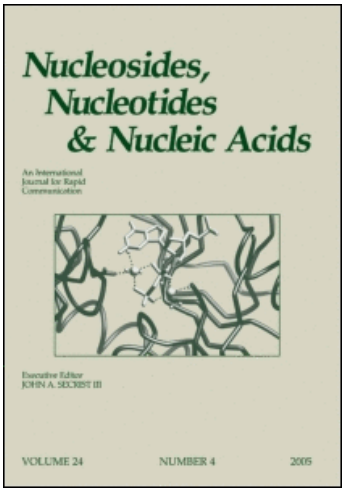

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SYNTHESIS OF 5-TETHERED CARBORANE-CONTAINING PYRIMIDINE NUCLEOSIDES AS POTENTIAL AGENTS FOR DNA INCORPORATION

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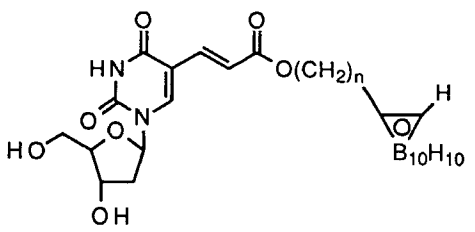
Abstract. Several 5-substituted-2'-deoxyuridines have been prepared in which the carborane moiety is attached at the terminus of a flexible hydrocarbon chain containing an ester linkage. These boron moieties as the B-10 enriched compounds have potentiality for use in the treatment of cancer by means of boron neutron capture therapy. A convenient synthetic route, in high yield, has been developed for the preparation of these 5-tethered carborane-containing pyrimidine nucleosides.

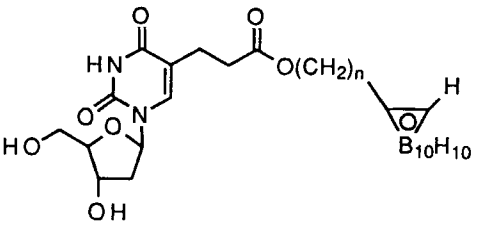
Introduction

Boron neutron capture therapy (BNCT) is a binary system that may have potential for the treatment of those solid tumors for which no therapies exist. This therapy is dependent upon the $^{10}B(n,\alpha)^{7}Li$ reaction.[1] In order to obtain non-toxic boron compounds for BNCT which selectively target proliferating tumor cells and ideally become incorporated into tumor DNA, new types of 5-substituted pyrimidine nucleosides, (1, 2), have been designed and synthesized, in which the carboranyl moiety is at the terminus of a flexible hydrocarbon chain. In order to increase the hydrophilicity of this chain, an ester linkage has been inserted into the hydrocarbon chain (Scheme I).

The rationale for the design and synthesis of such boron compounds is the result from affinity chromatographic studies.[2] These studies demonstrated that the binding of kinases to nucleotides was significantly enhanced by the use of polymethylene spacers between the column matrix and the nucleotides. The binding of the kinases to nucleotides was weak when the extension arms contained four or fewer methylene groups. However when the tether was increased to 10Å by interposing additional methylene groups, 6 to 8, there was



Target compounds 1



Target compounds 2

Scheme I

a substantial increase in the strength of enzyme binding. Enzyme binding may well be a prelude to metabolism. It is the application of such information to the development of DNA-incorporating nucleosides that is the basis for the research which is presented below.

Several 5-substituted-2'-deoxyuridine derivatives have been synthesized, and some of these compounds showed anti herpes simplex virus activity.[3] The basis for this activity is purported to be the incorporation of the corresponding nucleotide into viral DNA.

Yamamoto[4] and Schinazi[5] have attached boron moieties either directly or through a bulky substituent to the 5-position on the nucleosides. These were designed as potential carriers for BNCT. Though there is no direct evidence that such structures are incorporated into nucleic acids, formation of the nucleotide from 5-carboranyl-2'-deoxyuridine was conclusively demonstrated in cell culture. However the di- and triphosphate was not shown. This may be due to the fact that having a bulky substituent such as the carborane moiety attached directly on the 5-position may inhibit enzymatic conversion of the nucleotide to its corresponding di- and triphosphate. The formation of the latter is a necessary precondition for the incorporation of such nucleotides into DNA. Tethering the boron moiety through a flexible chain to the 5-position may permit the triphosphates to be generated and thereby permit their incorporation in nucleic acids.

The preliminary biochemical studies of 5-tethered carborane-containing pyrimidine nucleosides with human thymidine kinase demonstrated that these compounds can be phosphorylated to the corresponding 5'-monophosphate, and significant thymidine kinase inhibition occurred in contrast with 5-

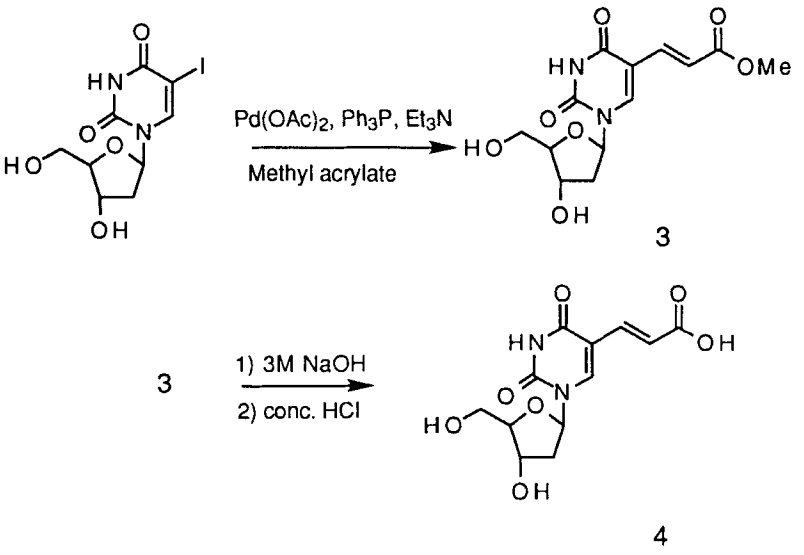
carboranyl-2'-deoxyuridine.[6] In this report, an efficient and simple procedure in high yield for the synthesis of 5-substituted long chain-2'-deoxyuridine derivatives (1, 2) from 5-iodo-2'-deoxyuridine via E-5-(2-carboxyvinyl)-2'-deoxyuridine is described.

Results and Discussion

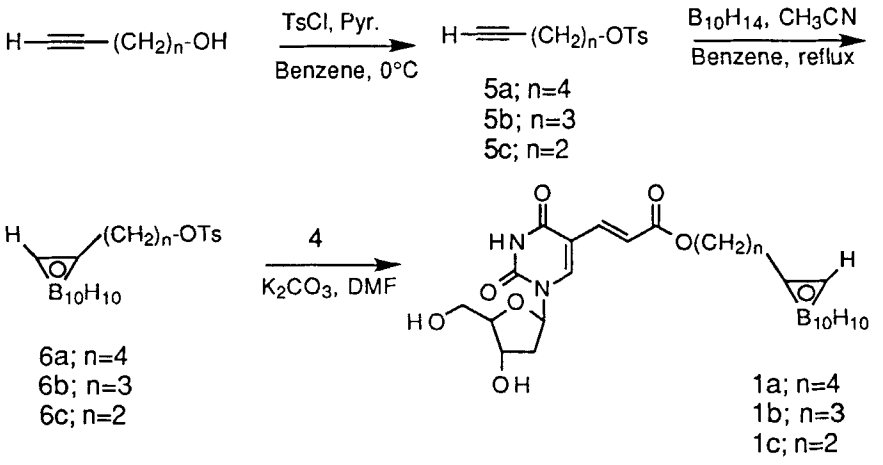
Based on the Heck reaction, a methyl ester of E-5-(2-carboxyvinyl)-2'-deoxyuridine (3) has been prepared using the palladium catalyst, $Pd(OAc)_2$, and 5-iodo-2'-deoxyuridine. The procedure developed by Dyer[7] has been improved and the yield of the coupling reaction has become quantitative by the use of an argon atmosphere and the separation and purification of the reaction mixture with column chromatography. Hydrolysis of the methyl ester (3), followed by acidification with concentrated hydrochloride in 5% methanol water at 0°C produced the previously reported free acid (4)[8] in approximately 90% yield (Scheme II). This acid was used to synthesize the various carborane-containing esters described herein.

The second component required for generating the appropriate esters are the tosylated carborane intermediates (6). These were synthesized with the exception of propargyl alcohol in 80~100% yield by tosylating the appropriate alkynyl alcohol using tosyl chloride in pyridine/benzene (1:1) mixtures at 0°C. The resulting product was then boronated using decaborane and acetonitrile (procedure A) or the decaborane bisacetonitrile complex (procedure B) in refluxing benzene for a period. The point of the procedure A is a one-pot reaction, but longer times are required, usually three to four days. However, the reaction can be completed within four to eight hours by following procedure B using the decaborane bisacetonitrile complex.[9] We prefer procedure B for boronation since long reflux times can result in product decomposition. The propargyl alcohol has appreciably less reactivity, and its tosylated derivative is also less reactive in forming the carborane. The result may arise from the electron interaction between the carbon-carbon triple bond and oxygen.

Numerous reports show that strong bases degrade the *ortho* carborane cluster, converting the *closo* structure to its anionic *nido* counterpart.[10] In order to avoid the degradation of the *closo* carborane entity in the formation of target compounds (1), we generated the carboxylic acid anion by using potassium carbonate. This is then reacted with the tosylated carborane in DMF to yield the desired compound in 62~77% yield (Scheme III). Under such mild conditions,



Scheme II



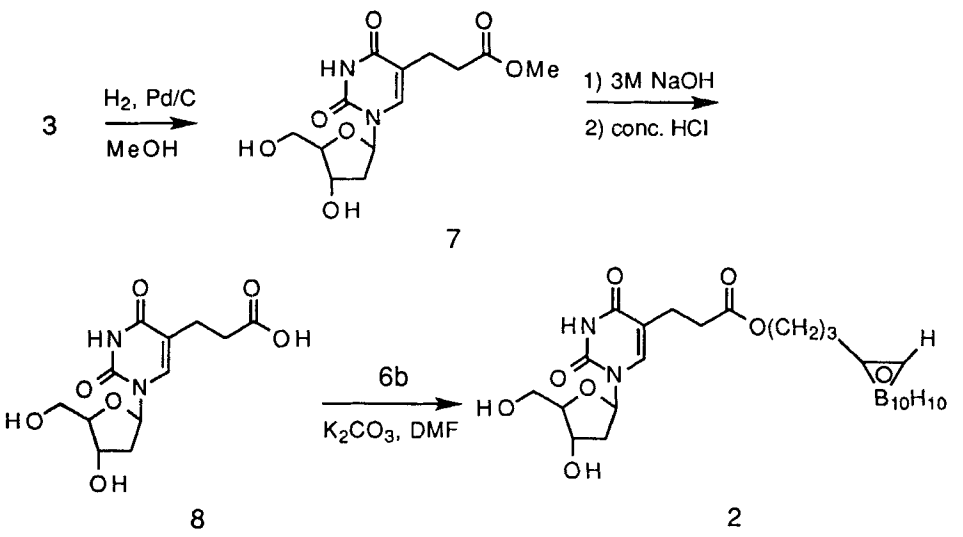
Scheme III

the target compounds can be obtained in good yield from intermediate compound (4) without hydroxyl group protection. There is no evidence by this procedure in the degradation of *closo* carborane entity, or of 3'- or 5'-O-substitution.

In order to compare the kinase binding properties of target compounds (1) with their saturated counterpart, target compound (2), catalytic hydrogenation of target compound (1b) was attempted. It was not successful. We infer that failure to reduce compound (1b) stems from either the bulkiness of group on the alcohol portion of the ester or the involvement of boron moiety in preventing hydrogen atom. Fortunately, the vinyl group of methyl ester (3) can be selectively hydrogenated in 88% yield on palladium catalyst at high pressure. This reaction was monitored by NMR for the loss of the vinyl hydrogen peaks at 7.32 (d, J=15.9) and 6.81 (d, J=15.9). The obtained methyl ester (7) was saponified and the resulting acid (8), after purification, was used for preparing target compound (2) by the same procedure described for synthesizing target compounds (1) (Scheme IV).

Experimental Section

General. All the experiments were carried out under a nitrogen or an argon atmosphere. ^{1}H and ^{13}C NMR spectra were recorded on a AF-250 FT-NMR spectrometer and the chemical shifts are indicated in ppm with the values relative to internal tetramethylsilane standard unless otherwise noted. Coupling constants (J) are reported in Hz. The signals of H-B in ^{1}H NMR are very broad and range from 1.2 to 4.2 ppm. Infrared spectra were carried out on a RFX40 FT-IR spectrometer (Laser precision Corp.) 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 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 were performed at Galbraith Laboratories Inc., Knoxville, TN. Melting points were determined on a Fisher-Johns apparatus and reported uncorrected. TLC plates with Silica Gel 60F-254 and Silica Gel 60 (70-230 mesh) from E. Merck were used for TLC and column chromatography. 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



Scheme IV

chromatography. Pyridine, acetonitrile and dimethyl formamide were dried with molecular sieves (4Å). Benzene was dried over sodium. THF and ether were distilled over sodium and benzophenone under argon prior to use. Other chemicals were purchased from commercial suppliers.

Preparation of E-5-(2-methoxycarbonylvinyl)-2'-deoxyuridine (3). To a solution of palladium acetate (48 mg, 0.21 mmol) and triphenylphosphine (120 mg, 0.46 mmol) in 40 mL of 1,4-dioxane was added 1.2 mL (8.6 mmol) of triethylamine, and the mixture was heated to reflux under argon with vigorous stirring for 30 min. To this refluxing solution was added (+)-5-iodo-2'-deoxyuridine (1.34g, 3.78 mmol) in 5 mL of 1,4-dioxane and methyl acrylate (0.8 mL, 8.89 mmol) separately, and the mixture was refluxed for 14 h. The hot reaction mixture was filtered through FW14 celite, washed with hot 1,4-dioxane, and the solvent was evaporated. The residue was purified by column chromatography on silica gel eluted with dichloromethane/methanol (6:1) to give the product as a crystalline solid in 100% yield (1.18 g, 3.78 mmol). TLC (chloroform/methanol, 4:1): R_f=0.5; mp 166-167°C; FT-IR (KBr): 3434, 3040, 2950, 1710, 1676, 1621, 1473, 1436, 1317, 1292, 1097, 970 cm^{-1}; ^1H NMR (CD_3OD) δ 8.41 (s, 1H), 7.32 (d, J=15.86, 1H), 6.81 (d, J=15.86, 1H), 6.17 (t, J=6.39, 1H), 4.34 (t, d, J=6.04, 3.87, 1H), 3.88-3.84 (m, 1H), 3.72 (d, d, d, J=12.95, 3.02, 2H), 3.65 (s, 3H), 2.27-2.17 (m, 2H); ^{13}C NMR (CD_3OD) δ

169.66, 163.60, 151.11, 144.69, 138.67, 118.54, 110.43, 89.23, 87.20, 71.74, 62.44, 51.99, 41.92; FAB-MS m/e (rel intensity) 102 (46), 117 (37), 136 (60), 154 (87), 160 (100), 165 (19), 197 (38), 220 (8), 289 (12), 313 (M^++H, 42); EI-HRMS calcd for $C_{13}H_{16}N_2O_7$: 312.0958, found: 312.0957. Anal. Calcd for $C_{13}H_{16}N_2O_7 \cdot 1/5\ H_2O$: C, 49.43; H, 5.23; N, 8.87. Found: C, 49.52; H, 5.38; N, 8.99.

Preparation of E-5-(2-carboxyvinyl)-2'-deoxyuridine (4). To a solution of methyl ester (3) (700 mg, 2.24 mmol) in 6 mL methanol and 6 mL water was added dropwise 6 mL of 2M sodium hydroxide solution at 0°C with vigorous stirring. The mixture was then stirred for an additional 2 h. The product was precipitated from solution by slowly adding concentrated hydrochloric acid to adjust the solution to a pH ~1.0. The methanol was removed on a rotary evaporator and the aqueous solution was filtered. The product was washed with cold water and dried in vacuum at room temperature overnight yielding a white powder in 89.7% yield (600 mg, 2.0 mmol). FT-IR (KBr): 3480, 3033, 2956, 2832, 1708, 1689, 1610, 1465, 1428, 1384, 1321, 1299, 1097, 970 cm^{-1}; ^1H NMR (CD_3OD) δ 8.39 (s, 1H), 7.29 (d, J=15.89, 1H), 6.77 (d, J=15.89, 1H), 6.17 (t, J=6.28, 1H), 4.36-4.31 (m, 1H), 3.88-3.84 (m, 1H), 3.72 (d, d, d, J=13.99, 2.99, 2H), 2.28-2.14 (m, 2H); ^{13}C NMR (DMSO-d^6) δ 167.81, 161.53, 149.12, 143.16, 137.18, 117.70, 108.28, 87.55, 84.69, 69.68, 60.76, 39.97; FAB-MS m/e (rel intensity) 107 (8), 117 (16), 137 (29), 157 (100), 183 (8), 214 (8), 232 (16), 254 (4), 299 (M^++H, 11); EI-HRMS calcd for $C_{12}H_{14}N_2O_7$: 298.0801, found: 298.0946; Anal. Calcd for $C_{12}H_{14}N_2O_7 \cdot 1/5\ H_2O$: C, 47.75; H, 4.81; N, 9.29. Found: C, 47.74; H, 4.79; N, 9.19.

The following is a general procedure for the tosylation of alkynyl alcohols.

Preparation of 5-hexyn-1-[(4'-methyl)phenyl]sulfonic ester (5a). To a stirred solution of 5-hexyn-1-ol (4.0 g, 40.75 mmol) in 25 mL pyridine was added dropwise over a period of 30 min a solution of tosyl chloride (9.32 g, 48.9 mmol) in 60 mL benzene at 0°C. After stirring for 14 h at 0°C, the mixture was filtered to remove the precipitated pyridine hydrochloride and the precipitate was washed with benzene. The filtrate was stirred in 250 g of ice-water. The mixture was extracted three times with 40 mL aliquots of ether. The combined ether extracts were washed successively with cold 1:1 hydrochloric acid solution to remove residual pyridine, with brine at pH 7 and dried over anhydrous magnesium sulfate. After solvent evaporation, the tosylated product was obtained as a colorless oil in 98% yield (10.1 g, 40.0 mmol). TLC

(hexane/ethyl acetate, 5:1): R_f=0.39; FT-IR (neat): 3291, 3040, 2952, 2869, 2117, 1635, 1589, 1494, 1455, 1349, 1307, 1292, 1211, 1189, 1174 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.77 (d, J=7.82, 2H), 7.33 (d, J=7.82, 2H), 4.03 (t, J=6.21, 2H), 2.43 (s, 3H), 2.15 (t, d, J=6.88, 2.64, 2H), 1.90 (t, J=2.64, 1H), 1.75 (t, t, J=6.21, 6.88, 2H), 1.59-1.50 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 144.62, 133.16, 129.73, 127.72, 83.27, 69.80, 68.84, 27.70, 24.14, 21.44, 17.60; FAB-MS m/e (rel intensity) 107 (24), 137 (60), 155 (100), 173 (64), 216 (4), 253 (M^++H, 37).

Preparation of 4-pentyn-1-(4'-methyl)phenylsulfonic ester (5b). The procedure for the preparation of this product was the same as described above. This product was purified by silica gel column chromatography eluted with hexane/ethyl acetate (2:1) in 80% yield. TLC (hexane/ethyl acetate): R_f=0.70; FT-IR (neat): 3291, 3040, 2962, 2927, 2119, 1598, 1496, 1465, 1455, 1359, 1307, 1292, 1211, 1189, 1176 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.77 (d, J=8.17, 2H), 7.33 (d, J=8.17, 2H), 4.13 (t, J=6.09, 2H), 2.43 (s, 3H), 2.25 (t, d, J=6.92, 2.64, 2H), 1.86 (t, J=2.64, 1H), 1.85 (t, t, J=6.09, 6.92, 2H); ^{13}C NMR ($CDCl_3$) δ 144.66, 132.98, 129.72, 127.71, 81.90, 69.31, 68.64, 27.63, 21.39, 14.53; FAB-MS m/e (rel intensity) 107 (17), 139 (39), 155 (100), 173 (57), 223 (9), 239 (M^++H, 93).

Preparation of 3-butyn-1-(4'-methyl)phenylsulfonic ester (5c). This product was prepared and purified by column chromatography on silica gel eluted with hexane/ethyl acetate (2:1) in 100% yield. TLC (hexane/ethyl acetate, 2:1): R_f=0.69; FT-IR (neat): 3291, 3040, 2962, 2850, 2117, 1598, 1357, 1307, 1292, 1211, 1189, 1174 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.79 (d, J=8.30, 2H), 7.34 (d, J=8.30, 2H), 4.09 (t, J=7.08, 2H), 2.54 (t, d, J=7.08, 2.66, 2H), 2.44 (s, 3H), 1.95 (t, J=2.66, 1H); ^{13}H NMR ($CDCl_3$) δ 144.90, 132.98, 129.81, 127.87, 78.35, 70.68, 67.38, 21.51, 19.40; FAB-MS m/e (rel intensity) 107 (8), 115 (11), 128 (8), 137 (40), 155 (63), 173 (83), 185 (3), 209 (6), 225 (M^++H, 100).

General procedure for the boronation of tosylated terminal alkynyl alcohols: Procedure A:[9a] A solution of the tosylated alkynyl alcohol, acetonitrile (15 equiv) and decaborane (1.4 equiv) in dry benzene was stirred at reflux temperature under argon for 3 to 4 days. The resulting mixture was concentrated on an evaporator to give a pale yellow oil, which was purified by column chromatography on silica gel by eluting with hexane/ethyl acetate (8:1). The pure product was obtained as a white precipitate by precipitated spontaneously from the chromatographic fraction.

Procedure B:[9b] A solution of decaborane in acetonitrile was stirred at reflux under argon for 4 h. The resulting mixture was cooled to ambient

temperature, filtered and washed with diisopropyl ether. The product was dried yielding the bis(acetonitrile)decaborane complex as a white powder.

A solution of the tosylated alkynyl alcohol and the bis(acetonitrile)decaborane complex (1.5 equiv) was refluxed in benzene with stirring under argon for 4-8 h. After evaporation of the solvent, the residue was purified by silica gel column chromatography and eluted with hexane/ethyl acetate (8:1 to 5:1) to give product as a white precipitate.

4-(1,2-Dicarba-closo-dodecarboranyl)butyl(4'-methyl)phenyl sulfonic ester (6a). This compound was prepared by procedure B in yield of 83%. TLC (hexane/ethyl acetate, 2:1): R_f=0.50; mp 81-83°C; FT-IR (KBr): 3060, 2975, 2860, 2616, 2588, 2553, 1598, 1473, 1355, 1187, 1172, 1070 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.77 (d, J=8.32, 2H), 7.35 (d, J=8.32, 2H), 4.00 (t, J=5.89, 2H), 3.48 (s, b, 1H), 2.45 (s, 3H), 2.13 (t, J=8.46, 2H), 1.66-1.55 (m, 2H), 1.49-1.22 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 145.04, 133.11, 129.96, 127.83, 74.65, 69.31, 61.10, 37.33, 28.10, 25.30, 21.59; FAB-MS m/e (rel intensity) 107 (20), 137 (88), 155 (29), 173 (100), 271 (10), 371 (M^++H, 6); EI-HRMS calcd for $C_{13}H_{26}B_{10}O_3S$ 372.2533, found 372.2575. Anal. Calcd for $C_{13}H_{26}B_{10}O_3S$: C, 41.91; H, 7.04; B, 29.57; S, 8.59. Found: C, 41.98; H, 7.04; B, 28.97; S, 8.73.

3-(1,2-Dicarba-*closo*-dodecarboranyl)propyl(4'-methyl)Phenyl sulfonic ester (6b). This compound was prepared by procedure A in yield of 71%. TLC (hexane/ethyl acetate, 2:1): R_f=0.59; mp 116-118°C; FT-IR (KBr): 3062, 2618, 2580, 1596, 1494, 1444, 1382, 1357, 1189, 1174 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.75 (d, J=8.10, 2H), 7.35 (d, J=8.10, 2H), 3.98 (t, J=5.77, 2H), 3.51 (s, b, 1H), 2.45 (s, 3H), 2.25 (t, d, J=7.25, 2.64, 2H), 1.81 (t, t, J=7.25, 5.77, 2H); ^{13}C NMR ($CDCl_3$) δ 145.22, 132.95, 130.01, 127.88, 76.28, 68.48, 61.60, 34.34, 28.67, 21.61; FAB-MS m/e (rel intensity) 107 (23), 136 (100), 154 (75), 173 (67), 289 (13), 357 (M^++H, 3); EI-HRMS calcd for $C_{12}H_{24}B_{10}O_3S$ 358.2377, found 358.2404. Anal. Calcd for $C_{12}H_{24}B_{10}O_3S$: C, 40.43; H, 6.79; B, 30.32; S, 8.99. Found: C, 39.73; H, 6.34; B, 30.61; S, 9.39.

2-(1,2-Dicarba-*closo*-dodecarboranyl)ethyl(4'-methyl)phenyl sulfonic ester (6c). This compound was prepared by procedure A in yield of 80%. TLC (hexane/ethyl acetate, 2:1): R_f=0.84; mp 110-112°C; FT-IR (KBr): 3058, 2950, 2850, 2605, 2576, 1596, 1353, 1189, 1174 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.76 (d, J=8.24, 2H), 7.37 (d, J=8.24, 2H), 4.08 (t, J=6.20, 2H), 3.65 (s, b, 1H), 2.59 (t, J=6.20, 2H), 2.45 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 145.62, 132.44, 130.15, 127.93, 71.19, 66.75, 60.41, 36.93, 21.66; FAB-MS m/e (rel intensity) 107 (24), 136 (100), 154 (93), 167 (12), 173 (36), 195 (5), 258 (4), 273 (6), 287 (6), 341

(14), 343 (M^++H, 23); EI-HRMS calcd for $C_{11}H_{22}B_{10}O_3S$ 344.2220, found 344.2248; Anal. Calcd for $C_{11}H_{22}B_{10}O_3S$: C, 38.58; H, 6.48; B, 31.57; S, 9.36. Found: C, 38.02; H, 6.14; B, 31.40; S, 10.01.

Preparation of target compounds (1). General procedure for esterification of E-5-(2-carboxyvinyl)-2'-deoxyuridine (4). To a solution of acid (4) in DMF was added anhydrous potassium carbonate (4 equiv). The mixture was stirred at 60°C for 2 h. Then, a solution of the tosylated carborane (1.2 equiv) in DMF was added, and the mixture was stirred at 65°C for 4~6 h. The hot mixture was monitored for the loss of starting material, acid (4), by thin layer chromatography on silica gel with ethyl acetate/methanol (5:1). After the reaction was completed, the solvent was evaporated under reduced pressure and the residue was separated by column chromatography on silica gel with chloroform/methanol (3:1) to give the product as a colorless sticky solid.

E-5-[2-(1,2-dicarbo-*closo*-dodecaboranylbutoxycarbonyl) vinyl]-2'-deoxyuridine (1a). The procedure for the preparation of this product was the same as described above. This product was purified in 62% yield by silica gel column chromatography eluted with chloroform/methanol (3:1). TLC (chloroform/methanol, 5:1): R_f=0.75; mp 128-130°C; FT-IR (KBr): 3455, 3040, 2850, 2520, 1695, 1627, 1471, 1384, 1319, 1290, 1189, 1089, 1039 cm^{-1}; ^1H NMR (CD_3OD) δ 8.38 (s, 1H), 7.33 (d, J=15.86, 1H), 6.82 (d, J=15.86, 1H), 6.18 (t, J=6.45, 1H), 4.35-4.33 (m, 1H), 4.04 (t, J=6.19, 1H), 3.88-3.85 (m, 1H), 3.73 (d, d, d, J=12.05, 3.60, 2.90, 2H), 3.43 (3, 1H), 2.26-2.19 (m, 2H), 1.55-1.46 (m, 2H), 1.42-1.37 (m, 4H); ^{13}C NMR (CD_3OD) δ 169.16, 163.62, 151.08, 144.73, 138.74, 118.67, 110.42, 89.24, 87.21, 71.74, 64.72, 63.63, 62.46, 41.93, 38.41, 32.81, 29.16, 26.97; EI-MS m/e (rel intensity) 137 (100), 166 (15), 198 (18), 267 (12), 380 (8), 497 (M^++H, 0.3); EI-HRMS calcd for $C_{13}H_{23}B_{10}N_2O_4$(-deoxyribose): 381.2588, found: 381.2626.

E-5-[2-(1,2-dicarbo-*closo*-dodecaboranylpropoxycarbonyl) vinyl]-2'-deoxyuridine (1b). This product was prepared the same as described above. It was purified by silica gel column chromatography following elution with ethyl acetate/methanol (3:1) in 65% yield. TLC (chloroform/methanol, 6:1): R_f=0.62; mp 150-152°C; FT-IR (KBr): 3440, 3010, 2850, 2520, 1733, 1697, 1683, 1652, 1471, 1384, 1184 cm^{-1}; ^1H NMR (ppm, CD_3OD) δ 8.45 (s, 1H), 7.40 (d, J=15.89, 1H), 6.83 (d, J=15.89, 1H), 6.25 (t, J=6.24, 1H), 4.41-4.36 (m, 1H), 4.07 (t, J=5.56, 2H), 3.95-3.91 (m, 1H), 3.80 (d, d, d, J=12.09, 3.80, 2.94, 2H), 2.36-2.22 (m, 2H), 1.81-1.45 (m, 4H); ^{13}C NMR (CD_3OD) δ 175.72, 169.81, 144.92, 139.02, 118.41, 110.38, 89.27, 87.22,

77.03, 71.73, 64.11, 63.90, 62.44, 50.78, 41.96, 35.56, 29.77; EI-MS m/e (rel intensity) 107 (5), 120 (7), 138 (138), 165 (37), 201 (35), 267 (12), 317 (8), 368 (14), 419 (4), 482 (M^+, 2); EI-HRMS calcd for $C_{12}H_{21}B_{10}N_2O_4$(-deoxyribose): 367.2432, found, 367.2492. Anal. Calcd for $C_{17}H_{30}B_{10}N_2O_7 \cdot 1.5H_2O$: C, 40.07; H, 6.53; B, 21.21; N, 5.50. Found: C, 40.22; H, 6.46; B, 20.76; N, 5,04.

E-5-[2-(1,2-dicarbo-*closo*-dodecaboranylethoxycarbonyl) vinyl]-2'-deoxyuridine (1c). This product was prepared the same as described above. It was purified in 72% yield by silica gel column chromatography eluting with chloroform/methanol (2:1). TLC (hexane/ethyl acetate /methanol, 2:7:1): R_f=0.60; mp 184-186°C; FT-IR (KBr): 3426, 3040, 2850, 2520, 1695, 1652, 1625, 1471, 1384, 1317, 1288, 1093, 1049 cm^{-1}; ^1H NMR (CD_3OD) δ 8.36 (s, 1H), 7.41 (d, J=15.85, 1H), 6.82 (d, J=15.85, 1H), 6.19 (t, J=6.74, 1H), 4.37-4.17 (m, 1H), 4.16-4.08 (m, 2H), 3.89-3.85 (m, 1H), 3.74 (d, d, d, J=11.97, 3.91, 2.62, 2H), 2.32-2.08 (m, 2H), 1.90-1.75 (m, 2H); ^{13}C NMR (CD_3OD) δ 168.54, 163.61, 151.07, 145.10, 139.45, 118.05, 110.33, 89.28, 87.29, 74.19, 71.75, 63.55, 63.06, 62.47, 41.95, 37.46; EI-MS m/e (rel intensity) 81 (100), 99 (18), 138 (46), 165 (33), 187 (28), 296 (5), 352 (5), 469 (M^++H, 1); EI-HRMS calcd for $C_{11}H_{19}B_{10}N_2O_4$(-deoxyribose): 353.2275, found, 353.2298.

Preparation of 5-(methoxycarbonylethyl)-2'-deoxyuridine (7). A solution of methyl ester (3) (500 mg, 1.6 mmol) in methanol (25 mL) containing palladium on carbon (10%, 25 mg) was hydrogenated under pressure of 45 psi at room temperature for 22 h. The mixture was filtered through FW14 celite and the filtrate was evaporated. The residue was dried under vacuum to give the product as an off-white solid in yield of 88%. TLC (chloroform/methanol, 6:1): R_f=0.51; FT-IR (KBr): 3600-3200, 3060, 2933, 2821, 1750-1620, 1473, 1443, 1419, 1384, 1278, 1203, 1089, 1054 cm^{-1}; ^1H NMR (CD_3OD) δ 7.78 (s, 1H), 6.19 (t, J=6.71, 1H), 4.35-4.29 (m, 1H), 3.85-3.81 (m, 1H), 3.75-3.61 (m, 2H), 3.57 (s, 3H), 2.51-2.45 (m, 4H), 2.18-2.06 (m, 2H); ^{13}C NMR (CD_3OD) δ 174.78, 165.36, 151.94, 138.87, 113.75, 88.57, 86.25, 71.98, 62.71, 52.16, 40.96, 33.35, 23.32; FAB-MS m/e (rel intensity) 117 (27), 136 (33), 160 (54), 167 (40), 176 (19), 199 (87), 221 (30), 315 (M^++H, 53); EI-HRMS calcd for $C_{13}H_{18}N_2O_7$: 314.1114, found, 314.1108.

Preparation of 5-(carboxypropyl)-2'-deoxyuridine (8). To a solution of methyl ester (7) (500 mg, 1.59 mmol) in 8 mL of mixture solvents (acetone/chloroform, 1:1) was added dropwise with vigorous stirring 4 mL of 2M sodium hydroxide solution at 0°C over a 10 min peiod. Stirring was continued

for 2 h. The reaction mixture was examined by thin layer chromatography on silica gel to assess loss of starting material methyl ester (7). When the reaction was completed 6 mL of concentrated hydrochloric acid was added slowly at 0°C. The resulting mixture was concentrated on the evaporator and the product was isolated by column chromatography on silica gel by elution with acetone/chloroform (4:1). The compound was isolated in 75% yield. TLC (chloroform/methanol, 2:1): Rf=0.40; FT-IR (KBr): 3550, 3477, 3400, 3032, 2958, 2940, 1724, 1689, 1467, 1384, 1282, 1224, 1201, 1180, 1112, 1089, 1070 cm^{-1}; ^1H NMR (CD_3OD) δ 7.79 (s, 1H), 6.20 (t, J=6.71, 1H), 4.36-4.31 (m, 1H), 3.86-3.82 (m, 1H), 3.76-3.63 (m, 2H), 2.55-2.48 (m, 4H), 2.19-2.12 (m, 2H); ^{13}C NMR (CD_3OD) δ 176.34, 165.66, 152.15, 138.97, 114.07, 88.82, 86.36, 72.14, 62.88, 41.19, 33.53, 22.53; EI-MS m/e (rel intensity) 117 (11), 138 (100), 167 (20), 184 (7), 198 (3), 300 (M^+, 0.03); EI-HRMS calcd for $C_{12}H_{16}N_2O_7$: 300.0958, found, 300.0930.

Preparation of target compound (2), 5-[(1,2-dicarba-*closo*-dodecaboranyl propoxycarbonyl)ethyl]-2'-deoxyuridine. This compound was similarly prepared in 76% yield by use of potassium carbonate (3.0 equiv) in a stirred solution of DMF for 3 h at 65°C. TLC (ethyl acetate/methanol, 6:1): Rf=0.75; mp 72-74°C; FT-IR (KBr): 3600-3200, 3060, 2933, 2592, 1730-1650, 1471, 1417, 1384, 1276, 1180, 1093, 1054, 1022 cm^{-1}; ^1H NMR (CD_3OD) δ 7.77 (s, 1H), 6.20 (t, J=6.73, 1H), 4.46 (s, b, 1H), 4.34-4.29 (m, 1H), 3.95 (t, J=6.16, 2H), 3.85-3.81 (m, 1H), 3.75-3.61 (m, 2H), 2.51 (t, J=10.80, 2H), 2.49 (t, J=10.80, 2H), 2.28-2.21 (m, 2H), 2.20-2.07 (m, 2H), 1.78-1.66 (m, 2H); ^{13}C NMR (CD_3OD) δ 174,32, 165.61, 152.15, 139.05, 113.84, 88.93, 86.48, 76.54, 72.21, 64.25, 63.79, 62.92, 41.30, 35.49, 33.70, 29.57, 23.58; FAB-MS m/e (rel intensity) 107 (19), 117 (70), 136 (51), 157 (37), 167 (100), 193 (7), 214 (8), 232 (7), 369 (65), 391 (4), 419 (4), 485 (M^++H, 28); EI-HRMS calcd for $C_{12}H_{23}B_{10}N_2O_4$(-deoxyribose): 369.2588, found: 369.2610. Anal. Calcd for $C_{17}H_{32}B_{10}N_2O_7 \cdot 1/3\ H_2O$: C, 41.62; H, 6.71; B, 22.04; N, 5.71. Found: C, 41.66; H, 6.73; B, 21.58; N, 5.45.

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