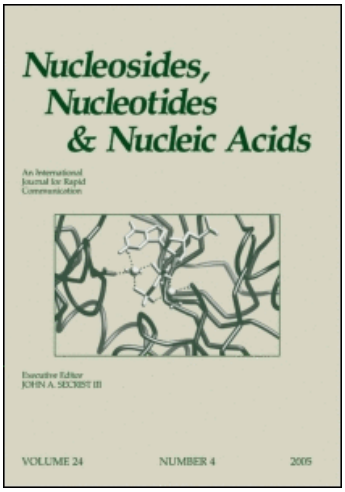

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SYNTHESIS AND BIOCHEMICAL ACTIVITY OF HYDROPHILIC CARBORANE-CONTAINING PYRIMIDINE NUCLEOSIDES AS POTENTIAL AGENTS FOR DNA INCORPORATION AND BNCT

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Abstract. A novel type of hydrophilic 5-tethered carborane-containing 2'-deoxyuridine derivative, SUB-7-DIOL, has been developed. This compound is a potential agent for DNA incorporation and BNCT, because it showed satisfactory aqueous solubility and demonstrated an excellent rate of phosphorylation by human thymidine kinase. This study also demonstrated the importance of tethering a flexible hydrocarbon chain between the carborane cage and the 5-position of the nucleoside, and the effectiveness of a water-solubilizing moiety attached to the carbon atom of the lipophilic carborane cage.

Introduction

The rationale for Boron Neutron Capture Therapy (BNCT) is to irradiate a nonradioactive boron-10 isotope with thermal neutrons to produce an unstable boron-11 nucleus, which undergoes fission generating an alpha particle and a lithium nucleus. These high linear energy transfer (LET) particles have the potential advantage over other types of radiation in that the destructive effects are confined to those cells in which this nuclear reaction occurs. A key requirement that will lead to the clinical application of BNCT is the development of tumor targeting boron compounds. A boron-containing nucleoside is one example of such a compound.[1,2]

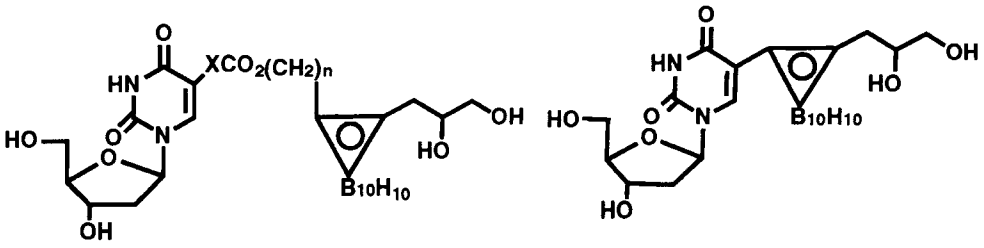
The rationale for choosing a nucleoside as a boron carrier is the hope that such a boron-containing compound will be taken up by rapidly proliferating tumor cells through the action of the nucleoside transport system, become entrapped within the tumor cells by being converted to the corresponding 5'-

monophosphate, and subsequently be incorporated into the cell's nucleic acids.[3-6]

A nucleoside possessing a carborane moiety attached directly to the 5-position showed poor biochemical activity.[7] That may be due to such a bulky substituent inhibiting enzymatic conversion of the nucleoside to its corresponding nucleotide. Thus in our previous investigation, the concept of tethering the bulky carborane cage through a flexible chain at the 5-position of deoxyuridine was proposed.[8-10] The results of those biochemical studies with human thymidine kinase (TK) demonstrated that all of the 5-tethered carborane-containing pyrimidine nucleosides can be phosphorylated to the corresponding 5'-monophosphate, and that the best of these, based on the rate of phosphorylation, was the saturated ester, 5-[(1,2-dicarba-*closo*-dodecaboranylpropoxycarbonyl)ethyl]-2'-deoxyuridine (SUB-7).[11] However, there is a major limitation with this compound, and that is its low aqueous solubility due, in large part, to the high lipophilicity of the carborane cage. In order to carry out the enzymatic studies, organic solvents, such as methanol, were needed to increase solubility.

Although naturally-occurring nucleosides are hydrophilic, the carborane-containing analogs possess such low aqueous solubility that their biochemical evaluation and their effective delivery under *in vivo* condition are compromised. In order to increase the solubility of carborane-containing nucleosides in aqueous solutions, Yamamoto and co-workers[12-14] have introduced polyols of the cascade type as a water-solubilizing moiety to the *o*-carborane and BPA derivatives, and have linked a glucose to the 5'-position of deoxyuridine. Tjarks et al.[15] have made anionic *nido* analogs of the *o*-carborane. Unfortunately, all of those compounds are poor competitors of thymidine, and are not taken up by tumor cells.

In order to overcome these problems, non-ionic hydrophilic carborane-containing compounds, **I** and **II**, have been the objective of our synthetic activities (Scheme 1).[16,17] These compounds have a dihydroxypropyl moiety attached to the carbon of the carborane cage that is not linked to the nucleoside. Compounds **I** and **II** have been synthesized from 5-iodo-2'-deoxyuridine. In order to compare them with 5-carboranyl-2'-deoxyuridine (CDU) and determine the importance of the tether chain on biochemical activity, the dihydroxypropyl group was also linked to the carborane cage of CDU to produce 5-[2-(2',3'-dihydroxypropyl)-1,2-dicarbo-*closo*-dodecaboranyl]-2'-deoxyuridine (CDU-DIOL).



I; X= ethyl, n = 3; **SUB-7-DIOL**
IIa; X = vinyl, n = 3; **UB-7-DIOL**
IIb; X = vinyl, n = 4; **UB-8-DIOL**

CDU-DIOL

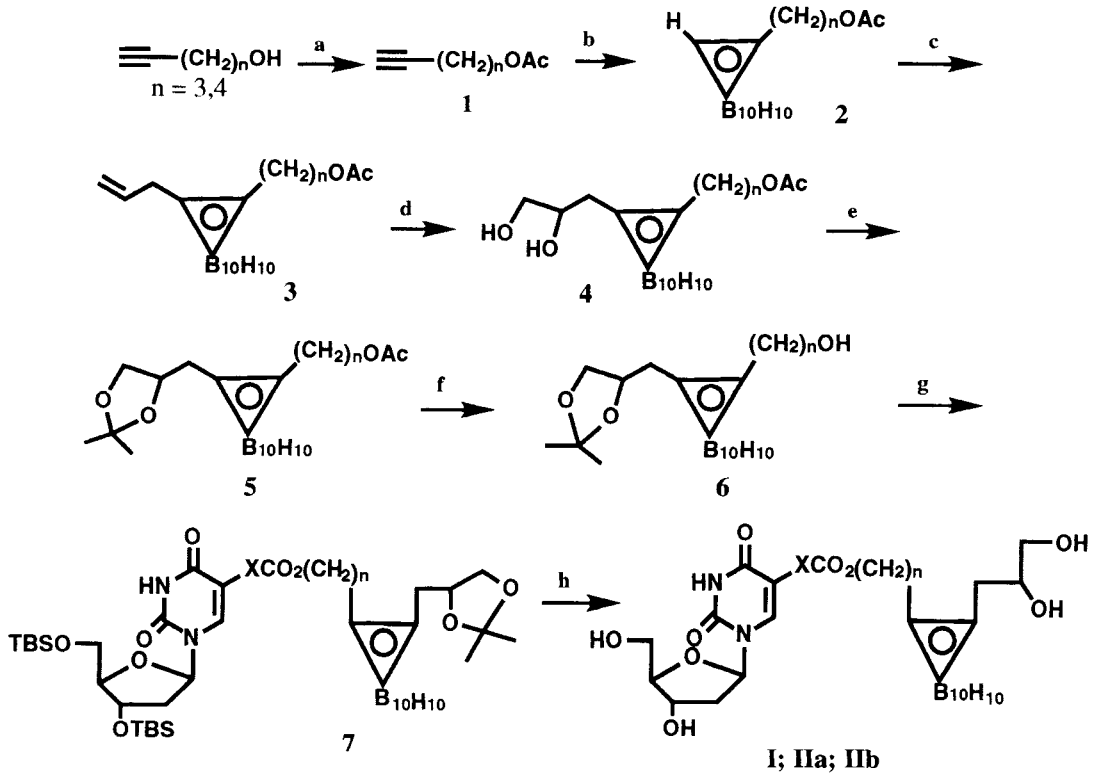
Scheme 1

In the biochemical studies, the rate of phosphorylation by human cytosolic thymidine kinase of these new compounds was compared with that of the corresponding nondihydroxypropyl linked analogs. Our objective was to determine the importance of the dihydroxypropyl moiety and the tethering chain on the biochemical activity of these compounds. A detailed description of the synthesis, characterization and biochemical studies of these compounds is reported.

Synthetic Chemistry

Attempted synthesis of target compound **I**, by palladium-catalyzed allylation of 5-[3-(1,2-dicarbo-*closo*-dodecaboranyl)propoxycarbonyl]ethyl-2'-deoxyuridine, was unsuccessful either by direct allylation or by using a TBDMS-protected analog. The successful approach in preparing **I** and **II** (Scheme 2) involved the coupling of two components. One was the 5-carboxyalkyl or carboxyalkenyl substituted 2'-deoxyuridine protected by TBDMS, which has been reported[11]. The second was a carborane-containing diol in which alcoholic functions were appropriately masked.

The steps in the synthesis of this second component involved the introduction of the allyl moiety on the carbon atom of a hydroxy-protected carborane.[18,19] In order to synthesize such structures, it was necessary first to protect the hydroxyl group of an acetylenic alcohol, prepare the carborane and then insert the allyl group. Various masking groups on the alcoholic function have been tried. These included the tetrahydropyranyl, the tosyl and the acyl



I: n = 3, X = ethylene; **IIa**: n = 3, X = vinyl; **IIb**: n = 4, X = vinyl; a) AcCl, Pyr.,C_6H_6, O°C; b) $B_{10}H_{14}$, CH_3CN, C_6H_6; c) $Pd_2(dba)_3$, dppe, allyl ethyl carbonate, THF; d) OsO_4, Pyr., NMMPNO; e) TsOH, $Me_2C(OMe)_2$; f) K_2CO_3, MeOH; g) E-5-(2-carboxyvinyl)-3',5'-di(*tert*-butyldimethylsilyloxy)-2'-deoxy uridine or 5-(2-carboxyethyl)-3',5'-di(*tert*-butyldimethylsilyloxy)-2'-deoxyuridine, DCC, DMAP, DMF; h) TFA, acetone/water.

Scheme 2

groups. Of these, the acyl group was the best choice based upon the overall yield.

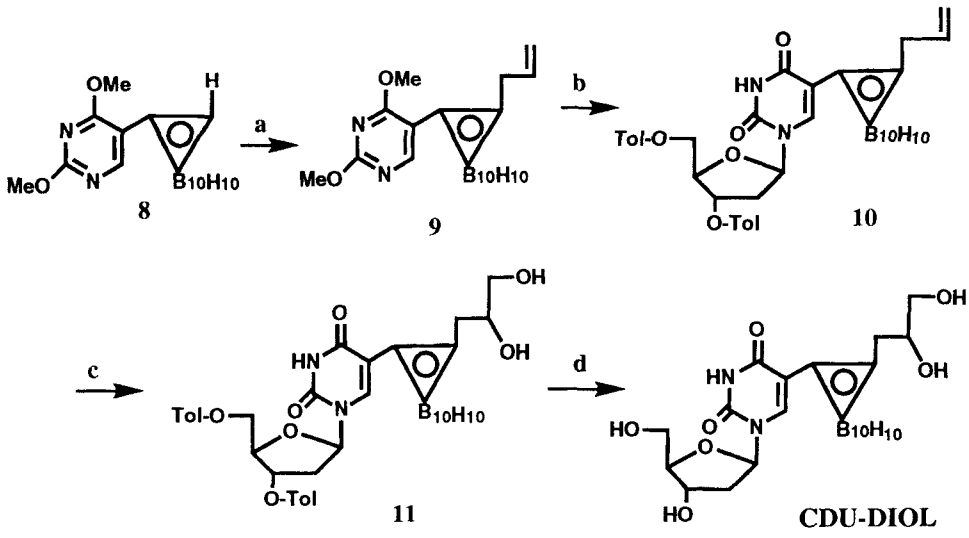
Palladium-catalyzed allylation of **2** was monitored by color change and thin layer chromatography on silica gel. Quantitative yields were obtained. Allyl ethyl carbonate was a better allylation reagent than allyl methyl carbonate. Dihydroxylation occured by using a catalytic amount of osmium tetraoxide and a

reoxidizing reagent, N-methylmorpholine N-oxide (NMMPNO).[19] Esterification of the carboxylic acid derivative, E-5-(2-carboxyethyl)-3',5'-di(*tert*-butyldimethylsilyloxy)-2'-deoxyuridine, with **6** in the presence of 1,4-dicyclohexylcarbodiimide (DCC), 4-dimethylaminopyridine (DMAP) and DMAP·HCl in DMF was successful.[20] A trace amount of DMAP·HCl was essential, not only to accelerate the reaction, but also to increase the yield. Both TBDMS and acetal protecting groups were removed in one step by trifluoroacetic acid without altering the carborane cage.

Yamamoto[21] and Schinazi[22] have synthesized CDU from 5-iodo-2'-deoxyuridine. If CDU could be allylated directly, then CDU-DIOL could be readily synthesized. Unfortunately, a low yield precluded its synthesis by such a straightforward approach, and the compound had to be prepared from 2,4-dimethyl-5-carboranylpyrimidine **8** (Scheme 3). **8** is prepared by established methodology[23]. Palladium catalytic allylation of **8** gave **9** readily. Compound **10** was prepared by the cross-coupling of **9** with 1-chloro-3,5-O-*p*-toluoyl-2-deoxyribose (α-chlororibose) in the presence of zinc chloride.[24] An excess of α-chlororibose was necessary in order to get a high β to α ratio of the product. Oxidation of **10**, followed by deprotection of the O-*p*-toluoyl group, gave CDU-DIOL in good yield.

Biochemical Studies

Human cytosolic thymidine kinase (TK) is an enzyme which converts thymidine (dThd), deoxyuridine (dUrd) and various nucleoside analogs to their respective nucleotides.[25,26] This phosphorylation is the primary pathway by which dThd and other dUrd analogs can be incorporated into DNA. The objective of this research is to find a boronated nucleoside whose rate of phosphorylation approaches that of naturally-occurring nucleosides, and to correlate the length of the tether and the presence of a water-solubilizing moiety with the biochemical activities of such pyrimidine nucleosides. The methodology established[11] has been used to evaluate these compounds, focusing on their rate of phosphorylation and/or capability as enzyme inhibitors. Linking a dihydroxypropyl moiety at the carborane cage significantly increased the aqueous solubility. The maximum solubility of SUB-7-DIOL was found to be 2.87 mM, comparing with SUB-7 (0.63 mM), as determined by measuring UV absorbance of the supernatant of the saturated suspension in water. In order to compare their velocities of phosphorylation , the same concentration (0.10 mM) of each compound was used in the assay mixture. The phosphorylation was



a) $Pd_2(dba)_3$, dppe, allyl ethyl carbonate; b) 1-chloro-3,5-O-*p*-toluoyl-2-deoxyribose, $ZnCl_2$; c) OsO_4, NMMPNO, Pyr.; d) NaOMe/MeOH

Scheme 3

carried out using [γ-^{33}P]-ATP as the phosphate donor, and the time course of the reaction was limited to 30 min. The phosphorylation products were detected by the radioactivity of the nucleotides and quantitated by β-scanning. The velocities of the reaction are shown in Figure 1.

The results from these studies indicated that SUB-7-DIOL is phosphorylated most efficiently. Its velocity of phosphorylation at 10 min approximated that of unmodified dUrd. This compound is tethered by seven atom units between the carborane cage and the 5-position of the nucleoside, and a dihydroxypropyl moiety attached at the carbon of the carborane cage. The results indicated that dihydroxypropyl moiety not only increased the compound's aqueous solubility, but also enhanced the rate of phosphorylation by comparison with its more lipophilic counterpart, SUB-7. However, CDU-DIOL showed no greater rate of phosphorylation than its lipophilic counterpart, CDU, even through the former has greater aqueous solubility.

In order to determine the influence of C5 substituent size on substrate turnover and the importance of tether chain, a series of 5-halo-substitued 2'-

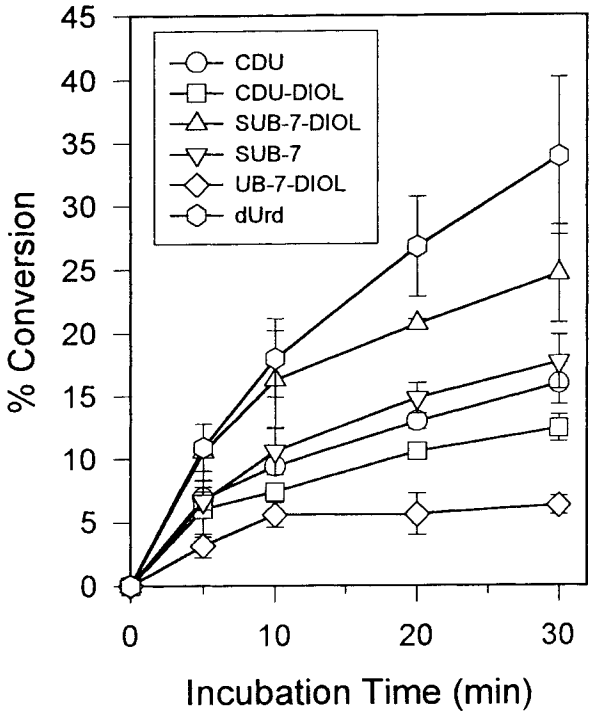


Figure 1. Rate of Phosphorylation of Various Boronated dUrd Derivatives by Human TK.

deoxyuridine were also evaluated enzymatically under the same conditions as the boronated nucleosides. The order of rate of phosphorylation was found to be dThr > 5-Br-dUrd > 5-I-dUrd > 5-F-dUrd = dUrd > SUB-7-DIOL > SUB-7 > CDU (data not shown). This order of the rate among the halo-substituted 2'-deoxyuridines is consistent with the order of inhibition of TK by these compounds found by Lee and Cheng.[27] Apparently, there is an optimal size for C5 substituent, as seen among the 5-halo-substitued 2'-deoxyuridines (5-Br-dUrd being the closest to the natural substrate, dThr). The bulky carborane group directly attached to 5-position of dUrd clearly interferes strongly. However, the flexible tether in SUB-7-DIOL and SUB-7 reverses the steric effect of the proximal carborane group.

Both this and the previous work[11] indicate that a *flexible saturated tether* significantly increases the rate of analog turnover (SUB-7 *vs.* UB-7/CDU[11], and SUB-7-DIOL *vs.* UB-7-DIOL/CDU in Figure 1). The increased aqueous

solubilities resulting from the addition of the diol moiety should have the important effect of improving drug delivery, and in case of the flexible tethered compound, a substantial increase in its turnover as a substrate is also seen (SUB-7-DIOL *vs.* SUB-7 in Figure 1). Possibly because of the steric hindrance inherent in CDU, the addition of the diol has very little, or even a negative effect. The poor response by UB-7-DIOL is not surprising, as our previous work revealed that the parent compound, UB-7, while being an effective inhibitor of TK, is turned over much less efficiently than the saturated SUB-7. It is possible that the flexibility is adversely affected by the vinyl group in contrast with the saturated ethyl moiety. The rate of substrate binding or product release is thereby altered.

In summary, we have developed a novel type of hydrophilic 5-tethered carborane-containing 2'-deoxyuridine derivative, SUB-7-DIOL, which showed suitable aqueous solubility and demonstrated a phosphorylation rate and inhibition of human TK comparable to naturally-occurring nucleosides. This compound is a potential agent for BNCT and a determination of its *in vitro* microdistribution in F98 rat glioma cells is underway.

Experimental Section

Synthetic Chemistry

General. All the experiments were carried out under an argon or nitrogen atmosphere. ^{1}H and ^{13}C NMR spectra were recorded on a AF-250 FT-NMR spectrometer and the chemical shifts, unless otherwise noted, are indicated in ppm with the values relative to an internal tetramethylsilane standard. Coupling constants (J) are reported in Hz. The signals for H-B in ^{1}H NMR are very broad and range from 1.2 to 4.2 ppm. Infrared spectroscopy was carried out on a RFX40 FT-IR spectrometer (Laser precision Co.) with samples prepared as KBr disks or neat. FAB^{+} mass spectra were obtained on a Finnigan MAT-900 mass spectrometer through ionization with Xe using a 3-nitrobenzyl alcohol (3-NBA) as the matrix compound. High resolution mass spectra (EI) were measured with a VG 70-250S spectrometer. For all the boron-containing compounds, the mass of the most intense peak of the isotope pattern is in agreement with the theoretical ones. Elemental analyses were performed at Atlantic Microlab Inc., Norcross, GA and Galbraith Laboratories Inc., Knoxville, TN. TLC plates with Silica Gel 60F-254 and Silica Gel 60 (70 - 230 mesh) from E. Merck were used for TLC and column chromatography respectively. Boronated compound visualization was achieved with UV light (254 nm), and spraying with 0.06%

$PdCl_2$/1% HCl and subsequent heating at 120 °C for 2 - 5 min. Reagent - grade solvents were used for column chromatography. Pyridine, acetonitrile and dimethyl formamide were dried with molecular sieves (4 Å). Benzene was dried over sodium. THF and ethyl ether were distilled over sodium and benzophenone, under argon, prior to use. Other chemicals were purchased from commercial suppliers.

Preparation of 4-pentyn-1-yl acetate (1a). To a solution of 4-pentyn-1-ol (5.0 g, 59.44 mmol) in pyridine/benzene (29 mL/70 mL) was added dropwise with stirring 6.4 mL of acetyl chloride (89.16 mmol) over a period of 50 min at 0 °C. The mixture was stirred for two hours at room temperature. After filtration of the pyridine hydrochloride precipitate, the filtrate was poured into 250 mL of ice-water, and extracted three times with 60 mL aliquots of ethyl ether. The combined ether extracts were washed successively with 1N hydrochloric acid solution, with brine and dried over anhydrous magnesium sulfate. The product was obtained in 90% yield as a light yellow oil after evaporation of the solvents. TLC (hexane/ethyl acetate, 5 : 1): R_f = 0.62; FT-IR (KBr): 3296, 2964, 2825, 2119, 1747, 1466, 1436, 1045 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.16 (t, J = 6.4, 2H, CH_2O), 2.30 (d,t, J = 6.9, 2.6, 2H, CH_2-acetylene), 2.18 (s, 3H, CH_3CO), 1.97 (t, J = 2.6, IH, H-acetylene), 1.87 (t,t, J = 6.4, 6.9, 2H, $CH_2\mathit{CH_2}CH_2$); ^{13}C NMR ($CDCl_3$) δ 170.6, 82.7, 68.8, 62.7, 27.4, 20.5, 14.9; EI-HRMS calcd for $C_7H_{10}O_2$: 126.0681, found: 126.0669.

Preparation of 5-hexyn-1-yl acetate (1b). The procedure for the preparation of this product was the same as described above. The product was obtained in quantitative yield from 5-hexyn-1-ol. TLC (hexane/ethyl acetate, 5 : 1): R_f = 0.61; FT-IR (KBr): 3296, 2952, 2870, 1743, 1456, 1434, 1389, 1367, 1246, 1047 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.09 (t, J = 6.39, 2H, CH_2O), 2.24 (d, t, J = 6.88, 2.61, 2H, CH_2-acetylene), 2.05 (s, 3H, CH_3CO), 1.97 (t, J = 2.63, 1H, H-acetylene), 1.79 - 1.73 (m, 2H, $\mathit{CH_2}CH_2O$), 1.71-1.57 (m, 2H, $\mathit{CH_2}CH_2CH_2O$); ^{13}C NMR ($CDCl_3$) δ 171.0, 83.6, 68.7, 63.8, 27.6, 24.9, 20.9, 18.0; EI-HRMS calcd for $C_8H_{12}O_2$ (M + H): 141.0915, found: 141.0929.

Preparation of 3-(1,2-dicarbo-*closo*-dodecaboranyl)propyl acetate (2a). A solution of **1a** (2.50 g, 19.82 mmol) and decaborane (3.40 g, 27.75 mmol) in acetonitrile/benzene (15 mL/150 mL) was refluxed, with stirring, for 2.5 days under argon. After evaporation of the solvents, the residue was purified by column chromatography on silica gel, eluted with hexane/ethyl acetate (5 : 1) to give the product as a white solid in 70% yield (3.39 g, 13.88 mmol). TLC (hexane/ethyl acetate, 5 : 1): R_f = 0.31; FT-IR (KBr): 3062, 2970,

2910, 2590, 1734, 1450, 1365, 1049 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.03 (t, J = 6.1, 2H, CH_2O), 3.59 (br, s, 1H, HC-carborane), 2.05 (s, 3H, CH_3CO), 1.88 - 1.76 (m, 2H, *CH_2*CH_2O); ; ^{13}C NMR ($CDCl_3$) δ 170.7, 74.4, 62.6, 61.3, 34.7, 28.3, 20.7; EI-HRMS calcd for $C_7H_{20}B_{10}O_2$: 246.2394: , found: 246.2367. Anal. Calcd for $C_7H_{20}B_{10}O_2$: C, 34.41; H, 8.25; B, 44.24. Found: C, 34.98; H, 8.37; B, 44.74.

Preparation of 4-(1,2-dicarbo-*closo*-dodecaboranyl)butyl acetate (2b). The procedure for the preparation of this product was the same as described above for **2a**. The product was obtained in 72% yield. TLC (hexane/ethyl acetate, 5 : 1): R_f = 0.61; FT-IR (KBr): 3052, 2966, 2592, 1730, 1722, 1460, 1387, 1363, 1270, 1068, 1031 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.03 (t, J = 6.01, 2H, CH_2O), 3.55 (m, 1H, HC-carborane), 2.82 - 2.06 (m, 2H, CH_2-carborane), 2.04 (s, 3H, CH_3CO), 1.56 - 1.54 (m, 4H, *CH_2*CH_2CH_2O); ^{13}C NMR (CD_3OD) δ 170.9, 74.9, 63.3, 61.1, 37.5, 27.8, 25.7, 20.8; EI-HRMS calcd for $C_8H_{21}B_{10}O_2$ (M - H): 259.2472, found: 260.2560. Anal. Calcd for $C_8H_{22}B_{10}O_2$: C, 37.19; H, 8.58; B, 41.84. Found: C, 37.19; H, 8.72; B, 41.62.

Preparation of 3-(2-allyl-1,2-dicarbo-*closo*-dodecaboranyl) propyl acetate (3a). A solution of 1,2-bis(diphenylphosphino)ethane (0.88 g, 2.20 mmol) and tris(dibenzylideneacetone)dipalladium(0) (1.27 g, 1.23 mmol) in 120 mL of dry THF was stirred for 30 min at room temperature under argon. Allyl ethyl carbonate (4.80 g, 36.84 mmol) was then added with stirring. After the color of the mixture changed from black to yellow, **2a** (3.0 g, 12.28 mmol) in 5 mL of THF was added. The mixture was refluxed overnight and then filtered through Celite 545. The product was obtained in 91% yield (3.18 g, 11.18 mmol) by silica gel column chromatography, eluted with hexane/ethyl acetate (5 : 1). TLC (hexane/ethyl acetate, 5 : 1): R_f = 0.38; FT-IR (KBr): 3060, 2958, 2616, 2583, 1735, 1449, 1437, 1056 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.78 (ddt, J = 16.5, 10.0, 7.2, 1H, H-vinyl), 5.20 (ddt, J = 10.0, 1.5, 1.0, 1H, H-vinyl), 5.11 (ddt, J = 16.5, 1.5, 1.0, 1H, H-vinyl), 4.06 (t, J = 6.1, 2H, CH_2O), 2.96 (d, J = 7.2, 2H, vinyl-CH_2-carborane), 2.32 - 2.17 (m, 2H, CH_2-carborane), 2.06 (s, 3H, CH_3CO), 1.94 - 1.80 (m, 2H, CH_2*CH_2*CH_2); ^{13}C NMR ($CDCl_3$) δ 170.8, 132.6, 119.5, 78.3, 78.1, 63.0, 39.4, 31.6, 28.7, 20.8; EI-HRMS calcd for $C_{10}H_{24}B_{10}O_2$: 286.2707, found: 286.2703. Anal. Calcd for $C_{10}H_{24}B_{10}O_2$: C, 42.23; H, 8.51; B, 38.01. Found: C, 42.42; H, 8.75; B, 37.56.

Preparation of 4-(2-allyl-1,2-dicarbo-*closo*-dodecaboranyl) butyl acetate (3b). The procedure for the preparation of this product was the same as described above for **3a**. The product was isolated in 92% yield by silica gel column chromatography, eluted with hexane/ethyl acetate (5 : 1). TLC

(hexane/ethyl acetate, 2 : 1): R_f = 0.69; FT-IR (KBr): 2960, 2588, 1741, 1460, 1434, 1388, 1365, 1238, 1066, 1031 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.78 (ddt, J = 17.0, 1.5, 1.0, 1H, H-vinyl), 5.19 (ddt, J = 17.0, 1.5, 1.0, 1H, H-vinyl), 5.10 (ddt, J = 17.0, 1.5, 1.0, 1H, H-vinyl), 4.07 (t, J = 6.0, 2H, CH_2O), 2.94 (d, J = 7.2, 2H, vinyl-CH_2-carborane), 2.20 (m, 2H, CH_2-carborane), 2.06 (s, 3H, CH_3CO), 1.64 - 1.62 (m, 2H,*CH_2*CH_2O), 1.59 (m, 2H,*CH_2*CH_2CH_2O); ^{13}C NMR ($CDCl_3$) δ 170.9, 132.6, 119.4, 78.9, 78.0, 78.0, 63.4, 39.3, 34.4, 28.1, 26.1, 20.9; EI-HRMS calcd for $C_{11}H_{26}B_{10}O_2$: 300.2863, found: 300.2823.

Preparation of 3-[2-(2',3'-dihydroxypropan-1-yl)-1,2-dicarbo-*closo*-dodecaboranyl]propyl acetate (4a). To a solution of **3a** (3.40 g, 11.97 mmol) and N-methylmorpholine N-oxide (2.8 g, 23.94 mmol) in water/acetone (7 mL/250 mL), 30 mL of 2.5 wt.% osmium tetraoxide (2.39 mmol) in 2-methyl-2-propanol and pyridine (0.6 g, 7.39 mmol) was added slowly at 0 °C. The mixture was stirred overnight at room temperature. To this mixture, 10 mL of 10 wt.% aqueous sodium thiosulfate was added to quench the reaction, and the solution was stirred for an additional two hours. After drying over anhydrous sodium sulfate, filtration and solvent evaporation, the residue was purified by column chromatography on silica gel, eluted with ethyl acetate/hexane (2 : 1) to give the product in quantitative yield (3.8 g, 11.97 mmol). TLC (ethyl acetate/hexane, 2 : 1): R_f = 0.32; FT-IR (KBr): 3600 - 3180, 2974, 2925, 2582, 1740, 1378, 1366, 1044 cm^{-1}; ^1H NMR (CD_3OD) δ 3.95 (t, J = 6.20, 2H, CH_2OAc), 3.70 - 3.61 (m, 1H, C*H*OHCH_2OH), 3.41 - 3.32 (m, 1H, CHOHC*H_2*OH), 3.28 - 3.18 (m, 1H, CHOHC*H_2*OH), 2.45 2.43 (m, 2H, C*H_2*CHOH), 2.40 - 2.30 (m, 2H, CH_2-carborane), 2.07 (s, 3H, CH_3CO), 1.85 - 1.73 (m, 2H, CH_2C*H_2*CH_2). ^{13}C NMR (CD_3OD) δ 172.7, 80.7, 72.1, 70.5, 66.9, 64.3, 40.0, 32.0, 29.6, 20.7; EI-HRMS calcd for $C_{10}H_{26}B_{10}O_4$: 320.2762, found: 320.2799. Anal. Calcd for $C_{10}H_{26}B_{10}O_4$: C, 37.72; H, 8.23; B, 33.95. Found: C, 37.82; H, 8.17; B, 32.49.

Preparation of 4-[2-(2',3'-dihydroxypropyl)-1,2-dicarbo-*closo*-dodecaboranyl]butyl acetate (4b). The procedure for the preparation of this product was the same as described above for **4a**. The product was obtained in quantitative yield by silica gel column chromatography, eluted with hexane/ethyl acetate (1 : 3). TLC (hexane/ethyl acetate, 1 : 2): R_f = 0.34; FT-IR (KBr): 3550 - 3150, 2958, 2898, 2875, 2580, 1722, 1460, 1433, 1392, 1367, 1255, 1105 cm^{-1}; ^1H NMR (CD_3OD) δ 3.97 (t, J = 6.2, 2H, CH_2OAc), 3.70 - 3.61 (m, 1H, *C*H(OH)CH_2OH), 3.72 (m, 1H, CH(OH)*CH_2*OH), 3.38 (m, 1H, CH(OH)*CH_2*OH), 2.47 (m, 2H, *CH_2*CHOH), 2.31 - 2.23 (m, 2H, CH_2-carborane),

1.93 (s, 3H, CH_3CO), 1.56 (m, 2H, CH_2CH_2O), 1.52 (m, 2H, $CH_2CH_2CH_2O$); ^{13}C NMR ($CDCl_3$) δ 171.4, 79.8, 77.8, 70.9, 66.2, 63.3, 38.8, 34.5, 28.1, 26.0, 20.9; EI-HRMS calcd for $C_{11}H_{27}B_{10}O_4$ (M - H): 333.2840, found: 333.2875. Anal. Calcd for $C_{11}H_{28}B_{10}O_4$: C, 39.74; H, 8.49; B, 32.52. Found: C, 40.01; H, 8.78; B, 32.66.

Preparation of 3-[2-(2',2'-dimethyl-1',3'-dioxacyclopentan-4'-yl)methyl-1,2-dicarbo-*closo*-dodecaboranyl]propyl acetate (5a). To a solution of **4a** (3.0 g, 9.43 mmol) and *p*-toluenesulfonic acid monohydrate (0.18 mg, 0.94 mmol) in 60 mL of DMF was added 2.32 mL of 2,2-dimethoxypropane (18.86 mmol), and the mixture was then stirred overnight. After filtration through alumina (80 - 200 mesh), and evaporation of DMF under vacuum, the product was isolated as a light yellow oil. After purification by silica gel column chromatography and elution with hexane/ethyl acetate (3 : 2), the product was obtained in 95% yield (3.21 g, 8.96 mmol). TLC (ethyl acetate/hexane, 1 : 1): R_f = 0.90; FT-IR (KBr): 2986, 2937, 2586, 1741, 1454, 1380, 1372, 1158 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.34 - 4.21 (m, 1H, $OCHCH_2O$), 4.18 - 4.11 (m, 1H, $OCHCH_2O$), 4.06 (t, J = 6.0, 2H, CH_2OAc), 2.44 (t, J = 5.5, 2H, CH_2-carborane), 2.37 - 2.27 (m, 2H, carboranyl-CH_2CHO), 2.06 (s, 3H, CH_3CO), 1.96 - 1.82 (m, 2H, CH_2CH2CH_2), 1.39 (s, 3H, CH_3CCH_3), 1.35 (s, 3H, CH_3CCH_3); ^{13}C NMR ($CDCl_3$) δ 170.6, 109.6, 79.1, 77.1, 74.4, 69.1, 63.0, 39.6, 31.8, 28.7, 26.8, 25.2, 20.7; EI-HRMS calcd for $C_{12}H_{27}B_{10}O_4$ (M - Me): 345.2840, found: 345.2835. Anal. Calcd for $C_{13}H_{30}B_{10}O_4$: C, 43.56; H, 8.44; B, 30.16. Found: C, 43.84; H, 8.41; B, 29.54.

Preparation of 4-[2-(2',2'-dimethyl-1',3'-dioxacyclopentan-4'-yl)methyl-1,2-dicarbo-*closo*-dodecaboranyl]butyl acetate (5b). The procedure for the preparation of this product was the same as described above for **5a.** The product was obtained in quantitative yield by silica gel column chromatography, eluted with hexane/ethyl acetate (1 : 3). TLC (hexane/ethyl acetate, 1 : 2): R_f = 0.34; FT-IR (neat): 2985, 2958, 2873, 2586, 1741, 1460, 1438, 1381, 1157, 1074 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.27 (q, J = 5.9, 1H, $OCHCH_2O$), 4.15 (dd, J = 8.3, 6.0, 1H, $OCHCH_2O$), 4.07 (t, J = 6.0, 2H, CH_2OAc), 3.58 (dd, J = 8.3, 6.0, 1H, $OCHCH_2O$), 2.52 - 2.43 (m, 1H, carboranyl-CH_2CHO), 2.42 - 2.34 (m, 1H, carboranyl-CH_2CHO), 2.31 - 2.19 (m, 2H, carboranyl-CH_2CH_2), 2.06 (s, 3H, CH_3CO), 1.65 - 1.60 (m, 4H, $OCH_2CH_2CH_2$), 1.39 (s, 3H, CH_3CCH_3), 1.35 (s, 3H, CH_3CCH_3); ^{13}C NMR ($CDCl_3$) δ 170.9, 109.6, 79.6, 76.9, 74.4, 69.1, 63.4, 39.5, 34.6, 28.2, 26.8, 26.1, 25.2, 20.9; EI-HRMS calcd for $C_{14}H_{33}B_{10}O_4$ (M + H): 375.3309, found: 375.3307. Anal.

Calcd for $C_{14}H_{32}B_{10}O_4$: C, 45.14; H, 8.66; B, 29.02. Found: C, 45.08; H, 8.88; B, 29.08.

Preparation of 3-[2-(2',2'-dimethyl-1',3'-dioxacyclopentan-4'-yl)methyl-1,2-dicarbo-*closo*-dodecaboranyl]propanol (6a). A solution of **5a** (2.45 g, 6.84 mmol) and anhydrous potassium carbonate (1.89 g, 13.68 mmol) in water/methanol (7 mL/100 mL) was stirred for four hours at room temperature under argon. After filtration of the precipitate and evaporation of the solvents, the product was isolated as a colorless sticky oil in quantitative yield (2.16 g, 6.84 mmol) by column chromatography on silica gel after elution with ethyl acetate/hexane (1 : 1). TLC (ethyl acetate/hexane, 1 : 1): R_f = 0.25; FT-IR (neat): 3500 - 3200, 2985, 2937, 2879, 2588, 1704, 1454, 1436, 1380, 1157 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.32 - 4.22 (m, 1H, O*CH*CH_2O), 4.17 - 4.13 (m, 1H, OCH*CH_2*O), 3.64 (t, J = 5.9, 2H, *CH_2*OH), 3.60 - 3.55 (m, 1H, OCH*CH_2*O), 2.58 - 2.34 (m, 4H, carboranyl-CH_2), 1.88 - 1.73 (m, 2H, CH_2*CH_2*CH_2), 1.39 (s, 3H, *CH_3*CCH_3), 1.35 (s, 3H, CH_3C*CH_3*); ^{13}C NMR (CD_3OD) δ 110.92, 81.70, 79.43, 75.87, 70.03, 61.70, 40.37, 33.78, 32.91, 27.11, 25.77; EI-HRMS calcd for $C_{11}H_{28}B_{10}O_3$: 318.2969, found: 318.2967.

Preparation of 4-[2-(2',2'-dimethyl-1',3'-dioxacyclopentan-4'-yl)methyl-1,2-dicarbo-*closo*-dodecaboranyl]butanol (6b). The procedure for the preparation of this product was the same as described above for **6a**. The product was isolated in 88.3% yield by silica gel column chromatography after elution with hexane/ethyl acetate (1 : 1). TLC (hexane/ethyl acetate, 1 : 1): R_f = 0.31; FT-IR (KBr): 3580 - 3100, 2985, 2937, 2873, 2573, 1457, 1436, 1157, 1072 cm^{-1}; ^1H NMR (CD_3OD) δ 4.22 - 4.12 (m, 1H, O*CH*CH_2O), 4.01 (dd, J = 8.2, 6.1, 1H, OCH*CH_2*O), 3.48 - 3.41 (m, 3H, OCH*CH_2*O and *CH_2*OH), 2.53 - 2.45 (m, 2H, carboranyl-CH_2CHO), 2.45 - 2.30 (m, 2H, carboranyl-*CH_2*CH_2),1.60 - 1.38 (m, 4H, $HOCH_2$*CH_2CH_2*), 1.28 (s, 3H, *CH_3*CCH_3), 1.24 (s, 3H, CH_3C*CH_3*); ^{13}C NMR ($CDCl_3$) δ 109.6, 80.0, 76.8, 74.5, 69.1, 62.0, 39.5,34.9, 31.9, 26.8, 26.1, 25.2; EI-HRMS calcd for $C_{12}H_{31}B_{10}O_3$ (M + H): 333.3204, found: 333.3215. Anal. Calcd for $C_{12}H_{30}B_{10}O_3$: C, 43.61; H, 9.15; B, 32.71. Found: C, 43.48; H, 9.45; B, 32.76.

Preparation of E-5-[3-[2-(2',2'-dimethyl-1',3'-dioxacyclo pentan-4'-yl)methyl-1,2-dicarbo-*closo*-dodecaboranyl]propoxy carbonyl]vinyl-3',5'-di(*tert*-butyldimethylsilyloxy)-2'-deoxyuridine (7a). To a solution of E-5-(2-carboxyvinyl)-3',5'-di(*tert*-butyldimethylsilyloxy)-2'-deoxyuridine (909 mg, 1.73 mmol), 1,4-dicyclohexylcarbodiimide (534 mg, 2.59 mmol), 4-dimethylaminopyridine (505 mg, 4.14 mmol) and 4-

dimethylaminopyridine hydrochloride (328 mg, 2.07 mmol) in 40 mL of DMF was added a solution of **6a** (600 mg, 1.90 mmol) in 5 mL of DMF at room temperature. The mixture was then stirred overnight. After evaporation of the solvents under vacuum, the residue was purified by silica gel column chromatography by elution with hexane/ethyl acetate (1 : 1). The product was obtained as a light yellow foam in 70% yield (998 mg, 1.21 mmol) after purification by silica gel column chromatography, eluted with hexane/ethyl acetate (3 : 2). TLC (hexane/ethyl acetate, 2 : 1): R_f = 0.65; FT-IR (KBr): 2970, 2931, 2857, 2582, 2119, 1704, 1463, 1365, 1255, 1153 cm^{-1}; ^1H NMR (CD_3OD) δ 8.00 (s, 1H, H_6), 7.31(d, J = 15.1, H-vinyl), 6.89 (t, J = 6.9, (d, J = 15.1, H-vinyl), 6.14 (t, J = 6.2, 1H, $H_{1'}$), 4.46 - 4.38 (m, 1H, $H_{4'}$), 4.21 - 4.15 (m, 1H, $H_{3'}$), 4.09 (t, J = 6.4, 2H, CO_2CH_2), 4.05 - 3.88 (m, 2H, $H_{5'}$), 3.85 - 3.70 (m, 2H, $OCHCH_2O$), 3.49 - 3.38 (m, 1H, $OCHCH_2O$), 2.51 - 2.31(m, 4H, CH_2-carborane), 2.28 - 2.10 (m, 2H, $H_{2'}$), 1.85 - 1.70 (m, 2H, $CH_2CH_2CH_2$), 1.28 (s, 3H, CH_3CCH_3), 1.24 (s, 3H, CH_3CCH_3), 0.86 (s, 9H, CMe_3), 0.84 (s, 9H, CMe_3), 0.07 (s, 6H, $SiMe_2$), 0.05 (s, 6H, $SiMe_2$); ^{13}C NMR ($CDCl_3$) δ 167.0, 161.0, 148.8, 142.2, 136.8, 118.9, 109.6, 109.5, 88.5, 86.0, 79.2, 77.2, 74.4, 72.3, 69.0, 63.0, 62.8, 55.6, 42.1, 39.5, 34.8, 31.8, 28.9, 26.7, 25.9, 25.8, 25.6 (2C), 25.6, 25.4, 25.3, 24.5 (2C), 18.3, 17.9, -4.8, -4.9, -5.4, -5.5; EI-HRMS calcd for $C_{35}H_{68}B_{10}N_2Is_2O_9$: 826.5394, found: 826.5397.

Preparation of E-5-[4-[2-(2',2'-dimethyl-1',3'-dioxacyclo pentan-4'-yl)methyl-1,2-dicarbo-*closo*-dodecaboranyl]butoxy carbonyl]vinyl-3',5'-di(*tert*-butyldimethylsilyloxy)-2'-deoxyuridine (7b). This product was prepared in the same manner as described above for **7a** and obtained as a light yellow foam in 79.2% yield (883 mg, 1.05 mmol). TLC (ethyl acetate/hexane, 1 : 1): R_f = 0.82; FT-IR (KBr): 2930, 2857, 2593, 2120, 1734, 1717, 1696, 1255 cm^{-1}; ^1H NMR (CD_3OD) δ 7.97 (s, 1H, H_6), 7.25 (d, J = 15.8, 1H, H-vinyl), 6.83 (d, J = 15.8, 1H, H-vinyl), 6.11 (t, J = 6.7, 1H, $H_{1'}$), 4.38 - 4.36 (m, 1H, $H_{4'}$), 4.25 - 4.20 (m, 1H, $H_{3'}$), 4.08 (t, J = 6.4, 2H, CO_2CH_2), 4.05 - 3.08 (m, 2H, $H_{5'}$), 3.80 - 3.69 (m, 2H, $OCHCH_2O$), 3.49 - 3.38 (m, 1H, $OCHCH_2O$), 2.49 - 2.30 (m, 4H, carboranyl-CH_2), 2.30 - 2.10 (m, 2H, $H_{2'}$), 1.85 - 1.70 (m, 2H, OCH_2CH_2), 1.69 - 1.49 (m, 2H, $OCH_2CH_2CH_2$), 1.25 (s, 3H, CH_3CCH_3), 1.21 (s, 3H, CH_3CCH_3), 0.84 (s, 9H, CMe_3), 0.82 (s, 9H, CMe_3), 0.04 (s, 6H, $SiMe_2$), 0.02 (s, 6H, $SiMe_2$); ^{13}C NMR (CD_3OD) δ 168.5, 163.0, 150.6, 143.8, 140.9, 138.5, 119.2, 110.7, 110.4, 89.5, 87.1, 81.3, 79.2, 75.7, 73.6, 69.9, 64.1, 56.7, 42.5, 40.3, 35.9, 35.5, 34.6, 32.1, 29.6, 29.3, 27.3, 27.2,

26.5, 26.4, 25.5, 19.3, 18.8, -4.3, -4.4; EI-HRMS calcd for $C_{36}H_{70}B_{10}N_2Si_2O_9$: 840.5550, found: 840.5560.

Preparation of 5-[2-[3-[2-(2',2'-dimethyl-1',3'-dioxacyclo pentan-4'-yl)methyl-1,2-dicarbo-*closo*-dodecaboranyl]propoxy carbonyl]ethyl]-3',5'-di(*tert*-butyldimethylsilyloxy)-2'-deoxyuridine (7c). To a solution of 5-(2-carboxyethyl)-3',5'-di(*tert*-butyldimethylsilyloxy)-2'-deoxyuridine (120 mg, 0.23 mmol), 1,4-dicyclohexylcarbodiimide (70 mg, 0.34 mmol), 4-dimethylaminopyridine (67 mg, 0.54 mmol) and 4-dimethylaminopyridine hydrochloride (43 mg, 0.27 mmol) in 20 mL of DMF was added a solution of **6a** (79 mg, 0.25mmol) in 5 mL of DMF. The mixture was then stirred for four hours at room temperature. After evaporation of the solvent, the product was obtained in 90% yield after purification by column chromatography on silica gel, eluted with hexane/ethyl acetate (3 : 2). TLC (hexane/ethyl acetate, 3: 2): R_f = 0.88; FT-IR (KBr): 2933, 2857, 2584, 2121, 1739, 1716, 1687, 1471, 1463, 1452, 1253 cm^{-1}; ^1H NMR (CD_3OD) δ 7.47 (s, 1H, H_6), 6.14 (t, J = 6.9, 1H, $H_{1'}$), 4.39 - 4.36 (m, 1H, $H_{4'}$), 4.17 - 4.10 (m, 1H, $H_{3'}$), 4.00 (t, J = 6.0, 2H, CO_2CH_2), 3.83 - 3.81 (m, 1H, *CH*OCH_2O), 3.73 - 3.70 (m, 2H, $H_{5'}$), 3.45 - 3.39 (m, 2H, $CH_2OC(CH_3)_2$), 2.50 - 2.38 (m, 6H, $CH_2CH_2CO_2$ and CH_2CH_2-carborane), 2.36 - 2.29 (m, 2H, $OCHCH_2$-carborane), 2.19 - 2.01 (m, 2H, $H_{2'}$), 1.85 - 1.70 (m, 2H, $CH_2CH_2CH_2$), 1.27 (s, 3H, CH_3CCH_3), 1.23 (s, 3H, CH_3CCH_3), 0.86 (s, 9H, CMe_3), 0.84 (s, 9H, CMe_3), 0.03 (s, 6H, $SiMe_2$), 0.02 (s, 6H, $SiMe_2$); ^{13}C NMR (CD_3OD) δ 173.8, 165.2, 151.9, 141.1, 138.4, 113.8, 110.8, 89.1, 86.2, 80.9, 79.5, 75.8, 73.8, 73.7, 70.0, 64.3, 61.4, 56.8, 41.7, 40.4, 36.0, 33.8, 32.6, 30.0, 27.3, 26.6, 26.5, 25.6, 23.9, 18.8, 14.5, -4.3, -4.5, -4.9, -5.0; EI-HRMS calcd for $C_{34}H_{67}B_{10}N_2Si_2O_9$ (M - Me): 813.5316, found: 813.5319.

Preparation of 5-[2-[3-[2-(2',3'-dihydroxypropan-1'-yl)-1,2-dicarbo-*closo*-dodecaboranyl]propoxycarbonyl]ethyl]-2'-deoxy uridine (I). To a solution of **7c** (160 mg, 0.19 mmol) in water/THF (5 mL/20 mL) was added dropwise at 0 °C, 5 mL of trifluoroacetic acid over a period of 30 min. The mixture was then stirred for an additional 2 - 3 hours at room temperature, and monitored by TLC for the loss of the starting material. After the addition of 5 mL of benzene, and evaporation of the solvents, the product was obtained as an off-white foam quantitatively from column chromatography on silica gel, eluted with ethyl acetate/methanol (20 : 1). TLC (ethyl acetate/methanol, 20 : 1): R_f = 0.58; FT-IR (KBr): 3583 - 3169, 2938, 2926, 2583, 1696, 1684, 1473 cm^{-1}; ^1H NMR (CD_3OD) δ 7.75 (s, 1H, H_6), 6.16 (t, J = 6.7, 1H, $H_{1'}$), 4.31 - 4.26 (m,

1H, $H_{4'}$), 3.95 (t, J = 6.0, OCH_2), 3.85 - 3.76 (m, 1H, $H_{3'}$), 3.75 - 3.55 (m, 2H, $H_{5'}$), 3.42 - 3.21 (m, 3H, HO*CHCH*$_2$OH), 2.49 - 2.34 (m, 4H,*CH*$_2$*CH*$_2$$CO_2$), 2.35 - 2.21 (m, 2H, HOCH*CH*$_2$-carborane), 2.20 - 2.01 (m, 4H, CH_2*CH*$_2$-carborane and $H_{2'}$), 1.81 - 1.61 (m, 2H, CH_2*CH*$_2$$CH_2$); ^{13}C NMR (CD_3OD) δ 174.4, 165.6, 152.1, 139.1,113.9, 88.9, 86.5, 81.2, 72.2, 66.9, 66.8, 64.4, 62.9, 41.3, 40.0, 33.7, 32.7, 29.9, 23.5, 15.4; EI-HRMS calcd for $C_{20}H_{38}B_{10}N_2O_9$: 560.3508, found: 560.3506.

Preparation of E-5-[3-[2-(2',3'-dihydroxypropan-1'-yl)-1,2-dicarbo-*closo*-dodecaboranyl]propoxycarbonyl]vinyl-2'-deoxyuridine (IIa). The procedure for the preparation of this product was the same as described above for **I**, and the product was obtained in 72% yield. TLC (ethyl acetate/methanol, 20 : 1): R_f = 0.48; FT-IR (KBr): 3590 - 3100, 3001, 2916, 2584, 1684, 1438, 1026 cm^{-1}; ^1H NMR (CD_3OD) δ 8.40 (s, 1H, H_6), 7.31 (d, J = 15.8, H-vinyl), 6.79 (d, J = 15.8, H-vinyl), 6.16 (t, J = 6.4, 1H, $H_{1'}$), 4.34 - 4.30 (m, 1H, $H_{4'}$), 4.06 (t, J = 6.1, 2H, OCH_2), 3.90 - 3.84 (m, 1H, $H_{3'}$), 3.80 - 3.64 (m, 3H, $H_{5'}$ and HO*CH*CH_2OH), 3.41 - 3.35 (m, 1H, HOCH*CH*$_2$OH), 3.37 - 3.27 (m, 1H, HOCH*CH*$_2$OH), 2.57 - 2.31 (m, 4H, *CH*$_2$-carborane), 2.25 - 2.10 (m, 2H, $H_{2'}$), 1.90 - 1.78 (m, 2H, CH_2*CH*$_2$$CH_2$); ^{13}C NMR (CD_3OD) δ 169.0, 151.4, 144.7, 138.9, 118.5, 110.4, 89.2, 87.3, 81.2, 80.6, 72.2, 71.7, 66.9, 64.3, 62.4, 49.9, 41.9, 40.0, 32.7, 30.1; EI-HRMS calcd for $C_{20}H_{35}B_{10}N_2O_9$ (M - H): 557.3273, found: 557.3276.

Preparation of E-5-[4-[2-(2',3'-dihydroxypropan-1'-yl)-1,2-dicarbo-*closo*-dodecaboranyl]butoxycarbonyl]vinyl-2'-deoxyuridine (IIb). This product was prepared in the same manner as described above for **I** and obtained in 98% yield. TLC (ethyl acetate/methanol, 20 : 1): R_f = 0.45; FT-IR (KBr): 3650 - 3100, 2925, 2584, 1685, 1630, 1469, 1141 cm^{-1}; ^1H NMR (CD_3OD) δ 8.37 (s, 1H, H_6), 7.28 (d, J = 15.8, H-vinyl), 6.78 (d, J = 15.8, H-vinyl), 6.15 (t, J = 6.9, 1H, $H_{1'}$), 4.35 - 4.28 (m, 1H, $H_{4'}$), 4.05 (t, J = 6.1, 2H, OCH_2), 3.87 - 3.80 (m, 1H, $H_{3'}$), 3.78 - 3.56 (m, 3H, $H_{5'}$ and HO*CH*CH_2OH), 3.40 - 3.31 (m, 1H, HOCH*CH*$_2$OH), 3.28 - 3.19 (HOCH*CH*$_2$OH), 2.57 - 2.38 (m, 2H, *CH*$_2$-carborane), 2.30 - 2.05 (m, 4H, CH_2*CH*$_2$-carborane and $H_{2'}$), 1.70 - 1.42 (m, 4H, OCH_2*CH*$_2$*CH*$_2$); ^{13}C NMR (CD_3OD) δ 169.2, 144.8, 138.8, 118.6, 110.4, 89.2, 87.2, 81.2, 80.7, 72.2, 71.7, 70.6, 66.9, 64.8, 62.4, 41.9, 39.9, 35.6, 32.1, 29.5, 27.4; FAB-MS m/e (rel intensity) 137 (31), 214 (22), 309 (38), 403 (52), 497 (67), 573 (M+H, 4); EI-HRMS calcd for $C_{21}H_{38}B_{10}N_2O_9$: 572.3508, found: 572.3502.

Preparation of 2,4-dimethoxy-5-(2-allyl-1,2-dicarbo-*closo*-dodecaboranyl)pyrimidine (9). The procedure for the preparation of this product was the same as described for **6** starting from **8**. This product was obtained in 82% yield by column chromatography on silica gel, eluted with hexane/ethyl acetate (2 : 1). TLC (hexane/ethyl acetate, 2 : 1): R_f = 0.66; ^{1}H NMR (CD_3OD) δ 8.59 (s, 1H, H_6), 5.61 (ddt, J = 16.5, 10.0, 7.2, 1H, CH_2:C*H*CH_2), 5.03 (dd, J = 10.0, 1.5, 1H, C*H*$_2$:$CHCH_2$), 4.80 (dd, J = 16.5, 1.5, 1H, C*H*$_2$:$CHCH_2$), 4.08 (s, 3H, OCH_3), 4.06 (s, 3H, OCH_3), 2.60 (d, J = 7.2, 2H, vinyl-CH_2);^{13}C NMR (CD_3OD) δ 168.9, 165.6, 164.0, 129.0, 128.4, 119.4, 105.9, 55.4, 54.4, 39.6; EI-HRMS calcd for $C_{11}H_{22}B_{10}N_2O_2$: 324.2612, found: 324.2635.

Preparation of 5-(2-allyl-1,2-dicarbo-*closo*-dodecaboranyl)-3',5'-di-*p*-toluoyl-2'-deoxyuridine (10). To a solution of **9** (79 mg, 0.25 mmol) and zinc chloride (3 mg, 0.025 mmol) in 20 mL of $CHCl_3$ was added dropwise, a freshly-prepared solution of 1-chloro-3',5'-di-*p*-toluoyl-2'-deoxyribose (194 mg, 0.50 mmol) in 5 mL of $CHCl_3$. The mixture was stirred for 6 - 8 hours at room temperature and monitored for the loss of starting material, by thin layer chromatography on silica gel with hexane/ethyl acetate (2 : 1). After the reaction was complete, the solvent was evaporated and the residue was separated by column chromatography on silica gel, eluted with hexane/ethyl acetate (2 : 1) to give the β-form product in 81% yield. TLC (hexane/ethyl acetate, 2 : 1): R_f = 0 71; ^{1}H NMR (CD_3OD) δ 8.12 (s, 1H, H_6), 8.05 - 7.95 (m, 4H, Ar-H), 7.30 - 7.20 (m, 4H, Ar-H), 6.10 (t, J = 6.7, 1H, $H_{1'}$), 5.61 (m, 1H, CH_2:C*H*CH_2), 5.03 (m, 1H, C*H*$_2$:$CHCH_2$), 4.80 (m, 1H, C*H*$_2$:$CHCH_2$), 4.34 (m, 1H, $H_{3'}$), 3.80 (m, 1H, $H_{4'}$), 3.71 (m, 2H, $H_{5'}$), 2.21 (m, 2H, $H_{2'}$), 2.60 (m, 2H, vinyl-CH_2), 2.45 (s, 3H, CH_3), 2.42 (s, 3H, CH_3); ^{13}C NMR (CD_3OD) δ 166.4, 166.3, 144.0, 143.9, 143.7, 143.6, 129.8 (2C), 129.7 (2C), 129.1 (3C), 127.2, 127.1, 127.0, 104.3, 103.6, 81.8, 80.8, 75.6, 74.6, 65.2, 64.3, 63.5, 63.0, 39.3, 21.6, 15.2, 15.0; EI-HRMS calcd for $C_{30}H_{38}B_{10}N_2O_7$: 648.3610, found: 648.3615.

Preparation of 5-[2-(2',3'-dihydroxypropan-1'-yl)-1,2-dicarbo-*closo*-dodecaboranyl]-3',5'-di-*p*-toluoyl-2'-deoxyuridine (11). To a solution of the β–form of **10** (220 mg, 0.33 mmol) and N-methylmorpholine N-oxide (77 mg, 0.66 mmol) in water/acetone (3 mL/15 mL) was added dropwise over a period of one hour at 0 °C, 7.3 mL of 2.5 wt.% osmium tetraoxide (0.58 mmol) in 2-methyl-2-propanol and pyridine (16 mg, 0.20 mmol) at 0 °C. The mixture was stirred at room temperature continuously for two hours. This

solution was monitored for the loss of starting material, After the reaction was complete, 10 mL of aqueous sodium thiosulfate was added, and the mixture was warmed to 50 °C and stirred for one hour. After filtration of the black precipitate, the filtrate was dried over anhydrous sodium sulfate and the solvent was removed under vacuum. The product was obtained in quantitative yield as a colorless sticky foam by column chromatography on silica gel, eluted with hexane/ethyl acetate (2 : 1). TLC (hexane/ethyl acetate, 2 : 1): R_f = 0.65. ^1H NMR ($CDCl_3$) δ 8.10 (s, 1H, H_6), 8.05 - 7.95 (m, 4H, Ar-H), 7.30 - 7.20 (m, 4H, Ar-H), 5.60 (t, J = 6.7, 1H, $H_{1'}$), 4.60 (m, 1H, $H_{3'}$), 3.95 -3.80 (m, 2H, $H_{4'}$ and C*H*OH), 3.70 - 3.40 (m, 4H, $H_{5'}$ and CH_2OH), 2.60 (m, 2H, CH_2CHOH, 2.45 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), 2.36 (m, 2H, $H_{2'}$); ^{13}C NMR (CD_3OD) δ 166.2, 166.0, 143.9, 143.8, 143.7, 143.6, 129.7 (2C), 129.6 (2C), 129.0 (2C), 127.2, 127.1, 126.9, 104.3, 103.5, 81.7, 80.8, 75.5, 74.6, 65.2, 64.3, 63.4, 62.9, 39.3, 39.2, 21.6, 15.2, 15.0; EI-HRMS calcd for $C_{30}H_{40}B_{10}N_2O_9$: 682.3664, found: 682.3668.

Preparation of 5-[2-(2',3'-dihydroxypropyl)-1,2-dicarbo-*closo*-dodecaboranyl]-2'-deoxyuridine (CDU-DIOL). To a solution of **11** (212 mg, 0.31 mmol) in 10 mL of methanol was added dropwise at room temperature, 2.4 mL of 0.5 M sodium methoxide in methanol over a period of 40 min. The mixture was stirred for an additional four hours and the reaction quenched by the addition of 1.2 mL of 17 wt.% HCl in methanol. The solution was dried over anhydrous magnesium sulfate, and after solvent evaporation, the residue was purified by column chromatography on silica gel, eluted with ethyl acetate/methanol (20 : 1). The product was obtained in 69% yield as an off-white foam. TLC (ethyl acetate/methanol, 20 : 1): R_f = 0.48. ^1H NMR (CD_3OD) δ 8.10 (s, 1H, H_6), 6.20 (t, J = 6.4, 1H, $H_{1'}$), 4.90 (m, 1H, $H_{3'}$), 4.40 (m, 2H, $H_{4'}$ and C*H*OH), 4.10 (m, 4H, $H_{5'}$ and CH_2OH), 2.40 (m, 2H, CH_2CHOH), 2.10 (m, 2H, $H_{2'}$); ^{13}C NMR (CD_3OD) δ 166.2, 166.0, 144.4, 143.7, 118.5, 110.2, 89.2, 87.3, 71.7, 71.3, 64.6, 54.2, 39.6, 30.1; EI-HRMS calcd for $C_{14}H_{28}N_2O_7$: 446.2827, found: 446.2824.

Enzymatic Analysis[11]

Materials. [γ-^{33}P]-ATP in 5 mM Tris-Glycine with 0.5 mM EDTA and 2.5 mM DTT was purchased from Andotek Life Sciences Company. BSA, DTT, ATP, dThd, dUrd and other biochemicals were obtained from Sigma Chemical Company. Human cytosolic thymidine kinase was purified (1560 X times) by affinity chromatography on dThd-Sepharose from an extract of human acute

lymphoblastic leukemic T-cells. These cells, collected from patients by leukophoresis, were provided by the Tissue Procurement Service of The Ohio State University Comprehensive Cancer Center. Frozen cellular extracts were stored until needed.

The accurate concentration of boronated nucleosides was determined by UV absorption at λ 267 nM with dUrd as a reference. E-5-[2-(methoxycarbonyl)vinyl]-2'-deoxyuridine was a reference for measuring the concentration of 5-vinyl substituted carborane-containing nucleosides.

Phosphorylation of boronated nucleoside derivatives was performed using [γ-^{33}P]-ATP as a phosphate donor. The reaction mixture contained 0.10 M Tris-HCl, pH 8.0, 0.17 μM [γ-^{33}P]-ATP (5 μCi), 6.0 mM $MgCl_2$, 10.0 mM DTT, 1.0% BSA, with 100 μM boronated pyrimidine nucleoside and 0.001 units of purified TK in a final volume of 30 μl. The reaction was carried out at room temperature for 5 min to 30 min. The reaction products were monitored on PEI-Cellulose TLC plates developed with isobutyric acid/ammonium hydroxide/water (v/v, 66/1/33), or on Silica Gel TLC plates developed by *n*-butanol/methanol (v/v, 1 : 1). The developed TLC plate was exposed to Biomax MR Kodak Scientific Imaging Film for 2 to 4 hours at -78 °C, and then the film was developed on CWP 14-plus Automatic Film Processor. Alternatively, the radioactivity (cpm) of the developed TLC plates was counted directly using AMBIS Image Acquision & Analysis.

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