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Synthesis of 1,3-Dl-O-Acetyl-5-O-Benzoyl-2-O -(O-Carboran-1-Ylmethyl)-D-Ribofuranose. A General Precursor for the Preparation of Carborane-Containing Nucleosides for Boron Neutron Capture Therapy

Werner Tjarks^a; Abul K. M. Anisuzzaman^a; Albert H. Soloway^a

^a The Ohio State University, College of Pharmacy, Columbus, Ohio

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SYNTHESIS OF 1,3-DI-*O*-ACETYL-5-*O*-BENZOYL-2-*O*-(*o*-CARBORAN-1-YLMETHYL)-
D-RIBOFURANOSE. A GENERAL PRECURSOR FOR THE PREPARATION OF
CARBORANE-CONTAINING NUCLEOSIDES FOR BORON NEUTRON CAPTURE
THERAPY

Werner Tjarks*, Abul K. M. Anisuzzaman, and Albert H. Soloway.
The Ohio State University, College of Pharmacy, 500 W. 12th Avenue,
Columbus, Ohio 43210.

Abstract

An eight-step synthesis of 1,3-di-*O*-acetyl-5-*O*-benzoyl-2-*O*-(*o*-carboran-1-ylmethyl)-D-ribofuranose **9** was carried out from 1,2:5,6-*O*-isopropylidene- α -D-allofuranose **1**. Condensation of **9** with trimethylsilyl protected uracil in the presence of trimethylsilyl trifluoromethanesulfonate, and subsequent deblocking of the resulting 1-[3-*O*-acetyl-5-*O*-benzoyl-2-*O*-(*o*-carboran-1-ylmethyl)-D-ribofuranosyl]uracil **10** (>95% β -configuration) by alkaline hydrolysis, yielded 1-[2-*O*-(*o*-carboran-1-ylmethyl)- β -D-ribofuranosyl]uracil **11**.

Introduction

Irradiation of nonradioactive boron-10 with thermal neutrons yields helium and lithium-7 nuclei [$^{10}\text{B}(\text{n},\alpha)^7\text{Li}$ -reaction]. These high linear energy transfer (LET) particles have a destructive range of 5 to 10 μm (\sim 1 cell diameter) in biological tissue. Thus, the energy would be deposited largely in those cells containing boron-10, while sparing nearby cells which have excluded this nuclide. This provides the rationale for the development of boron compounds and their potential use in the treatment of cancer by Boron Neutron Capture Therapy (BNCT). The premise for developing BNCT is that boron-containing compounds will be found which will selectively accumulate in tumors while being excluded from adjacent normal cells. It has been calculated that a uniform cellular concentration of approximately 30 μg boron-10/g of tumor will be required to achieve the needed biological effect.¹

Among many possible agents, boronated derivatives of nucleic acid precursors could be suitable to fulfill this requirement. We have recently synthesized three uridine derivatives with a *closo*-carborane cluster connected through an ether linkage to the 2'-, 3'-, or 5'-position of the carbohydrate portion

of the nucleosides.² These nucleosides, which are related to uridine and possess a bulky pendant group at the ribose moiety, were not designed for a possible incorporation into the DNA of tumor cells. However, the accumulation and retention of these compounds by rapidly proliferating neoplastic cells could be achieved through intracellular entrapment due to phosphorylation.

One of these carboranyl nucleosides, 1-[2-*O*-(*o*-carboran-1-ylmethyl)- β -D-ribofuranosyl]uracil, has been evaluated with F98 rat gliomas both *in vitro*²⁻⁴ and *in vivo*⁵. Though this nucleoside was not incorporated into DNA, as expected, it did indeed demonstrate significant cellular incorporation and retention. The biochemical mechanism for this persistence is now under active investigation.

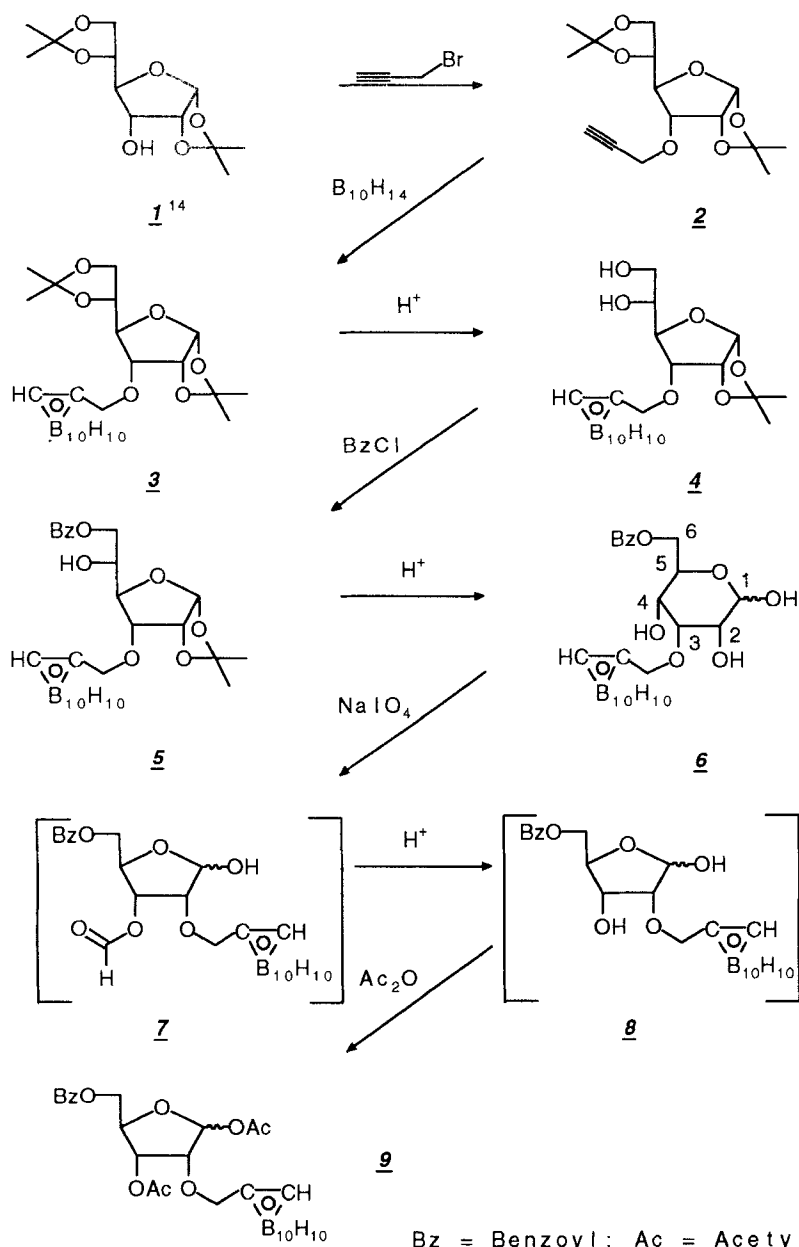
The described synthesis of this carborane-containing uridine derivative² has two major disadvantages: 1) the methodology is limited to the preparation of certain carboranyl pyrimidine nucleosides but cannot be adapted to the synthesis of purine nucleosides or the direct preparation of pyrimidine nucleosides possessing free amino functions;⁶ 2) the chromatographic separation of isomeric intermediates was very difficult and time consuming even for a 2.5 g preparation of 1-[2-*O*-(*o*-carboran-1-ylmethyl)- β -D-ribofuranosyl]uracil.

Encouraged by the promising biological results, we have now synthesized a carborane-containing D-ribose derivative which could serve as a versatile intermediate in the synthesis of a wide variety of carborane-containing nucleosides. In this report, the synthesis of this compound, 1,3-di-*O*-acetyl-5-*O*-benzoyl-2-*O*-(*o*-carboran-1-ylmethyl)-D-ribofuranose, is presented. The condensation of this boron-containing D-ribose derivative with trimethylsilyl protected uracil and subsequent deblocking steps produce the known 1-[2-*O*-(*o*-carboran-1-ylmethyl)- β -D-ribofuranosyl]uracil² in very high yield.

Results and Discussion

The eight-step reaction sequence for the synthesis 1,3-di-*O*-acetyl-5-*O*-benzoyl-2-*O*-(*o*-carboran-1-ylmethyl)-D-ribofuranose **9** is shown in **Scheme I**. The ribose derivative **9** can be used in the synthesis of carborane-containing nucleosides, for example **11**, predominantly in the β -configuration at the anomeric carbon, as shown in **Scheme III**. The rationale for choosing the icosahedral carborane cluster as the boron substituent for **11** (or analogous nucleosides) was the extraordinary chemical stability of this cage⁷ and a tenfold increase in boron content compared to other groups (e.g. dihydroxyboryl⁸⁻¹¹, cyanoborane¹², and borane¹³) which have been used for the synthesis of boronated pyrimidines and purines and their nucleosides. In addition, there is an increased lipophilicity of the nucleosides due to the carborane moiety which

Scheme I



could aid cellular penetration. Yamamoto has described the synthesis of ribo- and 2'-deoxyribonucleosides with a *o*-carborane cage either linked to the 2- or 5-position of the base.¹¹

Alkylation of allofuranose **1**¹⁴ (**Scheme I**) with propargyl bromide yielded **2** which was subsequently converted to the corresponding carboranyl derivative **3** by the reaction with a bis(acetonitrile)decaborane complex. The overall yield for both reactions was 64 %. Decaborane forms bis(ligand)derivatives with Lewis bases such as acetonitrile, alkylsulfides, and alkylamines which can in turn react with substituted acetylenes to give C-substituted *o*-carboranes.⁷ The reaction must be carried out in the absence of hydroxyl, sulfhydryl, and free amino functions since these can cause hydrolysis of the bis(ligand)decaborane complex.⁷ The acetylenic furanose **2**, in which the alcoholic functions are protected as ketals, does fulfill this requirement.

Compound **4** was obtained by acidic hydrolysis of the 5,6-*O*-isopropylidene protective group of **3**. The reaction was carried out in H₂O/AcOH (3:2, v/v) at 60 °C and was terminated after 7 h. The duration of the reaction was critical, since TLC indicated a continuously increasing formation of 3-*O*-(*o*-carboran-1-ylmethyl)-D-allopyranose, as an undesired side product. The yields found for **4** and 3-*O*-(*o*-carboran-1-ylmethyl)-D-allopyranose after chromatographic separation were 87 % and 7 %, respectively. A minor quantity (>2 %) of **3** could be recovered unchanged. A decreased temperature (50 °C) resulted in a prolonged reaction time (~40 h) without preventing the formation of the side product. Increasing the reaction temperature to 70 °C resulted in an enhanced, simultaneous cleavage of the 1,2-*O*-isopropylidene protective group. Thus, the chosen reaction conditions were appropriate, since the yield of **4** was high and chromatographic separation of the three compounds was readily accomplished (see R_f-values in the Experimental Section).

Compound **5** was synthesized from **4** by the action of benzoyl chloride in the presence of pyridine/dichloromethane at -25 °C. At higher temperatures, the bis benzoylated product, 5,6-di-*O*-benzoyl-3-*O*-(*o*-carboran-1-ylmethyl)-1,2-*O*-isopropylidene- α -D-allofuranose, was obtained in increasing amounts. Under the conditions described, the yields for **5** and 5,6-di-*O*-benzoyl-3-*O*-(*o*-carboran-1-ylmethyl)-1,2-*O*-isopropylidene- α -D-allofuranose were 91 % and 4 %, respectively. As in the previous reaction, effective chromatographic separation of both compounds could be achieved due to a great difference in the R_f-values.

Compound **5** was converted to the allose derivative **6** by acidic hydrolysis in 95 % yield. Chemical shifts and coupling constants for the signals of H-1 to

H-6 and C-1 to C-6 in the ^1H - and ^{13}C -NMR spectra of **6** (see Experimental Section), and a comparison of these data with literature data¹⁵, provide solid evidence that compound **6** possesses ~80 % β -allopyranose, ~10 % α -allopyranose, and ~10 % allofuranose configuration.

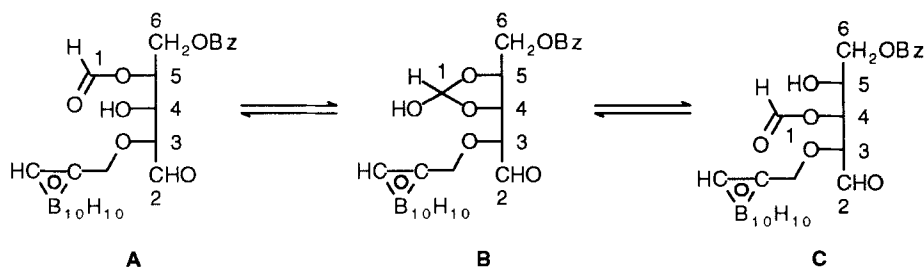
Reichman et al.¹⁶ have reported the synthesis of 6-*O*-benzoyl-3-fluoro-3-deoxy-1,2-di-*O*-isopropylidene-D-arabinose as an intermediate in a reaction sequence which is similar to that described here. This arabinose derivative possesses in contrast to compound **6** (~ 90 % allopyranose form) mainly a furanose configuration. The bulky carboranyl group in allose derivative **6**, having approximately the size of a rotating phenyl group¹⁷, seems to force the carbohydrate entity into the larger six-membered pyranose configuration to minimize structural tensions.

The predominating β -configuration for the allopyranose structures of **6** was expected. An axial position for the carboranylmethoxy group (and any other substituent) at C-3 and the sterically-preferred equatorial positions for all hydroxyl groups and the benzoyloxymethyl group should provide the most stable of the various allopyranose configurations/conformations. The directing influence of the carborane cage on the orientation of the hydroxyl group at the anomeric carbon is negligible and should, if at all, enhance the formation of the α -anomer.

Periodate-oxidation of compound **6** affords the unstable ribofuranose derivative **7**. Compound **7** was deformylated without purification by acidic hydrolysis to yield **8** which was directly acetylated to give **9**. The overall yield from **6** to **9** was 82 %. Compound **9** was obtained as an anomeric mixture consisting of 95 % β - and 5 % α -anomer. This was shown by the ^1H - NMR of **9** which exhibits a singlet at 6.07 ppm ($J_{1,2} = 0$ Hz, integration: 1H) and a doublet at 6.38 ppm ($J_{1,2} = 4.3$ Hz, integration: ~0.06 H) caused by the H-1 protons of the β - and α -anomer, respectively. Small or zero $J_{1,2}$ values establish a 1,2-*trans* relationship in furanose derivatives, especially when these compounds are constrained either by ring fusion or by a large group as in the present case.¹⁸ The ^{13}C -NMR spectrum of **9** shows signals for C-1 carbons at 99.8 ppm (β -anomer) and 96.3 ppm (α -anomer) in a 19 :1 intensity ratio. The observed chemical shifts for the C-1 carbons are indicative for ribose derivatives in β - and α -configuration.¹⁵

The reaction steps from **6** to **9** were carried out " *in situ* " for 2 reasons: 1) intermediate **7** appeared to be rather unstable. A significant quantity of its hydrolysis product **8** could already be detected during the periodate-oxidation of **6** by TLC; 2) target compound **9** is the ultimate product of the eight-step

Scheme II



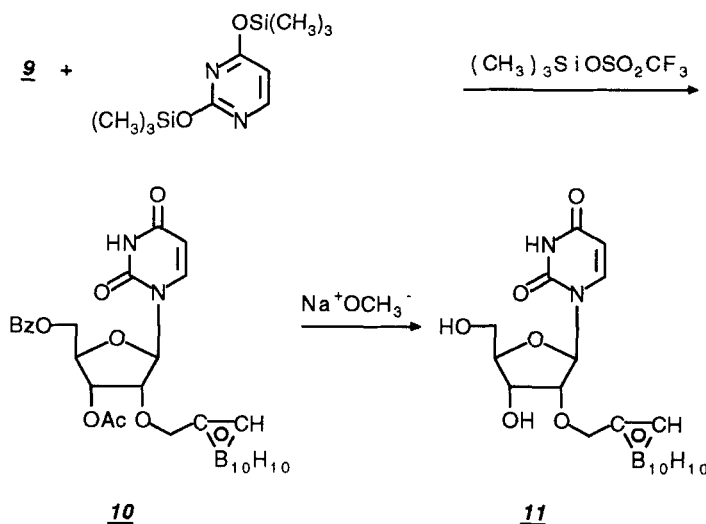
synthesis. Therefore, it is desirable to avoid purification procedures whenever possible to obtain this compound in the highest possible yield. The " *in situ* " synthesis of **9** from **6** can be considered as our first successful approach in this direction. It is conceivable that compounds **2**, **4**, and **9** are the only ones in the reaction sequence displayed in **Scheme I** which require a rigorous purification.

The structure of **7** was confirmed by the $^1\text{H-NMR}$ spectrum (MeOH-d_4) of its 1-*O*-acetyl derivative¹⁹ which is almost identical with that of ribofuranose derivative **9** except for a singlet at 8.21 ppm (characteristic for a formate proton), and just one signal for an acetyl group at 1.84 ppm. In addition, there is a significant down field shift for the signal of H-3 from 5.30 ppm for **9** to 5.47 ppm for **7** (see Experimental Section and REFERENCES). These spectroscopic data indicate a pentofuranose configuration for **7** with a formyl group in 3-position.

The existence of an intermediate such as allofuranose **7** was surprising since periodate-oxidation of compound **6**, which possesses ~90 % hexopyranose configuration, can lead to **7** only if the rate of pyranose to furanose conversion for **6** exceeds significantly the rate of cleavage of the C-1 - C-2 bond. However, it is well known that periodate-excision of C-1 under aqueous conditions, as in the present case, does lead almost exclusively to an attack on pyranose forms.²⁰ A second possibility would be a formyl migration after the cleavage, as it is known for similar acyl derivatives.²¹ Previous examples of 3-formate esters of pentofuranoses arose from periodate-oxidation of hexofuranoses.¹⁶

The situation is illustrated in **Scheme II**. Periodate-excision of hexopyranose derivative **6** does lead to the open-chain intermediate **A** which cannot cyclize to pentofuranose **7** because the hydroxyl function in position 5 is masked

Scheme III



by a formyl group. Oxidation in the case of a hexofuranose configuration of **6** would lead to intermediate **C** which can cyclize to **7** immediately. However, migration of the formyl group from position 5 (**A**) to position 4 (**C**), possibly involving a hydroxy dioxolane intermediate such as **B**²¹, is conceivable. The driving force for such a rearrangement would be the cyclization to the pentofuranose ring which is thermodynamically more stable than the open-chain structure of **A**.

The reaction of **9** with trimethylsilyl protected uracil in the presence of trimethylsilyl trifluoromethanesulfonate, and subsequent removal of the trimethylsilyl protective groups under slightly alkaline conditions, afforded the uridine derivative **10** (Scheme III) in 71% yield. A TLC-control of the reaction mixture showed two spots of low intensity resulting from uracil and **9** and one spot of high intensity caused by compound **10** (see Experimental Section). An additional spot, close to or partly overlapping with that of **10**, which would be indicative for an anomeric mixture, could not be detected. The ¹H- and ¹³C-NMR spectra of the chromatographically purified compound **10** display a doublet at 5.86 ppm (*J*_{1',2'} = 3.8 Hz) for H-1' and a signal at 103.2 ppm for C-1'. Both signals are characteristic for ribose derivatives in β-configuration.¹⁵ Smaller signals for the H-1' and C-1' nuclei of the possible anomeric counterpart, as in the case of

compound **9**, could not be observed. Analytical methods (TLC, HPLC) applied on the purified material did not provide any evidence for an anomeric mixture. Alkaline hydrolysis of the 5-*O*-benzoyl and 3-*O*-acetyl protecting groups of **10** with catalytic amounts of sodium methylate at 4 °C afforded **11** in 90 % yield. The analytical and spectroscopic data obtained for the purified compound are identical with those of 1-[2-*O*-(*o*-carboran-1-ylmethyl)- β -D-ribofuranosyl]uracil previously described² (see Experimental Section) and provide no evidence for an anomeric mixture.

It is conceivable that a minor quantity of the α -anomer was formed in the condensation reaction of **9** with trimethylsilyl protected uracil which could have been lost during the purification procedure. It is also possible that the α -anomer had the same R_f -value and retention time as its β -counterpart and the total amount was too small for a spectroscopic detection. However, a careful estimation of the obtained data indicates at least 95 % β -configuration for compound **10**. This demonstrates the strong *trans*-directing influence of the carborane moiety on substituents at the anomeric carbon. Therefore, it can be expected that the condensation of silylated thymine, N⁴-acetylcytosine, N²-acetylguanine, and N⁶-benzoyladenine (or other pyrimidines and purines) with ribofuranose **9** via the " Vorbrüggen-Method " ²²⁻²⁴ might also lead to a high β to α ratio for the resulting nucleosides.

Conclusion

The eight-step synthesis of 1,3-di-*O*-acetyl-5-*O*-benzoyl-2-*O*-(*o*-carboran-1-ylmethyl)-D-ribofuranose **9** from 1,2:5,6-*O*-isopropylidene- α -D-allofuranose **1**, although lengthy, afforded a 39 % overall yield. The reactions and workup procedures for all products were readily feasible with no chromatographic separation of isomeric intermediates required. This was a problem in the previously reported synthesis of carboranyl uridines.² The described synthesis of **9** is suitable for large-scale preparation and an increase of the overall yield is conceivable when unnecessary purification procedures are avoided. Condensation of **9** with silylated uracil in the presence of trimethylsilyl trifluoromethanesulfonate yielded 1-[3-*O*-acetyl-5-*O*-benzoyl-2-*O*-(*o*-carboran-1-ylmethyl)-D-ribofuranosyl]uracil **10** in more than 95% β -configuration. The described method is potentially applicable to the synthesis of other carborane-containing pyrimidine and purine nucleosides.

Experimental Section

FT-NMR spectra were recorded on a Bruker AM500 at 500 MHz (proton) and 125.5 MHz (carbon-13) in MeOH-*d*₄ unless stated otherwise. Chemical

shifts (δ) are reported in ppm downfield from an internal tetramethylsilane standard. Coupling constants (J) are reported in Hz. IR spectra were recorded on a RFX 40 FT-IR spectrometer (Laser Precision Corp.). The spectra for all compounds were in accordance with the proposed structures. Melting points were determined on a Fisher-Johns melting point apparatus and are reported uncorrected. Optical rotations were determined on Perkin-Elmer 241 polarimeter at 20 °C in MeOH. FAB⁺ mass spectra were obtained on a FG 70-250S mass spectrometer through ionization with Xe using a 3-nitrobenzyl alcohol matrix. For all boron-containing compounds, the mass of the most intense peak of the isotope pattern is indicated. The measured patterns agreed with the theoretical ones. Elemental analysis for all boron-containing compounds were performed by Analytische Laborien, Gummersbach, Germany; elemental analysis for compound **2** was conducted by Atlantic Microlab, Inc., Norcross, Georgia. Silica gel 60-F₂₅₄ glass plates were used for TLC. Compound visualization was achieved with UV light (254 nm), and spraying with either 5% H₂SO₄ (carbohydrate) or 0.06% PdCl₂ / 1% HCl (boron) and subsequent heating at 120 °C for 10-15 min. Analytical HPLC was performed with a C18 reversed-phase column (4.6 mm ID x 25 cm L [8 μ m]) + C18 reversed-phase guard module (4.6 mm ID x 1.5 cm L [8 μ m]). Silica gel 60 (70-230 mesh) was used for column chromatography. Reagent-grade solvents were used for reactions and chromatography. Pyridine and DMF were dried with molecular sieves (4 Å). Toluene and THF were distilled from sodium; MeOH, dichloromethane, and acetonitrile from Mg, CaCl₂, and P₂O₅, respectively.

1,2:5,6-Di-*O*-isopropylidene-3-*O*-(3-prop-1-ynyl)- α -D-allofuranose (2).

A 4.4 g (110 mmol) quantity of sodium hydride (60% dispersion in mineral oil) was slowly added to an ice-cooled solution of 28 g (107.5 mmol) 1,2:5,6-*O*-isopropylidene- α -D-allofuranose **1**¹⁴ in 150 mL of DMF. The mixture was stirred under anhydrous conditions for 30 min at 0 °C until the hydrogen evolution had ceased. After cooling to -10 °C, 9.6 mL (107.5 mmol) of propargyl bromide was slowly added and the solution was stirred for additional 60 min at -10 °C. The reaction mixture was diluted with 1L of H₂O and was extracted 5 x with 150 mL of diethyl ether. Subsequently, the combined organic layers were dried over anhydrous magnesium sulfate, filtered, and evaporated to dryness. The resulting residue was crystallized 2 x from isopropyl ether. Yield: 28.5 g (89 %); white crystals; mp 113 °C; [α]_D + 238.6° (*c* 1); R_f 0.46 (AcOEt / hexane, 1:1, v/v, [TLC]); MS 299 (M+H)⁺; Anal. Calcd for C₁₅H₂₂O₆: C, 60.39; H, 7.43; Found: C, 60.16; H, 7.46; ¹H-NMR (CDCl₃): δ 1.35, 1.37, 1.46, 1.57 (4s, 12H,

isopropylidene); 2.47 (t, 1H, $\text{CH}_2\text{-C}\equiv\text{CH}$, $J_{1,3} = 2.4$); 3.96 - 4.04 (m, 2H, H-3, H-4); 4.07, 4.09, 4.12, 4.13 (d of ABq, 2H, H-6a, H-6b, $J_{6a,6b} = 8.6$, $J_{5,6a} = 3.3$, $J_{5,6b} = 4.3$); 4.27, 4.30, 4.38, 4.42 (d of ABq, 2H, $\text{CH}_2\text{-C}\equiv\text{CH}$, $J_{a,b} = 16.1$); 4.35 (m, 1H, H-5); 4.71 (apparent t, 1H, H-2, $J_{2,3} = 4.1$), 5.78 (d, 1H, H-1, $J_{1,2} = 3.7$).

3-*O*-(*o*-Carboran-1-ylmethyl)-1,2:5,6-di-*O*-isopropylidene- α -D-allofuranose (**3).** A solution of 7.2 g (59 mmol) decaborane and 9.4 mL (177 mmol) of acetonitrile in 250 mL of toluene was refluxed under anhydrous conditions for 1 h. The solution was cooled to room temperature and 17 g (57 mmol) of 1,2:5,6-di-*O*-isopropylidene-3-*O*-(3-prop-1-ynyl)- α -D-allofuranose **2** was added. This reaction mixture was heated at 90 °C for 5 h when TLC indicated that the reaction was complete. Following evaporation of the toluene, the residue was taken up in diethyl ether, filtered, and the filtrate was evaporated to dryness. The remaining residue was purified by column chromatography. Yield: 16.6 g (70 %); white crystals; mp 76 °C; $[\alpha]_D + 166.9^\circ$ (c 2); R_f 0.51 (AcOEt / hexane, 1:1, v/v, [TLC, column]); MS 417 (M+H)⁺; Anal. Calcd for $\text{C}_{15}\text{H}_{32}\text{O}_6\text{B}_{10}$: C, 43.25; H, 7.74; B, 25.95; Found: C, 43.45; H, 7.62; B, 25.77; ¹H-NMR: δ 1.30 - 3.00 (br. m, 10H, B-H); 1.33, 1.39, 1.50 (3s, 12H, isopropylidene); 3.82, 3.91 (d of ABq, 2H, H-6a, H-6b, $J_{6a,6b} = 8.4$, $J_{5,6a} = 5.1$, $J_{5,6b} = 4.7$); 3.86 (dd, 1H, H-4, $J_{4,5} = 5.9$); 4.04, 4.14 (ABq, 2H, $\text{O-CH}_2\text{-C}_{\text{carborane}}$, $J_{a,b} = 10.6$); 4.05 (dd, 1H, H-3, $J_{3,4} = 8.4$); 4.19 (m, 1H, H-5); 4.61 (br. s, 1H, $\text{C}_{\text{carborane}}\text{-H}$); 4.67 (apparent t, 1H, H-2, $J_{2,3} = 4.2$); 5.75 (d, 1H, H-1, $J_{1,2} = 3.8$).

3-*O*-(*o*-Carboran-1-ylmethyl)-1,2-*O*-isopropylidene- α -D-allofuranose (**4).** A 11.2 g (26.9 mmol) quantity of 3-*O*-(*o*-carboran-1-ylmethyl)-1,2:5,6-di-*O*-isopropylidene- α -D-allofuranose **3** was stirred at 60 °C in 120 mL of H_2O / AcOH (3:2, v/v) for 7 h when TLC indicated that the starting material had largely reacted while the formation of 3-*O*-(*o*-carboran-1-ylmethyl)-D-allopyranose was increasing. The reaction mixture was cooled to room temperature and the solvent was evaporated in high vacuum (0.3 mm) at 35 °C. Compound **4** was separated from minor quantities of **3** and 3-*O*-(*o*-carboran-1-ylmethyl)-D-allopyranose (R_f :0.07, AcOEt / hexane, 7:3, v/v) by column chromatography. Yield: 8.8 g (87 %) of a clear glass; $[\alpha]_D + 125.8^\circ$ (c 1); R_f 0.23 (AcOEt / hexane, 7:3, v/v, [TLC, column]); MS 377 (M+H)⁺; Anal. Calcd for $\text{C}_{12}\text{H}_{28}\text{O}_6\text{B}_{10}$: C, 38.29; H, 7.50; B, 28.72; Found: C, 38.47; H, 7.44; B, 28.64; ¹H-NMR: δ 1.30 - 3.00 (br. m, 10H, B-H); 1.33, 1.49 (2s, 6H, isopropylidene); 3.51, 3.58 (d of ABq, 2H, H-6a, H-6b, $J_{6a,6b} = 11.2$, $J_{5,6a} = 7.0$, $J_{5,6b} = 4.9$); 3.80 (m, 1H, H-5); 3.93 (dd, 1H, H-3, $J_{3,4} = 8.4$); 4.00 (dd, 1H, H-4, $J_{4,5} = 3.5$); 4.01, 4.11(ABq, 2H, $\text{O-CH}_2\text{-C}_{\text{carborane}}$, $J_{a,b} = 10.5$); 4.59 (br. s, 1H, $\text{C}_{\text{carborane}}\text{-H}$); 4.66 (apparent t, 1H, H-2, $J_{2,3} = 4.3$); 5.75 (d, 1H, H-1, $J_{1,2} = 3.9$).

6-*O*-Benzoyl-3-*O*-(*o*-carboran-1-ylmethyl)-1,2-*O*-isopropylidene- α -D-allofuranose (5). A solution of 1.33 mL (11.5 mmol) benzoyl chloride in 20 mL of dichloromethane was added dropwise under anhydrous conditions over a period of 1 h to a mixture of 4.3 g (11.4 mmol) 3-*O*-(*o*-carboran-1-ylmethyl)-1,2-*O*-isopropylidene- α -D-allofuranose **4** and 1.35 mL (17.5 mmol) of pyridine in 50 mL of dichloromethane at -25 °C. After stirring for additional 1.5 h at this temperature, 5 mL of MeOH was added to terminate the reaction and the solvents were evaporated. Compound **5** was separated from a minor quantity of 5,6-di-*O*-benzoyl-3-*O*-(*o*-carboran-1-ylmethyl)-1,2-*O*-isopropylidene- α -D-allofuranose (R_f : 0.61, AcOEt / hexane, 7:3, v/v) by column chromatography. Yield: 5 g (91%) of a clear glass; $[\alpha]_D + 117.1^\circ$ (c 1.5); R_f 0.54 (AcOEt / hexane, 7:3, v/v, [TLC, column]); MS 381 (M+H)⁺; Anal. Calcd for C₁₉H₃₂O₇B₁₀: C, 47.49; H, 6.71; B, 22.50. Found: C, 47.63; H, 6.56; B, 22.60. ¹H-NMR: δ 1.30-3.00 (br. m, 10H, B-H); 1.34, 1.50 (2s, 6H, isopropylidene); 4.01, 4.10 (d of ABq, 2H, H-6a, H-6b, $J_{6a,6b} = 8.5$, $J_{5,6a} = 4.7$, $J_{5,6b} = 3.4$); 4.04, 4.13 (ABq, 2H, O-CH₂-C_{carborane}, $J_{a,b} = 10.4$); 4.17 (m, 1H, H-5); 4.32 (m, 2H, H-3, H-4); 4.49 (br. s, 1H, C_{carborane}-H); 4.7 (apparent t, 1H, H-2, $J_{2,3} = 4.2$); 5.79 (d, 1H, H-1, $J_{1,2} = 3.8$); 7.47 - 8.06 (m, 5H, arom.).

6-*O*-Benzoyl-3-*O*-(*o*-carboran-1-ylmethyl)-D-allopyranose (6). A 4 g (8.32 mmol) quantity of 6-*O*-benzoyl-3-*O*-(*o*-carboran-1-ylmethyl)-1,2-*O*-isopropylidene- α -D-allofuranose **5** was refluxed in 75 mL of H₂O / AcOH (3:2, v/v) for 2 h. The reaction mixture was cooled to room temperature and evaporated to dryness. The remaining residue was purified by column chromatography. Yield: 3.5 g (95%) of a clear glass; $[\alpha]_D + 11.8^\circ$ (c 2); R_f 0.15 (AcOEt / hexane, 1:1, v/v, [TLC, column]); MS 441 (M+H)⁺, 423 (M - H₂O + H)⁺; Anal. Calcd for C₁₆H₂₈O₇B₁₀: C, 43.63; H, 6.41; B, 24.54; Found: C, 43.88; H, 6.27; B, 24.70; ¹H-NMR (β -allopyranose): δ 1.30 - 3.00 (br. m, 10H, B-H); 3.33 (dd, 1H, H-2, $J_{2,3} = 2.7$); 3.68 (dd, 1H, H-4, $J_{4,5} = 9.9$); 3.87 (apparent t, 1H, H-3, $J_{3,4} = 2.7$); 3.96 (m, 1H, H-5); 4.29 (s, 2H, O-CH₂-C_{carborane}); 4.40, 4.59 (d of ABq, 2H, H-6a, H-6b, $J_{6a,6b} = 11.9$, $J_{5,6a} = 6.3$, $J_{5,6b} = 2.1$); 4.80 (d, 1H, H-1, $J_{1,2} = 8.0$); 4.98 (br. s, 1H, C_{carborane}-H); 7.45 - 8.06 (m, 5H, arom.); (α -allopyranose): 3.30 (apparent t, ~0.1H, H-2, $J_{2,3} = 1.7$); 5.14 (d, ~0.1H, H-1, $J_{1,2} = 1.7$). ¹³C-NMR (β -allopyranose): δ 59.8 (C_{carborane}-H); 65.6 (C-6); 69.3 (C-4); 73.5, 73.6 (C-2, C-5); 75.4 (CH₂-C_{carborane}); 75.7 (CH₂-C_{carborane}); 84.4 (C-3); 95.8 (C-1); 129.5, 130.6, 131.3, 134.2 (arom.); 168.0 (C=O, Bz); (α -allopyranose): 93.9 (C-1); (β -allofuranose): 103.4 (C-1); (α -allofuranose): 97.2 (C-1).

1,3-Di-*O*-acetyl-5-*O*-benzoyl-2-*O*-(*o*-carboran-1-ylmethyl)-D-ribofuranose (9). A solution of 2.51 g (5.67 mmol) 6-*O*-benzoyl-3-*O*-(*o*-carboran-1-ylmethyl)-D-allopyranose **6** and 1.34 g (6.25 mmol) of NaIO₄ was stirred for 1 h at room temperature in 75 mL of H₂O / EtOH (1:1, v/v), when TLC indicated the conversion of the starting material to 5-*O*-benzoyl-2-*O*-(*o*-carboran-1-ylmethyl)-3-*O*-formyl-D-ribofuranose **7** (R_f: 0.50, AcOEt / hexane, 1:1, v/v). Subsequently, most of the EtOH was evaporated at room temperature and the remaining aqueous phase was extracted 3 x with 25 mL of diethyl ether. The combined organic layer were dried over magnesium sulfate, filtered, and evaporated to dryness. The residue was redissolved in 50 mL of acetone / 7.5% HCl (1:1, v/v) and the solution was stirred at room temperature for 72 h. TLC indicated the complete conversion of compound **7** to 5-*O*-benzoyl-2-*O*-(*o*-carboran-1-ylmethyl)-D-ribofuranose **8** (R_f: 0.44, AcOEt/hexane, 1:1, v/v). Acetone was evaporated at room temperature and the aqueous phase was extracted 3 x with 25 mL of diethyl ether. The combined diethyl ether extracts were dried over magnesium sulfate, filtered, and evaporated to dryness. The residue was redissolved in 50 mL of pyridine / Ac₂O (9:1, v/v) and stirred under anhydrous conditions for 12 h at room temperature. Subsequently, the solvent was removed by distillation and the residue was purified by column chromatography. Yield: 2.3 g (82 %) of a clear glass; [α]_D +38.5° (c 1); R_f 0.59 (AcOEt / hexane, 1:1, v/v, [TLC, column]); MS 495 (M+H)⁺, 435 (M - C₂H₄O₂+H)⁺; Anal. Calcd for C₁₉H₃₀O₈B₁₀: C, 46.16; H, 6.12; B, 21.87; Found: C, 46.24; H, 5.95; B, 21.59; ¹H-NMR (β-ribofuranose): δ 1.30 - 3.00 (br. m, 10H, B-H); 1.84, 2.11 (2s, 6H, Ac); 4.04, 4.16 (ABq, 2H, O-CH₂-C_{carborane}, J_{a,b} = 11.0); 4.24 (d, 1H, H-2, J_{2,3} = 4.7); 4.35, 4.65 (d of ABq, 2H, H-5a, H-5b, J_{5a,5b} = 12.2, J_{4,5a} = 4.2, J_{4,5b} = 3.5); 4.47 (m, 1H, H-4); 4.54 (br. s, 1H, C_{carborane}-H); 5.30 (dd, 1H, H-3, J_{3,4} = 7.2); 6.07 (s, 1H, H-1, J_{1,2} = 0); 7.47 - 8.05 (m, 5H, arom.); (α-ribofuranose): 5.35 (dd, ~0.06H, H-3); 6.38 (d, ~0.06H, H-1, J_{1,2} = 4.3); ¹³C-NMR (β-ribofuranose): δ 20.6, 20.8 (CH₃, Ac); 61.2 (C_{carborane}-H); 64.4 (C-5); 73.0 (C-3, CH₂-C_{carborane}); 74.4 (CH₂-C_{carborane}); 81.2, 82.8 (C-2, C-4); 99.8 (C-1); 129.7, 130.7, 131.1, 134.5 (arom.); 167.4 (C=O, Bz); 171.0, 171.8 (C=O, Ac); (α-ribofuranose): 96.3 (C-1).

1-[3-*O*-Acetyl-5-*O*-benzoyl-2-*O*-(*o*-carboran-1-ylmethyl)-β-D-ribofuranosyl]-uracil (10). A solution of 200 mg (1.17 mmol) uracil in 15 mL of 1,1,1,3,3,3-hexamethyldisilazane, 10 mL of THF, and 1 mL of chlorotrimethylsilane was refluxed under anhydrous conditions. Ammonia evolved and ammonium chloride precipitated in the reflux condenser. After 3 h no further

precipitation of ammonium chloride could be observed and the reaction mixture was cooled to room temperature. The solvents were thoroughly evaporated at 50 °C and the oily residue was redissolved in 10 mL of acetonitrile. This solution was added dropwise over a period of 10 min at room temperature to a solution of 543.8 mg (1.1mmol) of 5-*O*-benzoyl-2-*O*-(*o*-carboran-1-ylmethyl)-1,3-di-*O*-acetyl-D-ribofuranose **9** and 251 mL (1.3 mmol) of trimethylsilyl trifluoromethanesulfonate in 15 mL of acetonitrile. The reaction mixture was stirred at room temperature with the exclusion of moisture for 4 h when TLC indicated that the reaction was almost complete. Acetonitrile was evaporated at room temperature and the residue was dissolved in 50 mL of diethyl ether. This solution was washed 3 x with 30 mL of a saturated sodium bicarbonate solution, dried over magnesium sulfate, filtered, and evaporated to dryness. The oily residue was purified by column chromatography. Yield: 454mg (71%) of a clear glass; $[\alpha]_D +29.8^\circ$ (c 0.5); R_f 0.26 (AcOEt / hexane, 1:1, v/v, [TLC, column]); MS 547 (M+H)⁺, 435 (M - uracil+H)⁺; Anal. Calcd for C₂₁H₃₀N₂O₈B₁₀: C, 46.15; H, 5.53; N, 5.13; B, 19.78; Found: C, 45.88; H, 5.40; N, 4.90; B, 19.60; ¹H-NMR: δ 1.30 - 3.00 (br. m, 10H, B-H); 2.13 (s, 3H, Ac); 4.06, 4.16 (ABq, 2H, O-CH₂-C_{carborane}, J_{a,b} = 11.1); 4.37 (dd, 1H, H-2', J_{2',3'} = 5.5); 4.51(m, 1H, H-4'); 4.53 (br. s, 1H, C_{carborane}-H); 4.58, 4.66 (d of ABq, 2H, H-5'a, H-5'b, J_{5'a,5'b} = 12.4, J_{4',5'a} = 4.5, J_{4',5'b} = 3.5); 5.25 (apparent t, 1H, H-3', J_{3',4'} = 5.9); 5.54 (d, 1H, H-5, J_{5,6} = 8.1); 5.86 (d, 1H, H-1', J_{1',2'} = 3.8); 7.64 (d, 1H, H-6); 7.49 - 8.04 (m, 5H, arom.); ¹³C-NMR: δ 20.6 (CH₃, Ac); 61.1 (C_{carborane}-H); 64.1 (C-5'); 71.7 (C-3'); 73.2 (CH₂-C_{carborane}); 74.2 (CH₂-C_{carborane}); 80.9, 82.3 (C-2', C-4'); 90.2 (C-5); 103.2(C-1'); 129.7, 130.6, 130.8, 134.7 (arom.); 141.5 (C-6); 151.9 (C-4); 165.7 (C-2); 167.5 (C=O, Bz); 171.5 (C=O, Ac).

1-[2-*O*-(*o*-carboran-1-ylmethyl)- β -D-ribofuranosyl]uracil (11). A 0.75 g (1.37 mmol) quantity of 1-[3-*O*-acetyl-5-*O*-benzoyl-2-*O*-(*o*-carboran-1-ylmethyl)- β -D-ribofuranosyl]uracil **10** was dissolved in 30 mL of methanol and 2 drops of a 2% solution of sodium methylate in methanol were added at 0 °C. The reaction mixture was left in a refrigerator at 4 °C for 2 days when TLC indicated the completion of the reaction. Subsequently, 7.5g of Dowex 50X8 - 100 ion-exchange resin (H⁺-form) was added at 0 °C to neutralize the solution. The resin was filtered off and the filtrate was evaporated to dryness. The remaining residue was purified by column chromatography. Yield: 494 mg (90%); white crystals; mp 136 - 137 °C; $[\alpha]_D +15.4^\circ$ (c 1); R_f = 0.45 (dichloromethane/MeOH, 7:1, v/v, [TLC, column]) ; HPLC - ret. time: 4.87 min (MeOH/H₂O, 85:15, v/v, flow rate: 0.75 ml/min). The ¹H-NMR, MS, and IR

spectra as well as the mp and the HPLC - ret. time of compound **11** are identical with those of 1-[2-*O*-(α -carboran-1-ylmethyl)- β -D-ribofuranosyl]uracil, described in Ref. 2. The mixed mp is 136 - 137 °C.

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