Preparation of a New Carboranyl Lactoside for the Treatment of Cancer by Boron Neutron Capture Therapy: Synthesis and Toxicity of Fluoro Carboranyl Glycosides for in vivo ^{19}F-NMR Spectroscopy

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Dedicated to Professor Horst Kessler on the occasion of his 60th birthday

Abstract: The synthesis of new *ortho*-carboranyl lactosides **8**, **17**, **19** and glucosides **22** and **23** for the use in boron neutron capture therapy is reported. Carboranyl lactosides **17** and **19** as well as the glucosides **22** and **23** contain a fluorine atom to allow a noninvasive determination of these compounds in tumor cells by ^{19}F-NMR spectroscopy. In cloning efficiency tests on human bronchial carcinoma cells the carboranyl lactosides **17** and **19** displayed almost no cytotoxicity. Thus, the considerably cytotoxic carboranyl alcohol **11** is detoxified when linked to a sugar moiety such as in carboranyl glucoside **22**.

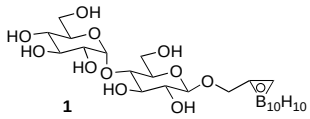
Keywords: antitumor agents · boron neutron capture therapy · carboranes · drug research · glycosides

Introduction

The limited therapeutic spectrum of available cytostatics is a problem in modern cancer therapy. Serious side effects can arise, which are dose limiting and often lead to a discontinuation of the treatment. One promising approach to selective cancer therapy with growing importance is the boron neutron capture therapy (BNCT).[1] This method makes use of the cytotoxic boron neutron capture reaction $^{10}B(^{1}n,^{4}He)^{7}Li$ and depends on a selective accumulation of boron in the malignant cells (20–30 μg boron per g tumor tissue). Substituted carborane derivatives are suitable as a result of their high boron content and their stability in aqueous media. However, most of these compounds cannot be employed in therapy because of their high toxicity and low water solubility.

In order to improve the water solubility carboranes were linked to sugar units.[2] Thus, recently we have reported on a short synthesis of glycosides of *ortho*-carborane (1,2-dicarba-*closo*-dodecaborane) such as of maltose **1** which are accumulated at tumor cells and exhibit a high water solubiltiy and low toxicity even in high concentrations.[3]

It is now our intention to improve the selectivity by inducing a predominant intake of the carboranes into malignant cells. We assume that the hydrophilic carboranyl glycosides do not penetrate the cell membrane but are accumulated within the glycerophospholipid bilayer of the membrane. This behavior is well known for gangliosides;[4] their lipophilic ceramide moiety is inserted into the cell membrane whereas the sugar part stays outside. Since the effectiveness of BNCT strongly depends on the distance of ^{10}B from the cell nucleus, such carboranyl glycosides being located within the cell membrane should be less toxic under irradiation with a neutron beam.[1e] However, if the sugar could be removed selectively from the carborane moiety, the lipophilic boron compound would enter into the cell. A selective removal of the sugar moieties could be obtained by using conjugates of glycohydrolases and monoclonal antibodies which bind to tumor-associated antigens.[5] Another problem of BNCT is the lack of a precise and simple method for the determination of the concentration of the boron content in a cell, since boron is not readily noninvasively detectable in tumor tissue by traditional diagnostic techniques such as standard magnetic resonance imaging protocols. This fact renders the timing BNCT quite difficult.[6] In contrast, the ^{19}F nucleus is much more suitable for in vitro and in vivo NMR spectroscopy, because of its high receptivity for detection, wide chemical shift dispersion and its absence from most living tissue.[7] Here we describe the synthesis of a novel carboranyl lactoside **8**, in which the carborane unit is linked to a hexyl chain. Furthermore, we have developed a synthesis of carboranyl glycosides of glucose and lactose **17**, **19**, **22**, and **23** containing a fluoro atom to allow the noninvasive detection of the glycosides in tumor tissue by ^{19}F-NMR spectroscopy.



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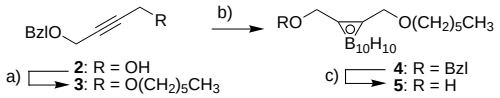
Results and Discussion

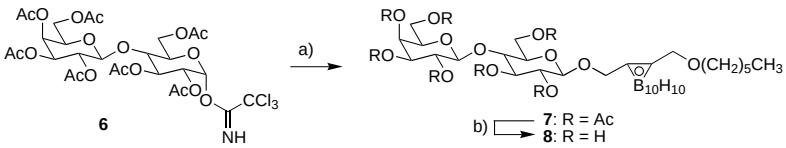
Synthesis: For the synthesis of the carboranyl glycosides **8**, **17**, **19**, **22**, and **23** protected alkynols were prepared, which after reaction with decaborane(14)[8] and deprotection led to the corresponding carboranyl alcohols. Reaction of the trichloroacetimidates of glucose and lactose[9] followed by solvolysis gave the desired glycosides.

For the synthesis of carboranyl lactoside **8**, ether **3** was synthesized in 81 % yield from alcohol **2**[10] and 1-bromohexane using potassium hydroxide in dimethyl sulfoxide.[11] Decaborane(14) was heated in acetonitrile for 30 min to afford the $B_{10}H_{12}(CH_3CN)_2$ adduct,[12] which was treated with **3** to give carboranyl ether **4** in 50 % yield. Hydrogenolytic cleavage of the *O*-benzyl group yielded alcohol **5** in 68 % yield (Scheme 1).



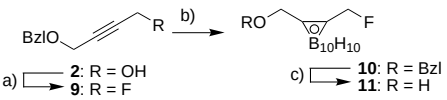
Scheme 1. Synthesis of carboranyl alcohol **5**. Reagents: a) 1-bromohexane, KOH, DMSO, 81 %; b) $B_{10}H_{14}$, CH_3CN, then **3**, toluene, 50 %; c) H_2, Pd/C, ethyl acetate, methanol, 68 %.

Reaction of lactose trichloroacetimidate **6** and carboranyl alcohol **5** in dichloromethane promoted by $BF_3 \cdot Et_2O$ gave the carboranyl-β-lactoside **7** stereoselectively in 76 % yield. Solvolysis of the acetyl groups with sodium methoxide in methanol led to the desired carboranyl lactoside **8** in 66 % yield (Scheme 2).



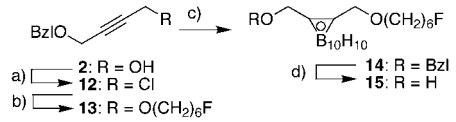
Scheme 2. Synthesis of carboranyl lactoside **8**. Reagents: a) **5**, $BF_3 \cdot Et_2O$, CH_2Cl_2, 76 %; b) NaOMe, MeOH, 66 %.

For the synthesis of the fluoro carboranyl glycosides, fluoro alkyne **9** was synthesized from alcohol **2** using *N*,*N*-diisopropyl-1-fluoro-2-methylpropenamine[13] in dichloromethane in 71 % yield. Reaction with decaborane(14) gave **10** in 61 % yield which was deprotected to yield the fluoro carboranyl alcohol **11** in 81 % yield (Scheme 3).



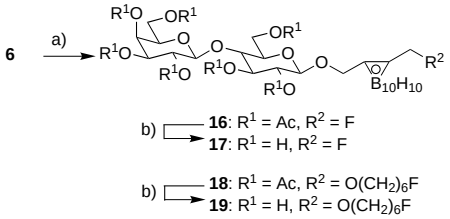
Scheme 3. Synthesis of fluoro carboranyl alcohol **11**. Reagents: a) *N*,*N*-diisopropyl-1-fluoro-2-methylpropenamine, CH_2Cl_2, 71 %; b) $B_{10}H_{14}$, CH_3CN, then **9**, toluene, 61 %; c) H_2, Pd/C, ethyl acetate, methanol, 81 %.

To enhance the incorporation of the carborane moiety into the cell membrane according to our concept we introduced a lipophilic side chain containing a fluoro atom. For this purpose alcohol **2** was transformed into the chloride **12** in 74 % yield using $SOCl_2$ and pyridine in dichloromethane, which was linked to 6-fluorohexanol in 69 % yield using KOH in dimethyl sulfoxide. Reaction of **13** with decaborane(14) afforded **14** in 69 % yield which was deprotected to give the alcohol **15** in 68 % yield (Scheme 4).



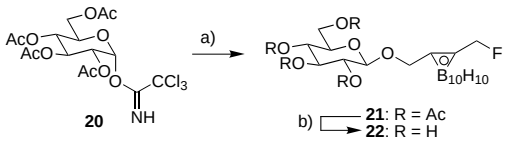
Scheme 4. Synthesis of fluoro carboranyl alcohol **15**. Reagents: a) $SOCl_2$, pyridine, 74 %; b) 6-fluorohexanol, KOH, DMSO, 69 %; c) $B_{10}H_{14}$, CH_3CN, then **13**, toluene, 69 %; d) H_2, Pd/C, ethyl acetate, methanol, 68 %.

For the synthesis of the fluorinated carboranyl lactosides **17** and **19** the two alcohols **11** and **15** were glycosidated with the lactose imidate **6** to give **16** in 58 % and **18** in 53 % yield, respectively. Solvolysis with sodium methoxide and methanol led to the desired compounds **17** in 72 % and **19** in 89 % yield.



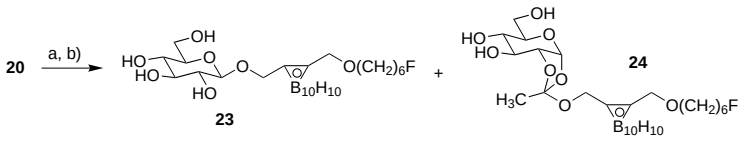
Scheme 5. Synthesis of fluoro carboranyl lactoside **17** and fluoro carboranyl lactoside **19**. Reagents: a) for preparation of **16**: **11**, $BF_3 \cdot Et_2O$, CH_2Cl_2, 58 %; for preparation of **18**: **15**, $BF_3 \cdot Et_2O$, CH_2Cl_2, 53 %; b) NaOMe, MeOH; 72 % for **17**, 89 % for **19**.

Besides the carboranyl lactosides **17** and **19** we have also synthesized the carboranyl glucosides **22** and **23**. Reaction of fluoro carboranyl alcohol **11** and glucose imidate **20** promoted by $BF_3 \cdot Et_2O$ afforded glucoside **21** in 57 % yield which was then deprotected to give **22** in 87 % yield (Scheme 6).



Scheme 6. Synthesis of fluoro carboranyl glucoside **22**. Reagents: a) **11**, $BF_3 \cdot Et_2O$, CH_2Cl_2, 57 %; b) NaOMe, MeOH, 87 %.

In a similar way, the alcohol **15** was treated with glucose imidate **20**; here a mixture of the corresponding peracetylated glucoside and the orthoester was obtained, which could not be separated by column chromatography. However, after deprotection a separation by column chromatography could be achieved to give the glucoside **23** and the orthoester **24** in 67 % and 9 % yield, respectively (Scheme 7).



Scheme 7. Synthesis of fluoro carboranyl glucoside **23**. Reagents: a) **15**, $BF_3 \cdot Et_2O$, CH_2Cl_2, mixture of glucoside and orthoester; b) NaOMe, MeOH, 67% of **23**, 9% of **24**.

The structures of the new compounds **7**, **8**, **16**–**19**, **21**–**23** have been determined mainly by ^{1}H- and ^{13}C-NMR spectroscopy. The 1-H at the anomeric center of the carboranyl lactosides as well as of the glucosides are observed at $\delta =$ 4.30–4.54 as a doublet with $J = 7.6$–7.9 Hz, indicating the presence of the β-anomers. The diastereotopic protons of the CH_2-group attached to the sugar moiety give separated doublets at $\delta = 3.9$–4.5 with a coupling constant of 12.3–12.6 Hz. Interestingly, also the protons of the second CH_2-group attached to the carborane moiety show two separated doublets at $\delta = 3.8$–4.1 with a coupling of 12.0–12.5 Hz for lactosides **7**, **8**, **18**, **19**, and glucoside **23**. For the second methylene group at the carborane moiety of the glycosides **16**, **17**, **21**, and **22** an additional coupling to fluorine is observed resulting in two separated doublets of doublets with $^2J(H,F) = 46.9$–47.2 Hz and $^2J(H,H) = 11.4$–11.7 Hz at $\delta =$ 4.77–5.02. The ^{1}H-NMR spectra of all carborane compounds show a very broad signal at $\delta = 0.7$–3.5, which is typical for the hydrogens at the boron atoms. Moreover an intensive B–H stretch signal at 2564–2600 cm^{-1} is found in the IR spectra.

Toxicities: Cloning efficiency tests on human bronchial carcinoma cells of line A549[14] revealed that the carboranyl lactosides **17** and **19** display almost no cytotoxicity in concentrations up to 300 μM, whereas the carboranyl alcohol **11** is considerably cytotoxic, with an ED_{50} value of 45 μM. These results indicate that carboranes can somehow be detoxified by glycosidation (Figure 1).

This is confirmed by our investigation using the fluoro carboranyl glucoside **22** with and without the addition of glucosidase. Thus, for **22** an ED_{50} value of 350 μM was determined, whereas in the presence of glucosidase (0.4 U mL^{-1}) an ED_{50} value of 157 μM was observed (Figure 2).

In the case of glucoside **22** the incubation took place without addition of fetal calf serum (FCS) or serum substitute (Basal Medium Supplement, BMS) in a serum-free medium (Ultra Culture) to prevent cleavage by glucohydrolase activity in the serum.[15]

Conclusion

The new carboranyl glycosides are in many aspects superior to the hitherto developed compounds for BNCT. We are presently investigating the interaction between fluoro carboranyl lactosides **17** and **19** and the cell membranes of cultured cells by NMR spectroscopy.

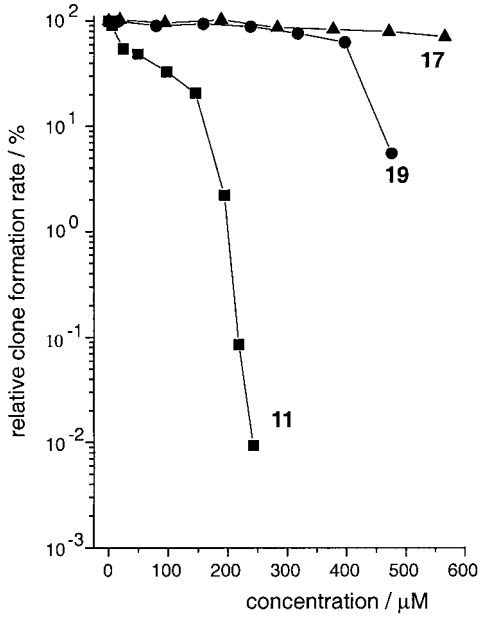


Figure 1. In vitro cytotoxicity of lactosides **17** (▲), **19** (●), and fluoro carboranyl alcohol **11** (■) on human bronchial carcinoma cells of line A549 after 24 h of incubation. The cytotoxicity was determined by comparing the relative rates of clone formation in the presence and absence of **11**, **17**, and **19**.

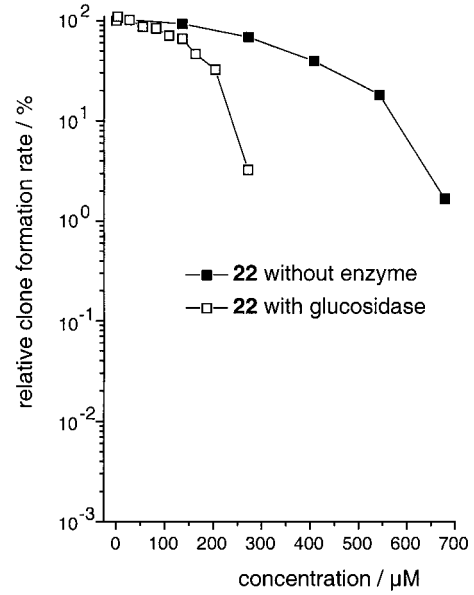


Figure 2. In vitro cytotoxicity of glucoside **22** on human bronchial carcinoma cells of line A549 after 24 h of incubation. Incubation was performed a) in a serum-free medium (Ultra Culture) without addition of β-D-glucosidase and b) with addition of β-D-glucosidase (0.4 U mL^{-1}).

Experimental Section

General: ^{1}H-NMR and ^{13}C-NMR spectra were recorded with a Varian VXR-500, XL-300, VXR-200 and Bruker AM-300 spectrometer; multiplicities were determined with an APT pulse sequence. MS: Varian MAT 311A. IR: Bruker IFS 25. Elemental analyses were carried out in the analytical laboratory of the University of Göttingen. All solvents were distilled prior to use. Reagents and materials were obtained from commercial suppliers and were used without further purification. *N*,*N*-diisopropyl-1-fluoro-2-methylpropenamine was purchased from Acros. All

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reactions were carried out under a positive pressure of argon and monitored by TLC (Macherey–Nagel, Polygram SIL G/UV_{254}). Column chromatography was performed on SiO_2 (Merck).

Benzyl 4-hexyloxy-2-butynyl ether (3): 4-Benzyloxy-2-butyn-1-ol **2** (10.9 g, 61.9 mmol) was added to KOH (9.61 g, 171 mmol, 2.8 equiv) in dry DMSO (30 mL). Then 1-bromohexane (10.2 g, 61.8 mmol, 1.0 equiv) was added dropwise during 60 min and the mixture was stirred at room temperature for 20 h and poured into 150 mL water. The water layer was extracted with Et_2O (5 × 30 mL) and the combined organic layers were washed with brine, dried with Na_2SO_4, and the solvent was evaporated in vacuo. The residue was first purified by column chromatography (petroleum ether/ethyl acetate 10:1) to give a yellowish liquid which was then purified by distillation (b.p. 149 °C, 0.5 mbar) to give **3** as a colorless liquid (13.1 g, 50.3 mmol, 81 %). R_f (petroleum ether/ethyl acetate 10:1) = 0.48; IR (KBr): $\tilde{\nu}$ = 2932, 2858 (C–H), 698, 740 cm^{-1} (arom); ^1H NMR (200 MHz, $CDCl_3$): δ = 0.90 (t, J = 6.6 Hz, 3H, CH_3), 1.27–1.44 (m, 6H, $(CH_2)_3CH_3$), 1.54–1.68 (m, 2H, CH_2CH_2O), 3.52 (t, J = 6.6 Hz, 2H, OCH_2CH_2), 4.20–4.23 (m, 4H, $2CH_2C{\equiv}C$), 4.61 (s, 2H, CH_2Ph), 7.26–7.38 (m, 5H, Ph-H); ^{13}C NMR (50 MHz): δ = 13.96 (CH_3), 22.53, 25.73, 29.44, 31.58 ($CH_3(CH_2)_4$), 57.34, 58.19 ($2CH_2C{\equiv}C$), 70.23, 71.48 (CH_2Ph, OCH_2CH_2), 81.83, 82.83 ($2C{\equiv}C$), 127.8, 128.0, 128.3, 137.3 (4 Ph-C); MS (EI): m/z: 260 (18) $[M]^+$, 107 (30) $[BzlO]^+$, 91 (100) $[Bzl]^+$; $C_{17}H_{24}O_2$ (260.4): calcd C 78.42, H 9.29; found C 78.82, H 9.17.

1-Benzyloxymethyl-2-hexyloxymethyl-1,2-dicarba-*closo*-dodecaborane (4): A mixture of decaborane(14) (1.02 g, 8.35 mmol, 1.4 equiv) in dry acetonitrile (15 mL) was heated at reflux for 30 min. Then toluene (15 mL) and the alkyne **3** (1.55 g, 5.95 mmol) were added and stirring at reflux was continued for 19 h. The reaction was quenched by addition of methanol (1 mL) and the solvents were evaporated in vacuo. Purification of the residue by column chromatography (petroleum ether/ethyl acetate 10:1) afforded carborane **4** (1.12 g, 2.96 mmol, 50 %) as a colorless oil. R_f (petroleum ether/ethyl acetate 10:1) = 0.59; IR (KBr): $\tilde{\nu}$ = 2954, 2932, 2868 (C–H), 2588 cm^{-1} (B–H); ^1H NMR (200 MHz, $CDCl_3$): δ = 0.89 (t, J = 6.5 Hz, 3H, CH_3), 1.27–1.54 (m, 8H, $CH_3(CH_2)_4$), 3.34 (t, J = 6.4 Hz, 2H, OCH_2CH_2), 3.88 (s, 2H, $CH_2C_{carb.}$), 3.97 (s, 2H, $CH_2C_{carb.}$), 4.55 (s, 2H, CH_2Ph), 7.27–7.39 (m, 5H, Ph-H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.03 (CH_3), 22.55, 25.65, 29.29, 31.50 ($CH_3(CH_2)_4$), 69.90, 70.95, 71.98, 73.43 (4 CH_2O), 76.22, 76.84 (2 $C_{carb.}$), 127.6, 128.1, 128.5, 136.7 (4 Ph-C); MS (EI): m/z: 107 (100) $[BzlO]^+$, 91 (50) $[Bzl]^+$; $C_{17}H_{34}B_{10}O_2$ (378.6): calcd C 53.94, H 9.05; found C 54.24, H 8.87.

1-Hexyloxymethyl-2-hydroxymethyl-1,2-dicarba-*closo*-dodecaborane (5): A mixture of protected carboranyl alcohol **4** (1.09 g, 2.88 mmol), methanol (7 mL), ethyl acetate (7 mL) and palladium on carbon (630 mg, 10 % Pd) was shaken under hydrogen (3 bar) for 6 h. Then the mixture was filtered and concentrated in vacuo. Purification by column chromatography (petroleum ether/ethyl acetate 6:1) afforded the alcohol **5** (563 mg, 1.95 mmol, 68 %) as a slightly yellow liquid. R_f (petroleum ether/ethyl acetate 4:1) = 0.48; IR (KBr): $\tilde{\nu}$ = 3438 (O–H), 2954, 2932, 2862 (C–H), 2590 cm^{-1} (B–H); ^1H NMR (200 MHz, $CDCl_3$): δ = 0.89 (t, J = 6.6 Hz, 3H, CH_3), 1.16–1.39 (m, 6H, $(CH_2)_3CH_3$), 1.51–1.61 (m, 2H, CH_2CH_2O), 3.12 (t, J = 7.6 Hz, 1H, OH), 3.54 (t, J = 6.6 Hz, 2H, OCH_2CH_2), 4.06 (s, 2H, $CH_2OCH_2C_{carb.}$), 4.12 (d, J = 7.6 Hz, 2H, CH_2OH); ^{13}C NMR (50 MHz): δ = 13.96 (CH_3), 22.46, 25.49, 29.13, 31.40 ($(CH_2)_4CH_3$), 64.33 (CH_2OH), 71.79, 72.65 ($CH_2OCH_2C_{carb.}$), 75.64, 78.87 ($2C_{carb.}CH_2$); MS (EI): m/z: 288 (30) $[M]^+$, 203 (13) $[M-C_6H_{13}]^+$, 185 (100); $C_{10}H_{28}B_{10}O_2$ (288.4): calcd C 41.64, H 9.78; found C 41.94, H 9.78.

1-(2,3,6,2′,3′,4′,6′-Hepta-*O*-acetyl-β-D-lactopyranosylmethyl)-2-hexyloxymethyl-1,2-dicarba-*closo*-dodecaborane (7): A mixture of lactose imidate **6** (763 mg, 0.98 mmol) and alcohol **5** (236 mg, 0.82 mmol) in CH_2Cl_2 was stirred over molecular sieves 4 Å for 10 min. Then $BF_3 \cdot Et_2O$ (0.10 mL) was added and the mixture was stirred for 20 h at room temperature. A solution of methanol/NEt_3 (2 mL, 3:1) was added and the organic layer was washed with water (2 × 20 mL), brine (20 mL) and dried with Na_2SO_4. After the solvent was evaporated in vacuo, the residue was purified by column chromatography (petroleum ether/ethyl acetate 1:1) to afford **7** as a white foam (564 mg, 0.62 mmol, 76 %). R_f (petroleum ether/ethyl acetate 1:1) = 0.51; $[\alpha]_D^{20} = -27.2$ (c = 0.5, $CHCl_3$); IR (KBr): $\tilde{\nu}$ = 2958, 2937, 2873 (C–H), 2589 (B–H), 1754 (C=O), 1371 ($OCOCH_3$), 1230 cm^{-1} (C–O); ^1H NMR (500 MHz, $CDCl_3$): δ = 0.87 (t, J = 7.0 Hz, 3H, CH_3CH_2), 1.23–1.31 (m, 6H, $CH_3(CH_2)_3$), 1.48–1.52 (m, 2H, OCH_2CH_2), 1.93, 2.01, 2.02, 2.03, 2.05, 2.09, 2.12 (7s, 21H, 7 CH_3), 3.42 (t, J = 6.6 Hz, 2H, OCH_2CH_2), 3.56 (ddd, J = 9.8, 4.8, 2.1 Hz, 1H, 5-H), 3.78 (t, J = 9.5 Hz, 1H, 4-H), 3.82–3.84 (m, 1H, 5′-H), 3.84 (d, J = 12.4 Hz, 1H, $C_{carb.}CH^{\alpha}H^{\beta}OCH_2$), 3.88 (d, J = 12.2 Hz, 1H, $C_{carb.}CH^{\alpha}H^{\beta}OCH_2$), 3.96 (d, J = 12.6 Hz, 1H, $OCOCH^{\alpha}H^{\beta}$), 4.04 (dd, J = 11.5, 3.3 Hz, 1H, 6-H or 6′-H), 4.04–4.06 (m, 1H, 6-H or 6′-H), 4.10 (dd, J = 11.1, 6.3 Hz, 1H, 6-H or 6′-H), 4.28 (d, J = 12.6 Hz, 1H, $OCOCH^{\alpha}H^{\beta}$), 4.44–4.48 (m, 3H, 1-H, 1′-H, 6-H or 6′-H), 4.89 (dd, J = 9.5, 7.8 Hz, 1H, 2-H), 4.92 (dd, J = 10.4, 3.3 Hz, 1H, 3′-H), 5.07 (dd, J = 10.4, 7.9 Hz, 1H, 2′-H), 5.16 (t, J = 9.2 Hz, 1H, 3-H), 5.31 (dd, J = 3.4, 0.9 Hz, 1H, 4′-H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.01 (CH_3CH_2), 20.50, 20.63, 20.75, 20.79 (4 CH_3), 22.54, 25.62, 29.27, 31.44 ($(CH_2)_4CH_3$), 60.73, 61.58 (C-6, C-6′), 66.52, 69.04, 70.68, 70.88, 71.09, 72.34, 72.84, 75.85 (C-2, C-3, C-4, C-5, C-2′, C-3′, C-4′, C-5′), 68.69 (OCH_2CH_2), 70.92, 72.11 ($2CH_2C_{carb.}$), 75.85 ($C_{carb.}$), 100.2, 101.0 (C-1, C-1′), 169.0, 169.4, 169.6, 170.0, 170.1, 170.1, 170.3 (7 OAc); MS (DCI): m/z: 926 $[M+NH_4+H]^+$; $C_{36}H_{62}B_{10}O_{19}$ (907.0): calcd C 47.67, H 6.89; found C 47.53, H 6.84.

2-Hexyloxymethyl-1-(β-D-lactopyranosylmethyl)-1,2-dicarba-*closo*-dodecaborane (8): Lactoside **7** (430 mg, 0.47 mmol) was dissolved in methanol (10 mL). A solution of sodium methoxide (0.10 mL, 5.4 mM in methanol) was added and the reaction was stirred for 65 min at room temperature. After the reaction was quenched by addition of Amberlyte IR-120 resin (H^+ form), the mixture was filtered, and methanol was evaporated in vacuo. Purification by column chromatography (gradient CH_2Cl_2/methanol 6:1 to 2:1) afforded **8** (192 mg, 0.31 mmol, 66 %) as a colorless foam. R_f (CH_2Cl_2/methanol 6:1) = 0.19; $[\alpha]_D^{20} = -13.2$ (c = 0.5, MeOH); IR (KBr): $\tilde{\nu}$ = 3386 (O–H), 2931, 2871 (C–H), 2586 cm^{-1} (B–H); ^1H NMR (500 MHz, [D$_4$]methanol): δ = 0.91 (t, J = 6.9 Hz, 3H, CH_3), 1.29–1.40 (m, 6H, $(CH_2)_3CH_3$), 1.53–1.59 (m, 2H, CH_2CH_2O), 3.26 (dd, J = 8.9, 8.0 Hz, 1H), 3.89 (ddd, J = 9.6, 4.5, 3.2 Hz, 1H, 5-H), 2.47–3.59 (m, 6H), 3.69 (dd, J = 11.5, 4.6 Hz, 1H), 3.77 (dd, J = 11.3, 7.4 Hz, 1H), 3.80–3.83 (m, 2H), 3.89 (dd, J = 12.2, 2.5 Hz, 1H), 4.03 (d, J = 12.3 Hz, 1H, $CH_2OCH^{\alpha}H^{\beta}$), 4.08 (d, J = 12.3 Hz, 1H, $CH_2OCH^{\alpha}H^{\beta}$), 4.15 (d, J = 12.4 Hz, 1H, $OCOCH^{\alpha}H^{\beta}$), 4.32 (d, J = 7.8 Hz, 1H, 1-H or 1′-H), 4.34 (d, J = 7.7 Hz, 1H, 1-H or 1′-H), 4.43 (d, J = 12.3 Hz, 1H, $OCOCH^{\alpha}H^{\beta}$); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.40 (CH_3), 23.61, 26.84, 30.41, 32.64 ($(CH_2)_4CH_3$), 61.72, 62.41 (C-6, C-6′), 69.79, 71.63, 72.80 (3 CH_2O), 70.18, 72.38, 74.30, 74.65, 76.33, 76.59, 76.94, 80.31 (C-2, C-3, C-4, C-5′, C-2′, C-3′, C-4′, C-5′), 104.7, 104.9 (C-1, C-1′); MS (DCI): m/z: 631 $[M+NH_4]^+$; $C_{22}H_{48}B_{10}O_{12}$ (612.7).

Benzyl 4-fluoro-2-butynyl ether (9): *N,N*-Diisopropyl-1-fluoro-2-methylpropenamine (3.34 g, 19.3 mmol) was added to a solution of 4-benzyloxy-2-butyn-1-ol **2** (3.33 g, 18.9 mmol) in dry CH_2Cl_2 (40 mL). After stirring at room temperature for 68 h, the organic layer was washed with water (2 × 20 mL), brine (20 mL), dried with Na_2SO_4, and the solvent was evaporated in vacuo. Distillation gave as first fraction *N,N*-diisopropyl isobutyramide and as second fraction **9** (2.41 g, 13.5 mmol, 71 %) as a colorless liquid (b.p. 77 °C, 0.2 mbar). R_f (petroleum ether/ethyl acetate 10:1) = 0.48; IR (KBr): $\tilde{\nu}$ = 3086, 3064, 3032, 2946, 2860 (C–H), 744, 700 cm^{-1} (arom); ^1H NMR (200 MHz, $CDCl_3$): δ = 4.25 (dt, ^5J(H,F) = 7.6, J' = 1.7 Hz, 2H, $OCH_2C{\equiv}C$), 4.61 (s, 2H, CH_2Ph), 5.02 (dt, ^2J(H,F) = 47.7 Hz, J' = 1.7 Hz, 2H, CH_2F), 7.30–7.45 (m, 5H, Ph-H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 57.16 (d, ^4J(C,F) = 3.4 Hz, CH_2OBzl), 70.61 (d, ^1J(C,F) = 165.5 Hz, CH_2F), 71.77 (CH_2Ph), 80.36 (d, ^2J(C,F) = 22.3 Hz, CCH_2F), 86.14 (d, ^3J(C,F) = 12.1 Hz, $CCCH_2F$); ^{19}F NMR (188 MHz, $CDCl_3$, external standard C_6F_6): δ = −53.20 (tt, ^2J(H,F) = 47.5, ^5J(H,F) = 7.5 Hz); MS (EI): m/z: 177 (19) $[M-H]^+$, 91 (100) $[Bzl]^+$, 77 (38) $[Ph]^+$; $C_{11}H_{11}OF$ (178.2): calcd C 74.14, H 6.22; found C 74.27, H 6.51.

1-Benzyloxymethyl-2-fluoromethyl-1,2-dicarba-*closo*-dodecaborane (10): Alkyne **9** (256 mg, 1.44 mmol) was transformed within 19 h to carborane **10** using decaborane(14) (248 mg, 2.03 mmol, 1.4 equiv) in acetonitrile (5 mL) and toluene (5 mL) as described for **4**. Purification by column chromatography (petroleum ether/ethyl acetate 20:1) afforded **10** (259 mg, 0.87 mmol, 61 %) as a colorless oil. R_f (petroleum ether/ethyl acetate 10:1) = 0.52; IR (film): $\tilde{\nu}$ = 2880, 2856 (C–H), 2602, 2586, 2568, 2564 (B–H), 1954, 1870 (arom), 734, 696 cm^{-1} (arom); ^1H NMR (200 MHz, $CDCl_3$): δ = 4.01 (s, 2H, $CH_2C_{carb.}$), 4.57 (s, 2H, CH_2Ph), 4.78 (d, ^2J(H,F) = 47.4 Hz, 2H, CH_2F), 7.26–7.38 (m, 5H, Ph-H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 70.13 (CH_2OBzl), 73.59 (CH_2Ph), 74.23 (d, ^2J(C,F) = 25.0 Hz, $C_{carb.}CH_2F$), 76.22 ($C_{carb.}CH_2O$), 81.49 (d, ^1J(C,F) = 188.4 Hz, CH_2F), 127.6, 128.3, 128.6, 136.2 (Ph-C); MS (EI): m/z: 296 (25) $[M]^+$, 92 (100) $[Bzl+H]^+$, 91 (83) $[Bzl]^+$, 79 (24) $[Ph+H]^+$; $C_{11}H_{21}B_{10}OF$ (296.4): calcd 298.2507; found 298.2506.

2-Fluoromethyl-1-hydroxymethyl-1,2-dicarba-*closo*-dodecaborane (11): Alcohol **10** (1.67 g, 5.63 mmol) was deprotected as described for **5** within 21 h using Pd/C (1.16 g). Purification by column chromatography (petroleum ether/ethyl acetate 3:1) afforded alcohol **11** (934 mg, 4.53 mmol, 81 %) as a colorless solid. IR (KBr): $\tilde{\nu}$ = 3420, 3402 (O–H), 2966, 2952, 2894, 2854 (C–H), 2586 cm^{-1} (B–H); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.29 – 2.57 (br s, 1H, OH), 4.05 (s, 2H, CH_2OH), 4.73 (d, ^2J(H,F) = 47.4 Hz, 2H, CH_2F); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 64.02 (CH_2OH), 74.42 (d, ^2J(C,F) = 19.6 Hz, CCH$_2$F), 78.45 (CCH$_2$OH), 81.60 (d, ^1J(C,F) = 137.7 Hz, CH_2F); MS (EI): *m*/*z*: 206 (100) $[M]^+$, 187 (76) $[M-F]^+$; $C_4H_{15}B_{10}OF$ (206.3): calcd 208.2037, found 208.2037; calcd C 23.29, H 7.33; found C 23.47, H 7.06.

Benzyl 4-chloro-2-butynyl ether (12): $SOCl_2$ (20.0 mL, 274 mmol, 2.7 equiv) was added dropwise during 2 h at a temperature between 5 °C and 10 °C to a solution of alcohol **2** (17.7 g, 100 mmol) in pyridine (30 mL) and CH_2Cl_2 (100 mL). The reaction was stirred for 2 h at room temperature and poured onto ice water. The organic layer was separated, washed with aqueous HCl (1N), water, brine, and dried with sodium sulfate. Evaporation of the solvents and distillation (b.p. 107 °C, 0.15 mbar) gave a yellow liquid which was filtered through a short column of silica (petroleum ether/ethyl acetate 5:1) to afford a slightly yellow liquid (14.5 g, 74.4 mmol, 74 %). R_f (petroleum ether/ethyl acetate 10:1) = 0.51; IR (KBr): $\tilde{\nu}$ = 3088, 3065, 3031, 2994, 2947 (C–H), 741, 698 cm^{-1} (arom); ^{1}H NMR (200 MHz): δ = 4.20 – 4.24 (m, 4H, 2CH_2C≡C), 4.61 (s, 2H, CH_2Ph), 7.33 – 7.38 (m, 5H, Ph-H); ^{13}C NMR (50 MHz): δ = 30.32 (CH_2Cl), 57.20 (CH$_2$OBzl), 71.67 (CH_2Ph), 81.19, 82.49 (2C≡C), 127.9, 128.0, 128.4, 137.1 (4Ph-C); MS (EI): *m*/*z*: 107 (42) $[BzlO]^+$, 91 (100) $[Bzl]^+$, 77 (50) $[Ph]^+$; $C_{11}H_{11}OCl$ (194.7): calcd C 67.87, H 5.70; found C 67.95, H 5.60.

Benzyl 4-(6-fluorohexyloxy)-2-butynyl ether (13): A mixture of 6-fluorohexanol (4.07 g, 33.9 mmol), KOH (4.12 g, 73.4 mmol), and DMSO (17 mL) was cooled in an ice bath until the DMSO was partly solified. Then the chloride **12** (5.84 g, 30.0 mmol) was added and the mixture was stirred for 25 h at room temperature. Workup as described for **3** and distillation afforded the ether **13** (5.72 g, 20.6 mmol, 69 %, b.p. 148 – 149 °C (0.1 mbar)) as a colorless liquid. R_f (petroleum ether/ethyl acetate 10:1) = 0.42; IR (film): $\tilde{\nu}$ = 2938, 2860 (C–H), 742, 698 cm^{-1} (arom); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.39 – 1.80 (m, 8H, (CH_2)$_4$CH$_2$F), 3.52 (t, J = 6.3 Hz, 2H, CH_2CH_2O), 4.20 (d, J = 1.4 Hz, 2H, CH_2C≡C), 4.22 (d, J = 1.4 Hz, 2H, CH_2C≡C), 4.43 (dt, ^2J(H,F) = 47.4, J' = 5.8 Hz, 2H, CH_2F), 4.60 (s, 2H, CH_2Ph), 7.26 – 7.37 (m, 5H, Ph-H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 24.94 (d, ^3J(C,F) = 5.4 Hz, CH$_2$CH$_2$CH$_2$F), 25.72 (CH$_2$CH$_2$CH$_2$O), 29.34 (CH$_2$CH$_2$O), 30.26 (d, ^2J(C,F) = 19.6 Hz, CH$_2$CH$_2$F), 57.34, 58.22 (2CH$_2$C≡C), 69.93 (OCH$_2$CH$_2$), 71.50 (PhCH$_2$), 81.93, 82.72 (2C≡C), 83.94 (d, ^1J(C,F) = 165 Hz, CH_2F), 127.8, 127.9, 128.3, 137.3 (4Ph-C); MS (EI): *m*/*z*: 278 (9) $[M]^+$, 91 (100) $[Bzl]^+$; $C_{17}H_{23}O_2F$ (278.4).

1-Benzyloxymethyl-2-(6-fluorohexyloxymethyl)-1,2-dicarba-*closo*-dodecaborane (14): Alkyne **13** (1.45 g, 5.21 mmol) was transformed within 20.5 h into carborane **14** using decaborane(14) (1.24 g, 10.1 mmol) in acetonitrile (20 mL) and toluene (20 mL) as described for **4**. Purification by column chromatography (petroleum ether/ethyl acetate gradient 20:1 → 10:1) afforded carborane **14** (1.42 g, 3.58 mmol, 69 %) as a colorless liquid. R_f (petroleum ether/ethyl acetate 10:1) = 0.44; IR (film): $\tilde{\nu}$ = 2938, 2866 (C–H), 2586 (B–H), 738, 698 cm^{-1} (arom); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.29 – 1.80 (m, 8H, OCH$_2$(CH_2)$_4$), 3.37 (t, J = 6.2 Hz, 2H, OCH_2CH$_2$), 3.91 (s, 2H, $CH_2C_{carb.}$), 3.99 (s, 2H, $CH_2C_{carb.}$), 4.46 (dt, ^2J(H,F) = 49.3, J' = 5.8 Hz, 2H, CH_2F), 4.61 (s, 2H, CH_2Ph), 7.30 – 7.40 (m, 5H, Ph-H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 24.92 (d, ^3J(C,F) = 5.4 Hz, CH$_2$CH$_2$CH$_2$F), 25.62 (OCH$_2$CH$_2$CH_2), 29.19 (OCH$_2$CH_2), 30.24 (d, ^2J(C,F) = 19.6 Hz, CH$_2$CH$_2$F), 69.85 (CH$_2$CH_2O), 70.89, 71.69 (2CH$_2$C$_{carb.}$), 73.39 (PhCH_2), 76.25, 76.77 (2C$_{carb.}$), 83.94 (d, ^1J(C,F) = 164.0 Hz, CH_2F), 127.6, 128.1, 128.5, 136.7 (Ph-C); ^{19}F NMR (188 MHz, $CDCl_3$, external standard $CFCl_3$): δ = – 218.9 (tt, ^2J(H,F) = 47.4 Hz, ^3J(H,F) = 25.3 Hz); MS (EI): *m*/*z*: 107 (100) $[BzlO]^+$, 91 (85) $[Bzl]^+$; $C_{17}H_{33}B_{10}O_2F$ (396.6): calcd 398.3395, found 398.3395; calcd C 51.49, H 8.39; found C 51.78, H 8.47.

2-(6-Fluorohexyloxymethyl)-1-hydroxymethyl-1,2-dicarba-*closo*-dodecaborane (15): Alcohol **14** (519 mg, 1.31 mmol) was deprotected as described for **5** within 4 h using Pd/C (426 mg) to afford alcohol **15** (273 mg, 0.89 mmol, 68 %) as a colorless liquid. R_f (petroleum ether/ethyl acetate 2:1) = 0.44; IR (film): $\tilde{\nu}$ = 3444 (O–H), 2938, 2866 (C–H), 2588 cm^{-1} (B–H); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.28 – 1.79 (m, 8H, (CH_2)$_4$CH$_2$F), 3.10 (t, J = 7.5 Hz, 1H, OH), 3.53 (t, J = 6.4 Hz, 2H, CH_2CH_2O), 4.04 (s, 2H, CH_2OCH_2C$_{carb.}$), 4.10 (d, J = 7.6 Hz, 2H, C$_{carb.}$CH_2OH), 4.43 (dt, ^2J(H,F) = 47.1, J' = 5.9 Hz, 2H, CH_2F); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 24.93 (d, ^3J(C,F) = 4.7 Hz, CH$_2$(CH$_2$)$_2$F), 25.50, 29.06 (CH$_2$CH$_2$(CH$_2$)$_3$F), 30.18 (d, ^2J(C,F) = 19.6 Hz, CH$_2$CH$_2$F), 64.26 (C$_{carb.}$CH$_2$OH), 71.73 (CH$_2$OCH$_2$C$_{carb.}$), 72.34 (CH$_2$CH$_2$O), 75.71 (C$_{carb.}$), 78.83 (C$_{carb.}$), 83.92 (d, ^1J(C,F) = 164.1 Hz, CH_2F); MS (EI): *m*/*z*: 119 (21) $[F(CH_2)_6O]^+$, 103 (100) $[F(CH_2)_6]^+$; $C_{10}H_{27}B_{10}O_2F$ (306.4): calcd 308.2926; found 308.2925.

2-Fluoromethyl-1-(2,3,6,2′,3′,4′,6′-hepta-*O*-acetyl-β-D-lactopyranosylmethyl)-1,2-dicarba-*closo*-dodecaborane (16): Reaction of lactose imidate **6** (400 mg, 0.51 mmol), alcohol **11** (106 mg, 0.51 mmol) in CH_2Cl_2 (20 mL) over molecular sieves 4 Å promoted by $BF_3 \cdot Et_2O$ (0.20 mL) for 4 h and workup as described for **7** afforded after purification by column chromatography (petroleum ether/ethyl acetate 1:1) lactoside **16** (244 mg, 0.30 mmol, 58 %) as a colorless foam. R_f (petroleum ether/ethyl acetate 1:1) = 0.36; $[\alpha]_D^{20}$ = – 21.5 (c = 1, $CHCl_3$); IR (KBr): $\tilde{\nu}$ = 2964, 2940 (C–H), 2592 (B–H), 1754 (C=O), 1372 (OCOCH$_3$), 1230 cm^{-1} (C–O); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.97, 2.05, 2.06, 2.07, 2.12, 2.15 (6s, 21H, 7CH$_3$), 3.60 (ddd, J = 9.7, 4.7, 1.8 Hz, 1H, 5-H), 3.80 (t, J = 9.5 Hz, 1H, 4-H), 3.86 – 3.89 (m, 1H, 5′-H), 4.04 (d, J = 12.5 Hz, 1H, OCOCH^{α}H$^{\beta}$), 4.06 – 4.15 (m, 3H, 6-H, 6′-H), 4.32 (d, J = 12.3 Hz, 1H, OCOCH$^{\alpha}H^{\beta}$), 4.48 (d, J = 7.8 Hz, 1H, 1-H or 1′-H), 4.51 (d, J = 7.7 Hz, 1H, 1-H or 1′-H), 4.52 – 4.53 (m, 1H, 6-H or 6′-H), 4.76 (dd, ^2J(H,F) = 47.6, J' = 11.2 Hz, 1H, CH^{α}H$^{\beta}$F), 4.77 (dd, ^2J(H,F) = 47.2, J' = 11.4 Hz, 1H, CH$^{\alpha}H^{\beta}$F), 4.92 (dd, J = 9.5, 7.9 Hz, 1H, 2-H), 4.96 (dd, J = 10.3, 3.4 Hz, 1H, 3′-H), 5.10 (dd, J = 10.4, 7.9 Hz, 1H, 2′-H), 5.19 (t, J = 9.2 Hz, 1H, 3-H), 5.35 (dd, J = 3.3, 1.0 Hz, 1H, 4′-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.44, 20.47, 20.57, 20.73, 26.85 (5CH$_3$), 60.71, 61.37 (C-6, C-6′), 68.50 (CH$_2$OCO), 66.53, 69.01, 70.69, 70.80, 70.88, 72.21, 72.89, 75.77 (C-2, C-3, C-4, C-5, C-2′, C-3′, C-4′, C-5′), 74.37 (d, ^2J(C,F) = 24.8 Hz, $C_{carb.}$CH$_2$F), 75.09 ($C_{carb.}$CH$_2$O), 81.29 (d, ^1J(C,F) = 188 Hz, CH_2F), 99.75, 101.0 (C-1, C-1′), 169.1, 169.4, 169.7, 170.0, 170.0, 170.2, 170.3 (7OAc); MS (DCI): *m*/*z*: 843 $[M+NH_4]^+$; $C_{30}H_{49}B_{10}O_{18}F$ (824.8): calcd C 43.69, H 5.99; found: C 43.88, H 6.15.

2-Fluoromethyl-1-(β-D-lactopyranosylmethyl)-1,2-dicarba-*closo*-dodecaborane (17): Lactoside **16** (86 mg, 0.11 mmol) in methanol (5 mL) was deprotected with sodium methoxide (60 µL, 5.4 mM in methanol) within 50 min as described for **8**. Purification by column chromatography (ethyl acetate/methanol 4:1) afforded **17** (40 mg, 0.08 mmol, 72 %) as a colorless foam. R_f (ethyl acetate/methanol 1:1) = 0.19; $[\alpha]_D^{20}$ = – 14.5 (c = 1, MeOH); IR (KBr): $\tilde{\nu}$ = 3406 (O–H), 2928, 2890 (C–H), 2592 cm^{-1} (B–H); ^{1}H NMR (500 MHz, [D$_4$]methanol): δ = 3.26 (dd, J = 8.9, 8.0 Hz, 1H), 3.41 (ddd, J = 9.4, 4.6, 2.4 Hz, 1H, 5-H), 3.47 (dd, J = 9.8, 3.2 Hz, 1H, 3′-H), 3.50 (t, J = 9.0 Hz, 1H), 3.53 (dd, J = 9.6, 7.9 Hz, 1H, 2-H or 2′-H), 3.55 – 3.59 (m, 2H, 2-H or 2′-H, 5′-H), 3.69 (dd, J = 11.5, 4.6 Hz, 1H, 6-H), 3.77 (dd, J = 11.4, 7.5 Hz, 1H, 6-H), 3.80 – 3.81 (m, 1H, 4′-H), 3.82 (dd, J = 12.2, 4.2 Hz, 1H, 6-H or 6′-H), 3.91 (dd, J = 12.4, 2.3 Hz, 1H, 6-H or 6′-H), 4.21 (d, J = 12.4 Hz, 1H, OCOCH^{α}H$^{\beta}$), 4.34 (d, J = 7.6 Hz, 1H, 1-H or 1′-H), 4.35 (d, J = 7.8 Hz, 1H, 1-H or 1′-H), 4.49 (d, J = 12.6 Hz, 1H, OCOCH$^{\alpha}H^{\beta}$), 4.98 (dd, ^2J(H,F) = 46.9, J' = 11.7 Hz, 1H, CH^{α}H$^{\beta}$F), 5.02 (dd, ^2J(H,F) = 46.9, J' = 11.7 Hz, 1H, CH$^{\alpha}H^{\beta}$F); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 61.75, 62.45 (C-6, C-6′), 69.85 (OCOCH$_2$), 70.22, 72.46, 74.32, 74.73, 76.39, 76.66, 77.02, 80.31 (C-2, C-3, C-4, C-5, C-2′, C-3′, C-4′, C-5′), 76.56 (d, ^2J(C,F) = 25.0 Hz, $C_{carb.}$CH$_2$F), 77.98 (OCOCH$_2$C$_{carb.}$), 82.65 (d, ^1J(C,F) = 185 Hz, CH_2F), 103.6, 105.0 (C-1, C-1′); MS (DCI): *m*/*z*: 549 $[M+NH_4]^+$; $C_{16}H_{35}B_{10}O_{11}F$ (530.6).

1-(2,3,6,2′,3′,4′,6′-Hepta-*O*-acetyl-β-D-lactopyranosyloxymethyl)-2-(6-fluorohexyloxymethyl)-1,2-dicarba-*closo*-dodecaborane (18): $BF_3 \cdot Et_2O$ (0.10 mL) was added under stirring to an ice-cold mixture of lactose imidate **6** (1.11 g, 1.42 mmol), alcohol **15** (289 mg, 0.94 mmol) and molecular sieves 4 Å in CH_2Cl_2 (40 mL) and stirring was continued at 0 °C for 5 min and then 200 min at 20 °C. Workup as described for **7** and purification by column chromatography (petroleum ether/ethyl acetate 1.5:1) afforded **18** (466 mg, 0.50 mmol, 53 %) as a white foam. R_f (petroleum ether/ethyl acetate 1:1) = 0.43; $[\alpha]_D^{20}$ = – 25.5 (c = 1, $CHCl_3$); IR (KBr): $\tilde{\nu}$ = 2942, 2870 (C–H), 2588 (B–H), 1754 (C=O), 1370 (OCOCH$_3$), 1230 cm^{-1} (C–O); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.34 – 1.43 (m, 4H, CH_2CH$_2$CH$_2$CH$_2$F), 1.52 – 1.58 (m, 2H, CH_2CH$_2$O), 1.63 – 1.74 (m, 2H, CH_2CH$_2$F), 1.94, 2.02, 2.03, 2.04, 2.06, 2.10, 2.13 (7s, 21H, 7CH$_3$), 3.44 (t, J = 6.4 Hz, 2H, OCH_2CH$_2$), 3.55 (ddd, J = 9.9, 4.6, 2.1 Hz, 1H, 5-H), 3.79 (t, J = 9.4 Hz, 1H, 4-H), 3.83 – 3.85 (m, 1H, 5′-H), 3.85 (d, J = 12.1 Hz, 1H, C$_{carb.}$CH^{α}H$^{\beta}$OCH$_2$, 3.89 (d, J = 12.2 Hz, 1H, C$_{carb.}$CH$^{\alpha}$H$^{\beta}$OCH$_2$), 3.96 (d, J = 12.5 Hz, 1H, OCOCH^{α}H$^{\beta}$C$_{carb.}$), 4.04 (dd, J = 7.7,

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3.4 Hz, 1H, 6-H), 4.06–4.08 (m, 1H, 6-H or 6′-H), 4.11 (dd, J = 11.1, 6.3 Hz, 1H, 6-H or 6′-H), 4.28 (d, J = 12.5 Hz, 1H, OCOCH$^{\alpha}H^{\beta}$C$_{carb.}$), 4.43 (dt, ^{2}J(H,F) = 47.4, J = 6.0 Hz, 2H, CH_2F), 4.46 (d, J = 7.7 Hz, 1H, 1-H or 1′-H), 4.48 (d, J = 7.9 Hz, 1H, 1-H or 1′-H), 4.45–4.49 (m, 1H, 6-H or 6′-H), 4.90 (dd, J = 9.5, 7.8 Hz, 1H, 2-H), 4.93 (dd, J = 10.4, 3.6 Hz, 1H, 3′-H), 5.08 (dd, J = 10.4, 8.0 Hz, 1H, 2′-H), 5.16 (t, J = 9.2 Hz, 1H, 3-H), 5.32 (dd, J = 3.4, 1.0 Hz, 1H, 4′-H); ^{13}C NMR (50 MHz, CDCl$_3$): δ = 20.46, 20.59, 20.72, 20.76 (4CH$_3$), 24.93 (d, ^{3}J(C,F) = 4.8 Hz, CH$_2$(CH$_2$)$_2$F), 25.60, 29.17 (CH$_2$)$_2$(CH$_2$)$_3$F), 30.24 (d, ^{2}J(C,F) = 19.6 Hz, CH$_2$CH$_2$F), 60.71, 61.53 (C-6, C-6′), 66.50, 69.00, 70.64, 71.04, 72.29, 72.83, 75.79 (C-2, C-3, C-4, C-5, C-2′, C-3′, C-4′, C-5′), 68.65, 71.79 (OCH$_2$CH$_2$, C$_{carb.}$CH$_2$O), 75.15, 76.81 (2CH$_2$C$_{carb.}$), 83.97 (d, ^{1}J(C,F) = 164 Hz, CH$_2$F), 100.2, 101.0 (C-1, C-1′), 169.0, 169.3, 169.6, 170.0, 170.0, 170.1, 170.3 (7OAc); MS (DCI): m/z: 934.9 [M+NH$_4$]$^+$; C$_{36}$H$_{61}$B$_{10}$O$_{19}$F (925.0).

1-(β-D-Lactopyranosyloxymethyl)-2-(6-fluorohexyloxymethyl)-1,2-dicarba-*closo*-dodecaborane (19): Lactoside **18** (365 mg, 0.40 mmol) in methanol (10 mL) was deprotected with sodium methoxide (100 μL, 5.4 mM in methanol) within 90 min as described for **8**. Purification by column chromatography (ethyl acetate/methanol 5:1) afforded **19** (221 mg, 0.35 mmol, 89%) as a colorless foam. R_f (ethyl acetate/methanol 5:1) = 0.37; [α]$_D^{20}$ = −13.2 (c = 1, MeOH); IR (KBr): $\tilde{\nu}$ = 3406 (O–H), 2938, 2872 (C–H), 2586 (B–H); ^{1}H NMR (500 MHz, [D$_4$]methanol): δ = 1.45–1.49 (m, 4H, (CH_2)$_2$(CH$_2$)$_2$F), 1.62 (quint, J = 6.7 Hz, 2H, CH_2CH$_2$O), 1.67–1.77 (m, 2H, CH_2CH$_2$F), 3.43 (ddd, J = 10.5, 4.3, 2.5 Hz, 1H, 5-H), 3.50 (dd, J = 9.7, 3.3 Hz, 1H), 3.54–3.62 (m, 1H, 5′-H), 3.72 (dd, J = 11.3, 4.6 Hz, 1H), 3.80 (dd, J = 11.5, 7.5 Hz, 1H), 3.85 (dd, J = 11.9, 4.6 Hz, 1H, 6-H$^{\alpha}$), 3.93 (dd, J = 12.0, 2.4 Hz, 1H), 3.83–3.84 (m, 1H), 4.07 (d, J = 12.2 Hz, 1H, C$_{carb.}$CH^{α}H$^{\beta}$OCH$_2$), 4.12 (d, J = 12.1 Hz, 1H, C$_{carb.}$CH$^{\alpha}H^{\beta}$OCH$_2$), 4.18 (d, J = 12.3 Hz, 1H, OCOCH^{α}H$^{\beta}$C$_{carb.}$), 4.35 (d, J = 7.7 Hz, 1H, 1-H or 1′-H), 4.37 (d, J = 7.8 Hz, 1H, 1-H or 1′-H), 4.45 (dt, ^{2}J(H,F) = 47.6, J' = 6.2 Hz, 2H, CH$_2$F), 4.56 (d, J = 12.3 Hz, 1H, OCOCH$^{\alpha}H^{\beta}$C$_{carb.}$); ^{13}C NMR (50 MHz, [D$_4$]methanol): δ = 26.06 (d, ^{3}J(C,F) = 5.2 Hz, CH$_2$(CH$_2$)$_2$F), 26.85, 30.34 (OCH$_2$(CH$_2$)$_2$), 31.46 (d, ^{2}J(C,F) = 19.9 Hz, CH$_2$CH$_2$F), 61.79, 62.44 (C-6, C-6′), 69.83, 71.68, 72.68 (3CH$_2$O), 70.21, 72.46, 74.37, 74.72, 76.41, 76.66, 77.01, 80.41 (C-2, C-3, C-4, C-5, C-2′, C-3′, C-4′, C-5′), 77.65, 78.72 (2C$_{carb.}$), 84.04 (d, ^{1}J(C,F) = 164 Hz, CH$_2$F), 103.7, 105.0 (C-1, C-1′); ^{19}F NMR (377 MHz, CDCl$_3$, external standard CFCl$_3$): δ = 219.1; MS (DCI): m/z: 649.7 [M+NH$_4$+H]$^+$; C$_{22}$H$_{47}$B$_{10}$O$_{12}$F (630.7).

2-Fluoromethyl-1-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosylmethyl)-1,2-dicarba-*closo*-dodecaborane (21): Glucose imidate **20** (878 mg, 1.78 mmol) and alcohol **11** (256 mg, 1.24 mmol) were stirred in CH$_2$Cl$_2$ (20 mL) over molecular sieves 4 Å for 10 min, then BF$_3\cdot$Et$_2$O (0.20 mL) was added and stirring was continued for 225 min. The molecular sieves was filtered off and the organic layer was washed with water, brine and dried with Na$_2$SO$_4$. After evaporation of the CH$_2$Cl$_2$ in vacuo the residue was recrystallized from MeOH to afford **21** as a colorless solid (378 mg, 0.70 mmol, 57%). R_f (petroleum ether/ethyl acetate 2:1) = 0.17; [α]$_D^{20}$ = −31.0 (c = 1, CHCl$_3$); IR (KBr): $\tilde{\nu}$ = 2976, 2956, 2948, 2896 (C–H), 2600 (B–H), 1758 (C=O), 1374 (OCOCH$_3$), 1234 cm^{-1} (C–O); ^{1}H NMR (500 MHz, CDCl$_3$): δ = 2.02, 2.03, 2.08, 2.09 (4s, 12H, 4CH$_3$), 3.70 (ddd, J = 10.0, 4.7, 2.4 Hz, 1H, 5-H), 4.07 (d, J = 12.4 Hz, 1H, OCOCH^{α}H$^{\beta}$C$_{carb.}$), 4.15 (dd, J = 12.5, 2.5 Hz, 1H, 6-H$^{\alpha}$), 4.24 (dd, J = 12.4, 4.7 Hz, 1H, 6-H$^{\beta}$), 4.37 (d, J = 12.5 Hz, 1H, OCOCH$^{\alpha}H^{\beta}$C$_{carb.}$), 4.54 (d, J = 7.9 Hz, 1H, 1-H), 4.77 (dd, ^{2}J(H,F) = 47.2, J' = 11.5 Hz, 1H, CH^{α}H$^{\beta}$F), 4.81 (dd, ^{2}J(H,F) = 47.5, J' = 11.5 Hz, 1H, CH$^{\alpha}H^{\beta}$F), 5.02 (dd, J = 9.7, 7.9 Hz, 1H, 2-H), 5.08 (dd, J = 9.9, 9.4 Hz, 1H, 4-H), 5.20 (t, J = 9.5 Hz, 1H, 3-H); ^{13}C NMR (50 MHz, CDCl$_3$): δ = 20.45, 20.56 (CH$_3$), 61.47 (C-6), 68.02, 70.58, 72.08, 72.19 (C-2, C-3, C-4, C-5), 68.60 (OCH_2C$_{carb.}$), 74.43 (d, ^{2}J(C,F) = 25.0 Hz, C$_{carb.}$CH$_2$F), 75.10 (C$_{carb.}$CH$_2$O), 81.29 (d, ^{1}J(C,F) = 188 Hz, CH$_2$F), 100.1 (C-1), 169.1, 169.2, 170.0, 170.4 (4OAc); ^{19}F NMR (377 MHz, CDCl$_3$, external standard CFCl$_3$): δ = 304.2 (t, ^{2}J(H,F) = 48 Hz); MS (DCI): m/z: 555 [M+NH$_4$]$^+$; C$_{18}$H$_{33}$B$_{10}$O$_{10}$F (536.6): calcd C 40.29, H 6.20; found C 40.22, H 6.21.

2-Fluoromethyl-1-(β-D-glucopyranosyloxymethyl)-1,2-dicarba-*closo*-dodecaborane (22): Glucoside **21** (90 mg, 0.17 mmol) in methanol (5 mL) was deprotected with sodium methoxide (80 μL, 5.4 mM in methanol) within 30 min as described for **8**. Purification by column chromatography (ethyl acetate/methanol 10:1) afforded **22** (54 mg, 0.15 mmol, 87%) as a white foam. R_f (ethyl acetate/methanol 10:1) = 0.39; [α]$_D^{20}$ = −25.0 (c = 1, MeOH); IR (KBr): $\tilde{\nu}$ = 3404 (O–H), 2926, 2890 (C–H), 2592 cm^{-1} (B–H); ^{1}H NMR (500 MHz, [D$_4$]methanol): δ = 3.18 (dd, J = 9.1, 7.9 Hz, 1H, 2-H), 3.22–3.33 (m, 3H, 6-H$^{\alpha}$, 3-H, 4-H), 3.62–3.65 (m, 1H, 5-H), 3.86 (dd, J = 12.0, 1.7 Hz, 1H, 6-H$^{\beta}$), 4.19 (d, J = 12.5 Hz, 1H, OCH^{α}H$^{\beta}$C$_{carb.}$), 4.30 (d, J = 7.9 Hz, 1H, 1-H), 4.51 (d, J = 12.6 Hz, 1H, OCH$^{\alpha}H^{\beta}$C$_{carb.}$), 4.99 (dd, ^{2}J(H,F) = 47.1, 11.6 Hz, 1H, CH^{α}H$^{\beta}$F), 5.00 (dd, ^{2}J(H,F) = 46.9, J' = 11.6 Hz, 1H, CH$^{\alpha}H^{\beta}$F); ^{13}C NMR (50 MHz, [D$_4$]methanol): δ = 62.63 (C-6), 69.72 (OCOCH_2C$_{Carb.}$), 71.37, 74.72, 78.06, 78.14 (C-2, C-3, C-4, C-5), 76.48 (d, ^{2}J(C,F) = 25.8 Hz, C$_{carb.}$CH$_2$F), 78.06 (C$_{carb.}$CH$_2$OCO), 82.56 (d, ^{1}J(C,F) = 185 Hz, CH$_2$F), 103.7 (C-1); MS (DCI): m/z: 387 (100) [M+NH$_4$+H]$^+$, 404 (30) [M+NH$_4$+NH$_3$+H]$^+$; C$_{10}$H$_{25}$B$_{10}$O$_6$F (368.4).

1-(β-D-Glucopyranosylmethyl)-2-(6-fluorohexyloxymethyl)-1,2-dicarba-*closo*-dodecaborane (23): Reaction of glucose imidate **20** (545 mg, 1.11 mmol) with alcohol **15** (263 mg, 0.86 mmol) in CH$_2$Cl$_2$ (20 mL) over molecular sieves 4 Å with BF$_3\cdot$Et$_2$O (0.10 mL) for 3 h and workup as described for **7** afforded after purification by column chromatography (petroleum ether/ethyl acetate 2:1) 2-(6-fluorohexyloxymethyl)-1-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosylmethyl)-1,2-dicarba-*closo*-dodecaborane (420 mg). The compound was contaminated with small amounts of the corresponding orthoester. Spectral data of the glucoside: R_f (petroleum ether/ethyl acetate 2:1) = 0.35; IR (KBr): $\tilde{\nu}$ = 2944, 2868 (C–H), 2590 (B–H), 1758 (C=O), 1372 (OCOCH$_3$), 1232 cm^{-1} (C–O); ^{1}H NMR (200 MHz, CDCl$_3$): δ = 1.37–1.78 (m, 8H, (CH_2)$_4$CH$_2$F), 2.02, 2.03, 2.09, 2.09 (4s, 12H, 4CH$_3$), 3.47 (t, J = 6.4 Hz, 2H, CH$_2$CH_2O), 3.69 (ddd, J = 9.8, 4.3, 2.3 Hz, 1H, 5-H), 3.88 (d, J = 12.4 Hz, 1H, CH$_2$OCH^{α}H$^{\beta}$C$_{carb.}$), 3.94 (d, J = 12.4 Hz, 1H, CH$_2$OCH$^{\alpha}H^{\beta}$C$_{carb.}$), 4.01 (d, J = 12.8 Hz, 1H, OCOCH^{α}H$^{\beta}$C$_{carb.}$), 4.12 (dd, J = 12.4, 2.6 Hz, 1H, 6-H$^{\alpha}$), 4.26 (dd, J = 12.4, 4.6 Hz, 1H, 6-H$^{\beta}$), 4.36 (d, J = 12.8 Hz, 1H, OCOCH$^{\alpha}H^{\beta}$C$_{carb.}$), 4.46 (dt, ^{2}J(H,F) = 47.0, J' = 6.1 Hz, 2H, CH$_2$F), 4.55 (d, J = 8.0 Hz, 1H, 1-H), 5.02 (dd, J = 9.6 Hz, 7.7 Hz, 1H, 2-H), 5.08 (t, J = 9.6 Hz, 1H, 4-H), 5.21 (t, J = 9.4 Hz, 1H, 3-H); ^{13}C NMR (50 MHz, CDCl$_3$): δ = 20.54, 29.62, 20.66 (CH$_3$), 24.94 (d, ^{3}J(C,F) = 5.4 Hz, CH$_2$(CH$_2$)$_2$F), 25.62, 29.19 (CH$_2$CH$_2$(CH$_2$)$_3$F), 30.23 (d, ^{2}J(C,F) = 19.6 Hz, CH$_2$CH$_2$F), 61.61 (C-6), 68.06, 70.71, 71.99, 72.28 (C-2, C-3, C-4, C-5), 68.73, 70.85, 71.99 (3CH$_2$O), 75.15, 76.88 (2C$_{carb.}$), 83.99 (d, ^{1}J(C,F) = 164 Hz, CH$_2$F), 100.5 (C-1), 169.12, 169.3, 170.1, 170.5 (4OAc); ^{19}F NMR (188.3 MHz, CDCl$_3$, external standard C$_6$F$_6$): δ = −56.50 (tt, ^{2}J(H,F) = 47.4, ^{3}J(H,F) = 25.4 Hz); MS (DCI): m/z: 656 [M+NH$_4$+H]$^+$; C$_{24}$H$_{45}$B$_{10}$O$_{11}$F (636.7).

Sodium methoxide (0.10 mL, 5.4 mM in methanol) was added to a solution of the mixture of glucoside and orthoester (370 mg) described above in methanol (10 mL) and the mixture was stirred for 45 min at room temperature. Workup as described for **8** gave after purification by column chromatography (ethyl acetate) orthoester **24** (24 mg, 47 μmol, 9%) and glucoside **23** (181 mg, 0.39 mmol, 67%). Spectral data of orthoester **24**: R_f (ethyl acetate) = 0.41; [α]$_D^{20}$ = −50.0 (c = 0.5, CHCl$_3$); IR (KBr): $\tilde{\nu}$ = 3396 (O–H), 2936, 2866 (C–H), 2584 (B–H), 1742 cm^{-1} (OCOO); ^{1}H NMR (300 MHz, [D$_4$]methanol): δ = 1.31–1.66 (m, 8H, (CH_2)$_4$CH$_2$O), 1.96 (s, 3H, CH$_3$), 3.10 (t, J = 8.5 Hz, 1H), 3.21–3.24 (m, 1H), 3.32–3.34 (m, 1H, 5-H), 3.42 (t, J = 6.2 Hz, 2H, OCH_2CH$_2$), 3.92 (d, J = 12.4 Hz, 1H, CH$_2$OCH^{α}H$^{\beta}$C$_{carb.}$), 3.97 (d, J = 12.1 Hz, 1H, CH$_2$OCH$^{\alpha}H^{\beta}$C$_{carb.}$), 4.05 (d, J = 12.0 Hz, 1H, OCOCH^{α}H$^{\beta}$C$_{carb.}$), 4.10 (dd, J = 12.1, 5.3 Hz, 1H), 4.20–4.32 (m, 2H), 4.32 (dt, ^{2}J(H,F) = 47.5, J' = 6.0 Hz, 2H, CH$_2$F); ^{13}C NMR (50 MHz, CDCl$_3$): δ = 21.25 (CH$_3$), 25.34 (d, ^{3}J(C,F) = 5.4 Hz, CH$_2$CH$_2$CH$_2$F), 25.94 (CH$_2$CH$_2$CH$_2$O), 29.58 (CH$_2$CH$_2$O), 30.60 (d, ^{2}J(C,F) = 19.6 Hz, CH$_2$CH$_2$F), 63.38 (C-6), 69.32 (OCH_2CH$_2$), 69.91, 73.70, 74.49, 76.02 (C-2, C-3, C-4, C-5), 71.43, 72.68 (2CH_2C$_{carb.}$), 75.82 (C$_{carb.}$), 84.41 (d, ^{2}J(C,F) = 164 Hz, CH$_2$F), 102.7 (C-1), 172.2 (OOCO); MS (DCI): m/z: 528 [M+NH$_4$−H]$^+$; C$_{18}$H$_{39}$B$_{10}$O$_8$F (510.6). Spectral data of glucoside **23**: R_f (ethyl acetate) = 0.22; [α]$_D^{20}$ = −21.0 (c = 0.5, MeOH); IR (KBr): $\tilde{\nu}$ = 3417 (O–H), 2939, 2867 (C–H), 2586 cm^{-1} (B–H); ^{1}H NMR (300 MHz, [D$_4$]methanol): δ = 1.40–1.77 (m, 8H, (CH_2)$_4$CH$_2$O), 3.19 (t, J = 8.1 Hz, 1H), 3.24–3.27 (m, 2H), 3.52 (t, J = 6.4 Hz, 2H, OCH_2CH$_2$), 3.61–3.67 (m, 1H, 5-H), 3.84–3.88 (m, 1H), 4.04 (d, J = 12.0 Hz, 1H, CH$_2$OCH^{α}H$^{\beta}$C$_{carb.}$), 4.09 (d, J = 12.0 Hz, 1H, CH$_2$OCH$^{\alpha}H^{\beta}$C$_{carb.}$), 4.14 (d, J = 12.5 Hz, 1H, OCOCH^{α}H$^{\beta}$C$_{carb.}$), 4.28 (d, J = 7.5 Hz, 1H, 1-H), 4.41 (dt, ^{2}J(H,F) = 47.8, J' = 6.0 Hz, 2H, CH$_2$F), 4.45 (d, J = 12.1 Hz, 1H, OCOCH$^{\alpha}H^{\beta}$C$_{carb.}$); ^{13}C NMR (50 MHz, [D$_4$]methanol): δ = 26.12 (d, ^{3}J(C,F) = 5.1 Hz, CH$_2$(CH$_2$)$_2$F), 26.90, 30.40 (OCH$_2$(CH$_2$)$_2$), 31.51 (d, ^{2}J(C,F) = 19.6 Hz, CH$_2$CH$_2$F), 62.68 (C-6), 69.81, 71.73, 72.72 (3CH$_2$O), 71.41, 74.80, 78.07, 78.22 (C-2, C-3, C-4, C-5), 77.79, 78.74 (2C$_{carb.}$), 84.79 (d, ^{1}J(C,F) = 164 Hz, CH$_2$F), 103.9 (C-1); MS (DCI): m/z: 486 [M+NH$_4$−H]$^+$; C$_{16}$H$_{37}$B$_{10}$O$_7$F (468.6).

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