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SYNTHESIS OF LIPOPHILIC TETHERED 5-*O*-CARBORANYL-2'-DEOXYURIDINES

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Summary: The synthesis of 5-(1-butynyl-4-*o*-carboranyl)-2'-deoxyuridine (**6**) and 5-(*o*-carboranylmethoxymethyl)-2'-deoxyuridine (**12**) as tethered o-carboranyl nucleosides intended for modified oligonucleosides and (BNCT) is described.

Keywords: Carboranes, Nucleosides, Coupling reaction, Insertion reaction, cancer therapy.

Résumé: Les composés 5-(1-butynyl-4-*o*-carboranyl)-2'-deoxyuridine (**6**) et 5-(*o*-carboranylmethoxymethyl)-2'-deoxyuridine (**12**) sont des nucléosides ayant un bras hydrocarboné intercalant en position 5 entre la base hétérocyclique et la cage représentant le carbonanyle (cluster trés lipophilique). Ces dérivés nucléosidiques sont recherchés pour l'obtention des oligonucléosides modifiés et aussi pour " boron neutron capture therapy " (BNCT)

Mots clés: Carboranes, Nucleosides, Coupling reaction, Insertion reaction, cancer therapy.

I. INTRODUCTION

Biomolecules containing boron atoms are desirable for boron neutron capture therapy (BNCT), a procedure used in the treatment of malignancies, particularly for brain gliomas and melanomas[1]. This cancer therapeutic modality combines the utilization of boron-containing compounds targeted to the tumor cells and neutron irradiation as an initiator to produce micronuclear reactions confined mostly within tumors.

In order to deliver a sufficient quantity of fissionable ^{10}B atoms to tumor cells, much attention has been paid to the synthesis of molecules containing boron clusters (carboranes)[2-3], since these boron cages can provide a relatively high number of ^{10}B atoms. Several carboranyl derivatives have been prepared, including carboranyl nucleoside analogu[4-10]. Schinazi et *al*[10,11] demonstrated the intracellularly phosphorylation of 5-*o*-Carboranyl-2'-deoxyuridine (CDU) in malignant cells. A tethered spacer between the base and the bulky boron cage enhances nucleoside binding to kinases involved in its phosphorylation[12]. Furthermore, in a previous report on carboranyl oligonucleotides, significant interaction of a bulky carboranyl substituent at 5-position with adjacent bases within oligonucleotide chains was noted, suggesting that a hydrocarbon tether should reduce this undesirable interaction[13]. Rong and Soloway[14] have introduced at the 5-position of pyrimidine nucleoside a tethered chain between the

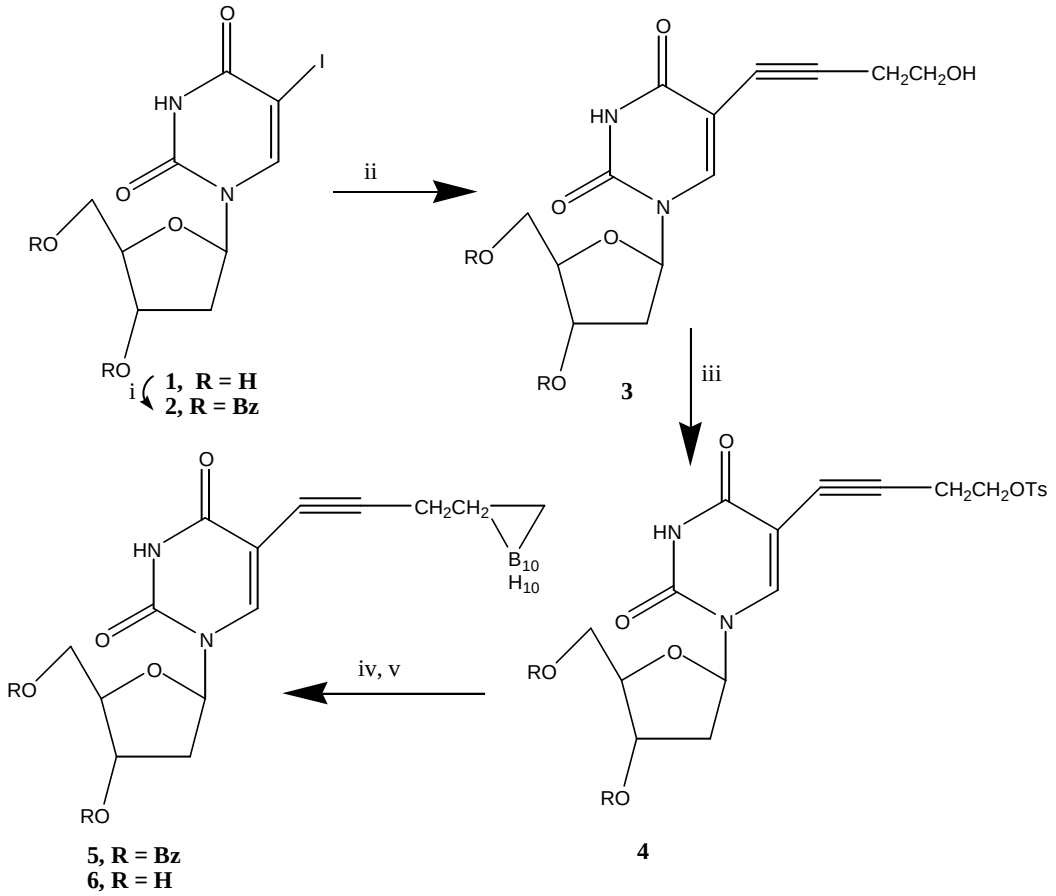
pyrimidine base and the boron cage through an ester function. However, these may not be biologically resistant to esterases.

This report describes the synthesis of 5-tethered carboranyl pyrimidine nucleosides, where one of the spacers is a hydrocarbon chain attached to an ethynylic group, 5-(1-butynyl-4-*o*-carboranyl)-2'-deoxyuridine (**6**) (scheme 1) while, the second one is an ether link leading to 5-(o-carboranylmethoxymethyl)-2'-deoxyuridine (**12**) (scheme 2).

as well as ether bound should not be susceptible to cellular or viral esterases.

II. CHEMISTRY

Compound (**6**) (Scheme 1) was synthesized from 5-Iodo-2'-deoxyurudine (IdUrd) (**1**) as follows. Protection of hydroxyl groups of (**1**) with benzoyl chloride in pyridine followed by the coupling of dibenzoyl iodonucleoside (**2**) with 3-butyn-1-ol in the presence of $(Pph_3)_2PdCl_2/CuI/Et_3N$[15-16] at 45°C in THF for 4 hr gave compound (**3**) (40% yield) after chromatography and recrystallization.



Scheme 1: synthesis of 6.
i: BzCl/Py/50°C/6h/85%; ii: 3-Butyn-1-ol/$Pd(PPh_3)_2Cl_2$/CuI/Et_3N/THF/45°C/4h/40%; iii: TsCl/DMAP/CH_2Cl_2/rt/20h/80%; iv: o-carborane/PhLi/THF/-78°C/1.5h/27%; v : NaOMe/MeOH/0°C/25%

Based on molecular modeling studies a tether should provide sufficient rigidity and spacing to prevent interaction with the adjacent base within an oligonucleotide chain. In addition, the hydrocarbon chain

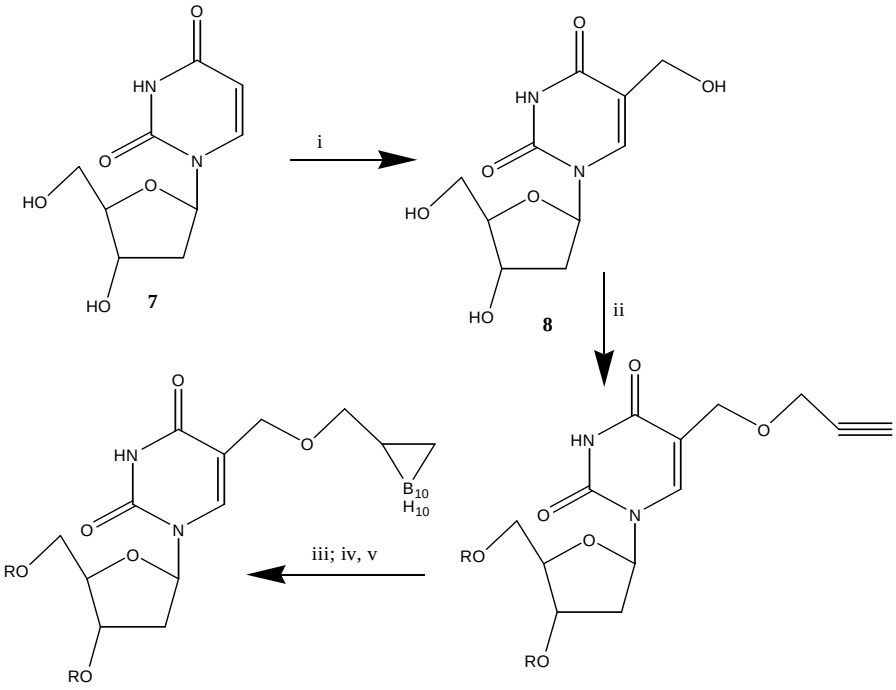
This intermediate was transformed to its toluenesulfonate ester (**4**) (60%) by reaction with toluenesulfonyl chloride in the presence of 4-dimethylamino pyridine (DMAP) for 20 hr in CH_2Cl_2 at room

temperature. Lithium salts of carborane[17-18] generated in situ have been reported to give a variety of nucleophilic reactions with alkylhalides, aldehydes, and epoxides. Therefore, the high reactivity of the carborane lithium salt was applied to displace the toluenesulfonate ester group of compound (**4**). Addition of compound (**4**) (0.5 eq) in THF solution to the lithium salt of o-carborane (generated in situ by addition of PhLi (1 eq) to a solution of o-carborane in THF at 0°C gave compound (**5**) (27%), as a nido enriched two isomers mixture (*closo* and *nido*). Deprotection of benzoyl groups was performed with NaOMe (2 eq) in MeOH at 0°C for 3 hr and flash chromatography gave a nido isomer (**5**) as an amorphous solid.

Another novel type of tethered nucleoside (**12a**) (scheme 2) was obtained starting from 2'-deoxyuridine (dUrd) (**1**).

selectively the key intermediate (**9**) (35%). After the 3'- and 5'- hydoxyl groups of the sugar moiety were protected to the p-toluoyl (p-Tol)(**10**) or acetyl (**11**) derivatives, the terminal ethynyl function was used for the carboranyl cage building up. This reaction was carried out in one pot using terminal alkyne compounds (**10** or **11**), decaborane, acetonitrile in anhydrous toluene at 90°C for 48 hr providing the protected analogues **(12a**) and (**12b**) in 35% yield. These intermediates (**12a**) and (**12b**) were deprotected with NaOMe in MeOH to give mostly *nido* isomer (**13a**).

The *closo* isomer (**13b**) (scheme 3) have been prepared by glycolisation reaction between the key intermediate 5-methoxypropynyluracil (**15**) and 1-chloro-3,5-o-ditoluoyl-2-deoxyribofuranoside.



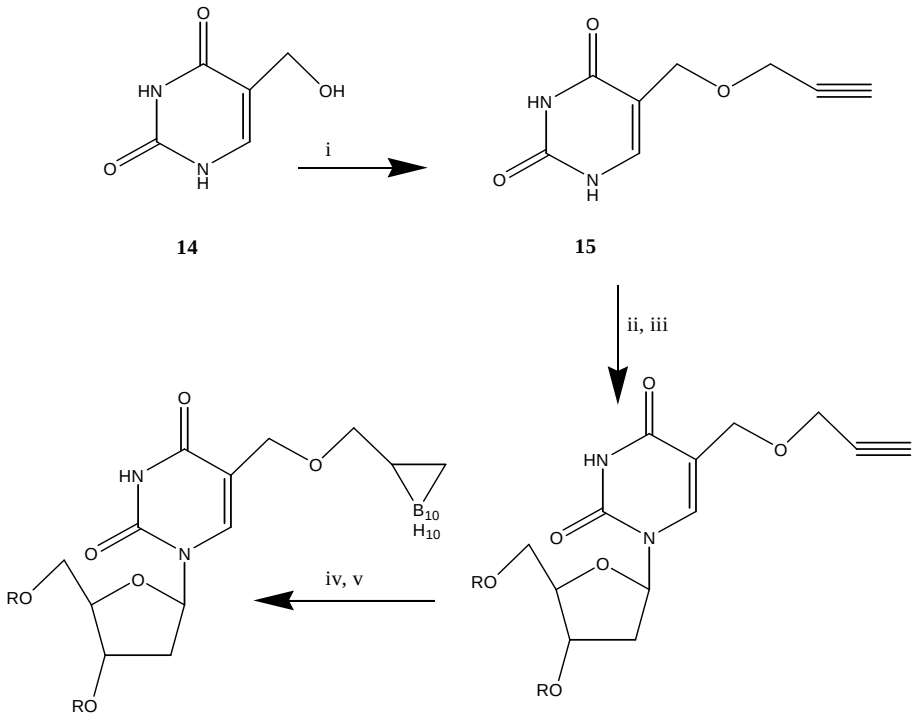
Scheme 2: synthesis of **13a**;
i: $(CH_2O)n$/0.5 M KOH/60°C/5days/35%; ii: Propargyl alcohol/HCl/75°C/4h/55%; iii: p-TolCl/Py/rt/20h/80%; iv: decaborane/CH_3CN/Toluene/90°C/17h/35%; v: NaOMe/MeOH/0°C/4h/45%

Hydroxymethylation[19] of (**7**) with paraformaldehyde in alkali conditions (sodium hydroxide) gave (**8**), which reacted with propargyl alcohol in acidic conditions[20-21] at 75°C for 4 hr, gave

When BSA/TMS/TMSOTf in Toluene or BSA/TMS/$SnCl_4$ in dichloromethane were used for the glycosylation, a mixture of anomers α/β was obtained respectively in (75/25) and (85/15) ratio. In contrast,

when silylated 5-methoxypropynyluracil and 1-chloro-3,5-o-ditoluoyl-2-deoxyribofuranoside were coupled with CuI (1 eq) catalyst in anhydrous $CHCl_3$, nucleoside β anomer was exclusively isolated in a satisfactory yield (95%) . The carboranyl cluster was then built on the triple bound end followed by de-protection of Toluoyl groups gave compound (**13b**) which was consistent with previous sample synthesized from 2'-deoxyuridine.

Characterization and analyses were performed on the intermediates and final compounds. Chromatography purifications were done on gel sylice 60 mesh; HPLC analysis were performed using Whatman A C18 RP column; UV spectra were obtained on Beckman DU 640 spectrophotometer; ^{1}H and ^{13}C NMR's performed on Varian 400 MHz; mass spectra were conducted on Finnigan TSQ 7000.



Scheme 3: synthesis of **13b**
i: propargyle alcohol/HCl con./75°C/17h/90%; ii. sylilation of compound**15;**
iii: sylilated **15**/sugar/CuI/25°C/$CHCl_3$/4h/95%; iv. decaborane/CH_3CN/Toluene/90°C/48H/40%;
v. MeONa/MeOH/0°C/4hr/45%

IV. CONCLUSION

The availability of a suitable route to compounds **6** and **13** provides an opportunity to use them as building blocks for oligonucleotides synthesis and as lypophilic boron containing nucleosides for BNCT.

III. EXPERIMENTAL SECTION

Starting materials and chemicals were purchased from Aldrich company.

5-(4-hydroxybutynyl)-3',5'-dibenzoyl-2'-deoxyuridine (3): dibenzoyl iodonucleoside (2) 1,2g (2.13 mmol) with 3-butyn-1-ol 0.426g (2.77mmol) in the presence of $(PPh_3)_2PdCl_2$ 0.150g (0.1 eq), CuI 0.040g (0.1 eq) and Et_3N 0.6 ml (2 eq) were stirred in anhydrous THF 15 ml at 45°C for 4 h under argon atmosphere. The reaction mixture was quenched with methanol, the crude compound was isolated as described in literature, followed by flash liquid chromatography

purification gave 0.375g (35%) of pure (3). mp: 156.9°C; ^{1}H NMR ($CDCl_3$ ∂ppm: 8.5 (s, 1H, HN), 8.2 (m, 4H, Bz), 7.8 (s, 1H, H6), 7.6 (m, 2H, Bz), 7.4 (m, 4H, Bz), 6.4 (m, 1H, H1'), 5.5 (m, 1H, H3'), 4.8 (m, 2H, H5'), 4.6 (s, 1H, H4'), 3.6 (t, 2H, CH2), 3.1 (t,3H, CH2), 2.2 (m, 2H, H2')

5-(4-o-*p*tosylbutynyl)-3',5'-dibenzoyl-2'-deoxyuridine (4): Compound (3) 67mg (0.13 mmol) in anhydrous $CHCl_3$ 1 ml, Et_3N 0.2 ml was added followed with TsCl 28mg (0.14 mmol) under inert atmosphere. The mixture stirred at room temperature for 17 h, then quenched by H_2O. Isolation and flash chromatography purification gave 34mg (51% yield) of compound (4). mp: 93.6°C; ^{1}H NMR ($CDCl_3$) ∂ppm: 8.5 (s, 1H, HN), 8.2 (m, 4H, Bz), 7.8 (s, 1H, H6), 7.6 (m, 6H, Bz § Ts), 7.4 (m, 6H, Bz § Ts), 6.4 (m, 1H, H1'), 5.5 (m, 1H, H3'), 4.8 (m, 2H, H5'), 4.6 (s, 1H, H4'), 4.5 (t, 2H, CH2), 3.9 (s, 3H, CH3), 3.6 (t, 2H, CH2), 2.0 (m, 2H, H2')

5-(1-butynyl-4-*o*-carboranyl)-3',5'-dibenzoyl-2'-deoxyuridine (5). Carborane 16mg (0.109 mmol) in THF 1.5 ml was stirred at -78°C under nitrogen atmosphere, phenyllithium 70 µl (0.109 mmol) was added through a syringe, the mixture stirred for 20 min then the subtrate (4) in anhydrous THF 3 ml was added through a syringe within 1 min period. The mixture was allowed to react at -78°C for 30 min then at room temperature for 2 h and then quenched with H_2O. Crude (5) was isolated with 5 ml CH_2Cl_2/H_2O, the organic layer was brought to dryness, the residue purified by liquid chromatography on sylice elution with CH_2Cl_2/MeOH 95/5 v/v to give 27% yield of (5). mp 77-79°C; ^{1}H NMR ($CDCl_3$)∂ppm: 8.5 (s, 1H, HN), 8.2 (m, 4H, Bz), 7.8 (s, 1H, H6), 7.6 (m, 1H, Bz), 7.4 (m, 4H, Bz), 6.4 (m, 1H, H1'), 5.5 (m, 1H, H3'), 4.8 (m, 2H, H5'), 4.6 (s, 1H, H4'), 4.5 (s, H, CHCBxH10), 3.6 (t, 2H, CH2), 3.2-2.0 (m, BxH10, CH2, H2'); anal. Calcd for $C_{29}H_{34}B_9N_2O_7$: C, 56.19; H, 5.53; N, 4.52. Found: C, 56.76; H, 5.40; N, 4.45.

5-(1-butynyl-4-*o*-carboranyl)-2'-deoxyuridine (6). Intermediate (5) 0.100g in anhydrous MeOH 2 ml and NaOMe (2.2 eq) were stirred at room temperature under nitrogen atmosphere for 3 hr, and neutralized with Dowex 50 W X 2 PyH+ resin. After centrifugation the surpernatant was separeted, brought to dryness, the crude product was purified by flash chromatography with CH_2Cl_2/MeOH 95/5 v/v elution yielding 25% of (6). UV in 95% EtOH: λmax = 202 and 213 nm, λmin = 299 nm. ^{1}H NMR (DMSO-d6)∂ppm: 8.8 (s, 1H, HN), 8.0 (s, 1H, H6), 6.2 (m, 1H, H1'), 4.3 (m, 1H, H3'), 4.0 (s, 1H, CHCBxH10), 3.9 (s, 1H, H4'), 3.6-3.4 (m, 4H, CH2 § H5'), 3.1-1.9 (br, BxH10, CH2, H2'). MS: atmospheric pressure chemical ionization (APCI) (M+1) calcd for $C_{15}H_{27}B_{10}N_2O_5$ m^+/z 425.2 found m^+/z 426.0.

5-hydroxymethyl-2'-deoxyuridine (8) see reference [19].

5-methoxypropynyl-2'-deoxyuridine (9). Compound **(8)** 0.545g (2.11 mmol) in suspension in propargyl alcohol 5 ml, concentrated HCl 0.5 ml was added to the suspension and stirred at room temperature until complete dissolution, the mixture was warmed up at 75°C over night. After cooling to room temperature the mixture was diluted in CH_2Cl_2 15 ml, and the liquid phase removed. The remaining oil was taken in methanol 20 ml and neutralized with Dowex 50 W X 2 OH form and filtred, solvent removed under reduced pressure, the crude product (8) was purified by liquid chromatography elution with CH_2Cl_2/MeOH 90/10 v/v to give 25% yield of pure compound (8). ^{1}H NMR (DMSO d6) ∂ppm: 11.0 (s, 1H, NH), 7.9 (s, 1H, H6), 6.0 (m, 1H, H1'), 5.2 (m, 1H, OH), 5.0 (s, 1H, acetylenic), 4.87 (m, 1H, OH), 4.2 (m, 1H, H3'), 3.9 (s, 2H, CH2O), 3.57 (m, 3H, OCH2 & H4'), 3.38 (m, 2H, H5'), 2.95 (m, 2H, H2'). ms: ESI (M+1) calcd for $C_{12}H_{16}N_2O_6$ 284 found m^+/z = 285.3

5-(o-carboranylmethoxymethyl)-2'-deoxyuridine (13a). A mixture of intermediate **(9)** 0.214g (0.4 mmol), decaborane 0.05g (0.4 mmol) and dry acetonitrile 42µL in suspension in anhydrous toluene 4 mL under nitrogen atmosphere was stirred under reflux for 24 hr, decaborane 0.4 mmol and acetonitrile 0.8 mmol were added, refluxing continued for additional 24 hr. The mixture was cooled to room temperature then concentrated under reduced pressure. The crude residue was purified by liquid chromatography elution with CH2Cl2/MeOH 95/5 (v/v) to give 58 mg of pure compound **(13a)** (22% yield). mp:93-95°C. UV (MeOH): λmax = 203 and 237 nm. ^{1}H NMR (DMSO d6)∂ppm: 11.4 (s, 1H, NH), 7.94 (s, 1H, H6), 6.07 (m, 1H, H1'), 5.27 (m, 1H, OH), 5.1 (broad, 1H, CHC), 4.87 (m, 1H, OH), 4.2 (m, 1H, H3'), 4.0 (s, 2H, CH2O), 3.57 (m, 3H, OCH2 & H4'), 3.40 (m, 2H, H5'), 2.98-1.6 (broad, 12H, carboranyl & H2'). ms: ESI (M+1) calcd for $C_{13}H_{27}B_{10}N_2O_6$ 417.2 found m^+/z =417.2 ms: ESI (M-1) calcd for $C_{13}H_{25}B_{10}N_2O_6$ 415.2 found m\z 414.2. Pyrrolidine test to get *nido* form: ESI (M-1) calcd for $C_{13}H_{25}B_9N_2O_6$: 404.2, found m^+\z 403.7.

5-methoxypropynyl-uracil (15). 5-hydroxymethyluracil **(14)** 2.0g (14.08 mmol) was in suspension in propargyl alcohol 20 mL and HCl conc. 0.5 mL was added with stirring at room temperature until complet dissolution. The solution was stirred at 75°C for 5 hr. TLC monitoring CH2Cl2/MeOH 85/15 (v/v) mobile phase revealed a new spot. The reaction mixture was cooled diluted with ether 5 mL, the precipitate removed by filtration and washed with abundant ether, dried to gave compound (13) 2.30g (91% yield). no more purification was needed. mp: 207.6-208.6°C; IR (KBr): 2142 cm^{-1}, 3268 cm^{-1} and 692 cm^{-1} (acetylene C-H); 1132 cm^{-1} (CH2-O-CH2); ^{1}H NMR (DMSO d6)∂ppm: 7.5 (s, 1H, H6), 5.0 (m, 1H, CCH), 3.9 (s, 2H, CH_2O), 3.56 (m, 2H, OCH_2).

5-(methoxypropynyl)-3',5'-ditoluoyl-2'deoxyuridine (16): Compound **(15)** 1.8g (10 mmol), BSA 8 mL, TMSCl 2 mL and triethylamine (TEA) 2 mL were stirred at 60°C overnight under nitrogen atmosphere. The reaction solution was concentrated while hot, and the residue co-evaporated with anhydrous CH2Cl2 then, dissolved in dry dichloromethane 15 mL. Then, the chlorosugar 3.7g in 30 mL of anhydrous dichloromethane was added followed by CuI (1 eq), the reaction suspension stirred under nitrogen atmosphere. After 3 hr TLC monitoring in ethyl acetate/hexane (3/7 v/v) mobile phase, revealed complete transformation to a mixture of *α/β* (1/9) ratio. Filtration through celite, the filtrate worked up by liquid extraction with saturated sodium bicarbonate 30mL, brine 30 mL then water. The organic layer was dried over sodium sulfate, filtered, solvent evaporated to dryness. The crude product was purified by liquid chromatography elution ethyl acetate/hexane (3/7 v/v) to give 2.12g (40% yield of *β* anomer, fast moving spot) mp: 171.5-172.5°C, IR (KBr) : 2140 cm^{-1}, 3270 cm^{-1} and 690 cm^{-1} (acetylenic C-H); 1130 cm^{-1} (CH2-O-CH2). ^{1}H NMR (DMSO d6)∂ppm: 10.8 (s, 1H, NH), 8.0 (m, 4H, Bz), 7.9 (s, 1H, H6), 7.4 (m, 4H, Bz), 6.17 (m, 1H, H1'), 5.1 (m, 1H, acetylenic C-H), 4.2 (m, 1H, H3'), 4.0 (s, 2H, CH2O), 3.57 (m, 3H, OCH2 & H4'), 3.40 (m, 5H, CH3 § H5'), 2.98-1.6 (m, 2H, H2'). ms (ESI) (M-1) m+/z = 531.6

5-(o-carboranylmethoxymethyl)-3',5'-ditoluoyl-2'deoxyuridine (13b) See experimental section for compound **(13a)**. ^{1}H NMR (DMSO d6)∂ppm: 11.4 (s, 1H, NH), 8.0 (m, 4H, Bz), 7.9 (s, 1H, H6), 7.4 (m, 4H, Bz), 6.17 (m, 1H, H1'), 5.1 (broad, 1H, C-H), 4.2 (m, 1H, H3'), 4.0 (s, 2H, CH2O), 3.57 (m, 3H, OCH2 & H4'), 3.40 (m, 5H, CH3 § H5'), 2.98-1.6 (m, BxH10 § H2')

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