds for glycosylation followed by oxidation to obtain the desired glycophosphonates. In a first approach, a phosphite-functionalized sugar was prepared and subsequently treated with the dilithiated carbaborane. Nifantyev et al. published a synthesis of **10** from phosphorus trichloride and **4** in the presence of triethylamine (see Scheme 4).[10] The $^{31}P\{^1H\}$ NMR spectrum shows an intense signal for phosphite **7** at ca. 117 ppm, a small signal for trisubstituted phosphite **8** at ca. 146 ppm, two very small signals at 155 ppm for disubstituted phosphite **9**, and a very small signal for the desired product **10** at 167 ppm. Separation of **10** from the mixture was not possible.

The reaction was also carried out with the sodium salts of **4** and **6**. In this case, phosphite **7** was smoothly formed, as indicated by ^{31}P NMR spectroscopy. Nifantyev et al. reported that **10** can be rearranged to **7** by heating in dioxane at 80 °C. Obviously, the rearrangement takes place even at room temperature. An analogous reaction with methyl dichlorophosphite instead of phosphorus trichloride led to similar results. These findings clearly show that the preparation of glycophosphonites is accompanied by serious problems and cannot be used for reactions with carbaboranes.

An alternative approach is preparation of halophosphonite-functionalized carbaboranes followed by glycosylation. On the basis of this method, compounds **11** and **12** were synthesized according to Scheme 5. Despite our experience with the synthesis of menthyl- and borneyl-substituted bis-phosphonites,[11] both **11** and **12** were only formed in ca. 50% yield, as estimated from ^{31}P NMR spectra of the reaction mixture. A relatively large amount of byproducts and phosphorus trichloride were formed. Isolation of both compounds by recrystallization failed, because only the side products crystallized and the products gradually decomposed to the side products even at −20 °C.

Replacement of the alkoxyl groups in **11** and **12** by amido groups led to the novel amidophosphonites **13**, **14**, and **15** (Figure 2), whose syntheses will be published by our group.[12] These compounds were expected to react with **6** under salt elimination to form the desired galactosyl-functionalized amidophosphonites. Hence, the galactosylation was studied with the *ortho*-carbaborane derivatives **13**, **14**, and **15** (Figure 3).

In the cited reference,[12] we showed that methanolysis of chlorophosphonite-functionalized *ortho*-carbaboranes is hindered due to strong P···P interactions. Hence, we expected the same problems for the galactosylation of these compounds. Nevertheless, we studied the reaction of **13**, **14**,

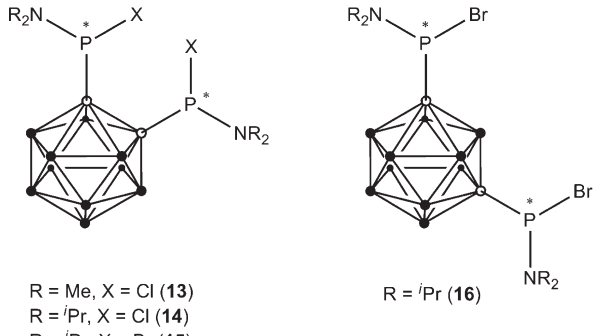


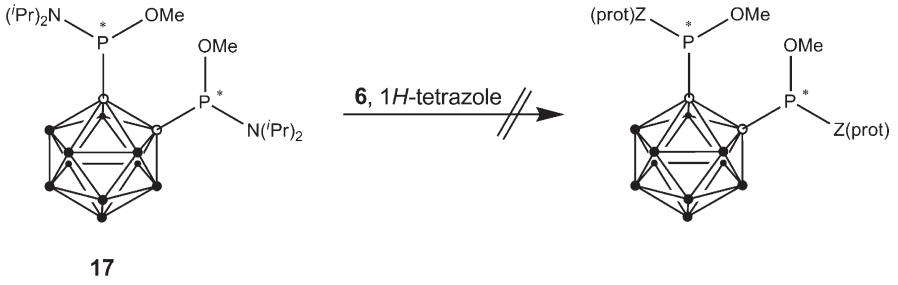
Figure 3. Amidophosphonite-substituted *ortho*- and *meta*-carbaborane derivatives.

(10) Nifantyev, E. E.; Koroteev, M. P.; Lysenko, S. A.; Rumantseva, S. A.; Kochetkov, N. K. *Carbohydr. Res.* **1982**, *111*, 67–73.

(11) (a) Bauer, S.; Lönnecke, P.; Hey-Hawkins, E. *Abstracts of Euroboron 4, Poster presentation 75PO*; Universität Bremen: Bremen, Germany, 2007; p 156. (b) Bauer, S.; Tschirschwitz, S.; Lönnecke, P.; Frank, R.; Kirchner, B.; Clarke, M. L.; Hey-Hawkins, E. *Eur. J. Inorg. Chem.* Manuscript accepted.

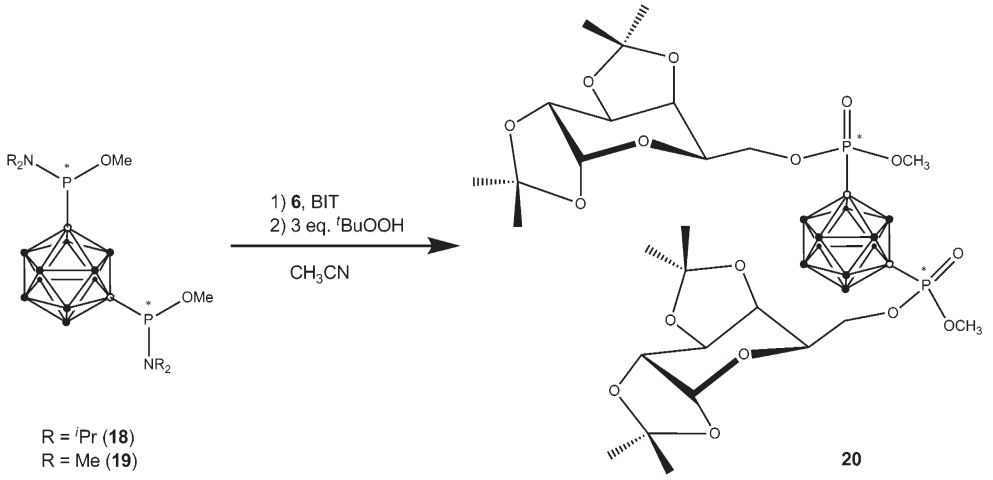
(12) Stadlbauer, S.; Frank, R.; Maulana, I.; Lönnecke, P.; Kirchner, B.; Hey-Hawkins, E. *Inorg. Chem.* Manuscript submitted.

Scheme 6. Attempted Condensation of **17** with Galactose **6**



17

Scheme 7. Condensation of *meta*-Carbaboranyl Bis-phosphonites **18** and **19** with **6**



Promoter: 1*H*-tetrazole, benzimidazolium triflate

and **15** with an excess of protected galactose **6** and various amine bases or by using the sodium or potassium salt of **6**. Decomposition occurred in all cases. On the basis of the results of theoretical calculations on the methanolysis and according to the experimental observation that *meta*-carbaboranyl bis-phosphonites underwent methanolysis smoothly,[12] we studied the reaction with the *meta*-carbaborane derivative **16** (Figure 3). The reaction was performed by adopting the phosphite methodology, which has been proved to be successful for the synthesis of mono-,[13] di-, and trisaccharide analogues[14] of moenomycin. Surprisingly, the reaction with **6** under promotion by 1*H*-1,2,4-triazole and pyridine did not lead to the expected bis-glycophosphonite but to the formation of several decomposition products. Triethylamine as a base also induced decomposition. Maybe the sterically hindered galactose can be blamed for this result.

The activation of an amido group by a weak acidic catalyst such as 1*H*-tetrazole and subsequent substitution by a nucleophilic hydroxyl group, for example, from a nucleoside, are widely used in the synthesis of oligonucleotides.[15] We adopted this method for the synthesis of glycophosphonate-substituted carbaboranes. Compound **17** was chosen for the investigation of galactosylation with **6** under catalysis by 1*H*-tetrazole (Scheme 6).

The reaction was investigated in dichloromethane and acetonitrile. In both solvents, even at reflux for 24 h, no reaction took place. Having conducted the reaction in DMF at 140 °C for 2 h, quantitative $P-C_{carbaborane}$ bond disruption was observed, as indicated by formation of a phosphite triester and *ortho*-carbaborane; the latter could be isolated in nearly quantitative yield by column chromatography. Similar results were obtained when methanol was used instead of **6**. These observations can be explained in analogy to the inhibited methanolysis of the carbaboranyl bis-chlorophosphonites. It can be assumed that the nucleophilic attack of the tetrazolide anion at the phosphorus atom is impeded due to strong $P\cdots P$ interaction. The $P-C_{Carbaborane}$ bond was more likely to break than the substitution to occur. In accordance with this theory, a *meta*-carbaborane derivative should react without any problems. Therefore, the galactosylation of the *rac*/*meso* mixture of bis-phosphonite **18**[12] with a slight excess of **6** and 1*H*-tetrazole was investigated (Scheme 7). After the reaction mixture was heated for several hours under reflux, four small signals at ca. 163 ppm in the $^{31}P\{^1H\}$ NMR spectrum were observed. These signals can be assigned to the product, which forms four diastereomers due to the chirality of both phosphorus atoms and sugar units. The reaction was found to stagnate at about 60% conversion even when a large excess of 5 equiv of **6** and the promoter was used at reflux after 60 h. Heating the mixture in a microwave oven gave a similar conversion after 9 h. Due to the long reaction time at high temperatures, a larger amount of byproducts was detected in both cases. We supposed that the acidity of the promoter was not sufficient. 5-(4-Nitrophenyl)tetrazole (5-NPT) was reported to be more effective, due

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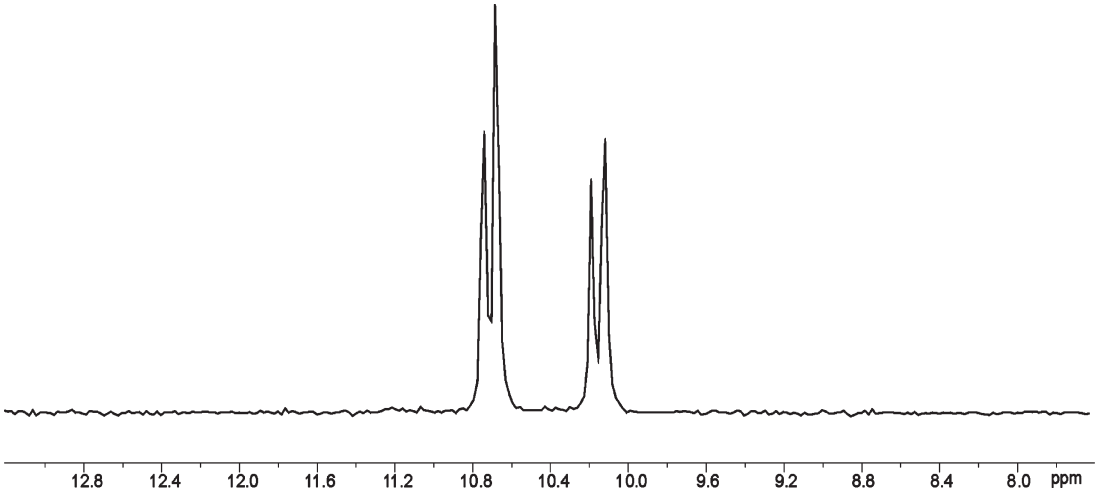
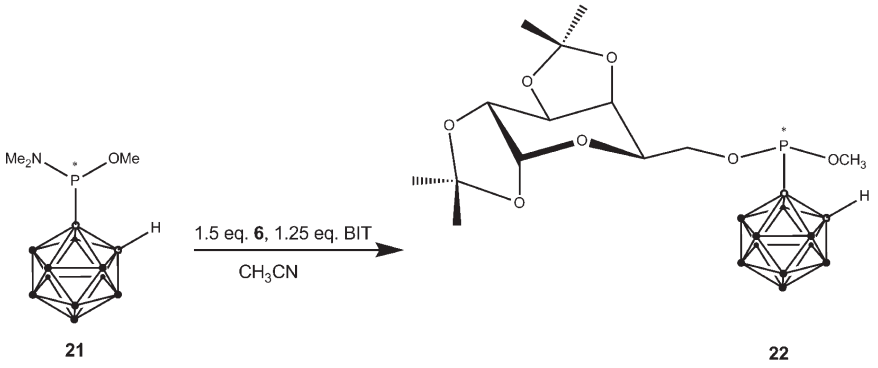


Figure 4. $^{31}P\{^{1}H\}$ NMR spectrum of **20** in $CDCl_3$.

Scheme 8. Galactosylation of *ortho*-Carbaboranyl Phosphonite **21**



to its higher acidity, by Froehler and Matteuci[16] and by Pon.[17] We investigated galactosylation with promotion by 5-NPT but found only quantitative decomposition. Noyori et al. reported that azolium salts, especially *N*-phenylimidazolium triflate and benzimidazolium triflate (BIT), are highly effective promoters for DNA and RNA oligomer synthesis.[18] Performing the condensation of *rac*/*meso*-**18** and 3 equiv of **6** with promotion by BIT reduces the reaction time to 8 h under reflux or 3 h in a microwave oven, accompanied by a decreased extent of side reactions. For further optimization, the bulky *N*,*N*-diisopropylamido group in **18** was replaced by the sterically less-demanding *N*,*N*-dimethylamido group. Condensation of *rac*/*meso*-**19** with **6** smoothly led to the desired bis-glycophosphonite within 3 h at room temperature. Oxidation in situ with *tert*-butyl hydroperoxide gave the target carbaboranyl bis-phosphonate **20** as a white foam in 29% yield after isolation by column chromatography and preparative HPLC. For the target bis-phosphonate **20**, four signals can be observed in the $^{31}P\{^{1}H\}$ NMR spectrum due to the four possible diastereomers (Figure 4).

In principle, the reactivity of the *meta*-carbaborane derivatives is in excellent agreement with the theory of P···P interactions. Due to the absence of a second phosphorus atom, the monosubstituted *ortho*-carbaborane derivative **21** should react smoothly as well because of the missing P···P interactions. Indeed, **21** underwent condensation with **6** in acetonitrile with promotion by BIT (NMR experiment). Over 6 h of galactosylation at room temperature smoothly led to the corresponding galactosyl phosphonite **22** (Scheme 8), which exhibits two signals at ca. 156 ppm in the $^{31}P\{^{1}H\}$ NMR spectrum.

Conclusion

We have developed a synthetic route to glycophosphonate derivatives of carbaboranes, which might be useful as boron-delivery agents for BNCT. Synthetic routes using chlorophosphonate and chlorophosphonite derivatives of carbaboranes failed to give the desired compounds. Adopting the phosphoramidite methodology was successful in the case of the *meta*-carbaboranes. Further optimization by using an *N*,*N*-dimethylamido group at the phosphorus atom and benzimidazolium triflate as a promoter provides highly selective access to the target compounds. The failure in the case of the *ortho*-carbaborane derivatives can be traced back to strong P···P interactions.

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