Synthesis and in Vitro Evaluation of 5-*closo*- and 5-*nido*-Orthocarboranyluridines as Boron Carriers

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(Received July 4, 1997)

Sugar-part modified *closo*-carboranyluridines, 5-(*o*-carboran-1-yl)-2′,3′-dideoxy-3′-thiauridine **5** and 5-(*o*-carboran-1-yl)-2′,3′-dideoxy-2′α-phenylthiouridine **6**, were synthesized. These newly synthesized *closo*-carboranyluridines, **5** and **6**, and previously synthesized 5-(*o*-carboran-1-yl)uridine **1** were converted to the corresponding *nido*-carboranyluridines **18**, **19**, and **17**, respectively. Water-solubility of *nido*-type **17** was about 100 times higher than that of its *closo*-counterpart **1**. Water-solubilities of sugar modified *nido*-types **18** and **19** were about 1000 times higher than those of their *closo*-counterparts **5** and **6**. Cytotoxicities of the *nido*-types (**17** and **19**) were about 10 times lower than those of the corresponding *closo*-counterparts (**1** and **6**, respectively). Cellular uptake of the *nido*-types (**17** and **19**) was in the level similar to that of the *closo*-counterparts (**1** and **6**, respectively), although it is often believed that cellular uptake of hydrophilic carboranes (*nido*-forms) is much lower than that of lipophilic *closo*-carboranes.

Boron neutron capture therapy (BNCT) of cancer is based on the nuclear reaction that occurs when boron-10 is irradiated with thermal neutrons to yield high-energy alpha particles and recoiling lithium-7 nuclei.[1] A key requirement of BNCT is the selective delivery of an adequate concentration of boron-10 to tumors (30 μg/g tumor tissue).[2] Calculations have shown[3] that the therapeutic effectiveness will be 2—5 times greater if ^{10}B-containing compounds are localized within the cell nucleus, in contrast with the same ^{10}B concentration uniformly distributed throughout the cell. This fact has been the rationale for the attempts to synthesize boron-containing nucleic acid precursors. Such structures may achieve higher concentration differentials in rapidly proliferating cancer cells compared to the mitotically less active normal cells. Our group was the first to synthesize 5-carboranyluridine (**1**, CU) and 5-carboranyldeoxyuridine (**2**, CDU) (Chart 1).[4,5] Actually, cellular uptake of CU and CDU into malignant cells was very high[6] in comparison with the previously known ^{10}B carriers, such as *p*-boronophenylalanine (BPA) and sodium mercaptoundecahydrododecaborate ($Na_2B_{12}H_{11}SH$, so-called BSH) which have been used clinically for treatment of skin cancers and brain tumors, respectively. Unfortunately, however, those carboranyl-uridine **1** and -deoxyuridine **2** exhibited relatively high toxicity toward normal tissue.[4a]

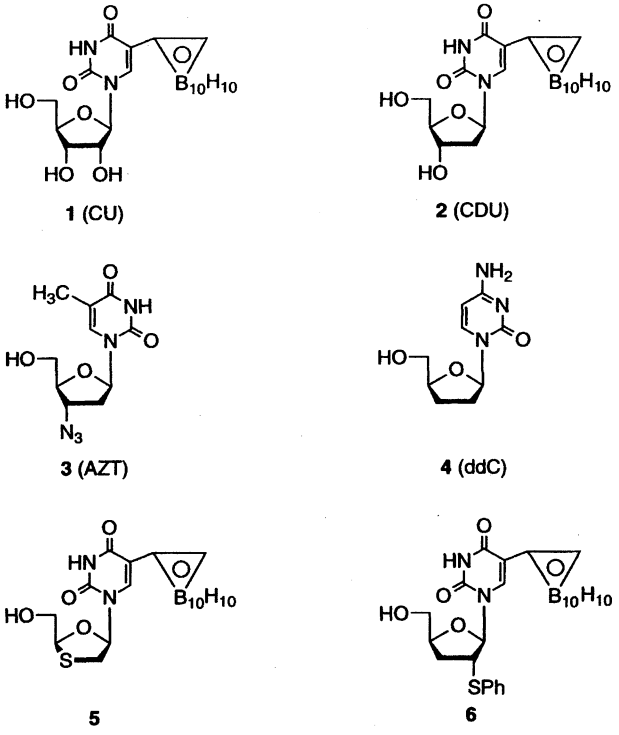


Chart 1.

It has been reported that the toxicity of antiretroviral agents, such as AZT (**3**) and ddC (**4**), can be suppressed by changing the structure of sugar moieties.[7] It occurred to us that sugar-modified carboranyluridines might exhibit lower toxicity with high cellular uptake. We communicated previously the synthesis of sugar-modified 5-orthocarboranyluridines, 5-(*o*-carboran-1-yl)-2′,3′-dideoxy-3′-thiauridine **5** and 5-(*o*-carboran-1-yl)-2′,3′-dideoxy-2′α-phenylthiouridine **6**, and their biological properties.[8] Although selective uptake of **6** into TIG-1-20 cells was accomplished by changing the sugar part of carboranyluridine to a sulfur-containing one, cytotoxicities of **5** and **6** were similar to or even higher than those of **1** and **2** having ordinary sugar parts.[8]

Another possibility for decreasing the cytotoxicity of the boron carriers is to increase their water solubility. We observed that the cytotoxicity of BPA (*p*-boronophenylalanine) to B-16 melanoma and TIG fibroblast cells was decreased

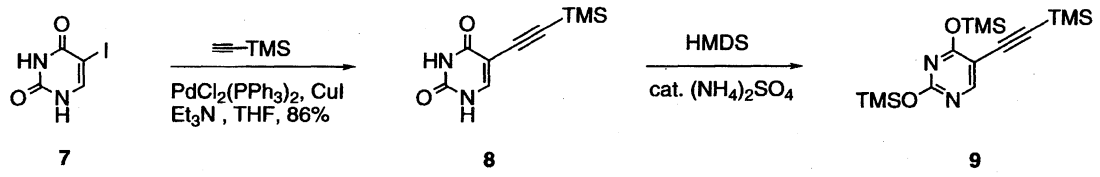
by attaching a water solubilizing element, cascade polyols, to the carboxylic acid group of BPA,[9] and the cytotoxicity of MACB (1-carboranyl-3-(2-methylaziridino)-2-propanol) to B-16 and TIG fibroblast cells was decreased also by attaching the cascade polyols at the carborane carbon atom.[10] On the other hand, it has been revealed that attaching a sterically too bulky water soluble moiety, such as cascade tetraol unit, to BPA led to a decrease of the boron incorporation into the cancer cells and to a dramatic decrease of the killing effect on in vitro NCT.[11] Accordingly, we decided to increase the water solubility of carboranyluridines (**1**, **5**, and **6**) by changing their *closo* carborane framework into *nido* structure. *closo*-Orthocarborane ($C_2B_{10}H_{12}$) is lipophilic and nonpolar, but *nido*-orthocarborane ($C_2B_9H_{12}^-M^+$, M=Na,$\cdots$) is hydrophilic and takes an ionic structure. We now report the synthesis of *nido*-orthocarboranyluridines (including sugar-modified types) and their biological properties in addition to the detailed study of the biological properties of *closo*-types of the sugar-modified derivatives **5** and **6**.

Results and Discussion

Synthetic Study. (1) Sugar-Modified *closo*-Orthocarboranyluridines 5 and 6. Synthesis of the base part is illustrated in Scheme 1. The carbon–carbon triple bond necessary for carborane formation was introduced to the 5-position of uracil **7** by the modified Sonogashira Pd–Cu catalyzed alkyne coupling reaction.[12] Treatment of **8** with hexamethyldisilazane produced silylated heterocycle **9**, which was used in the next condensation step (Scheme 2).

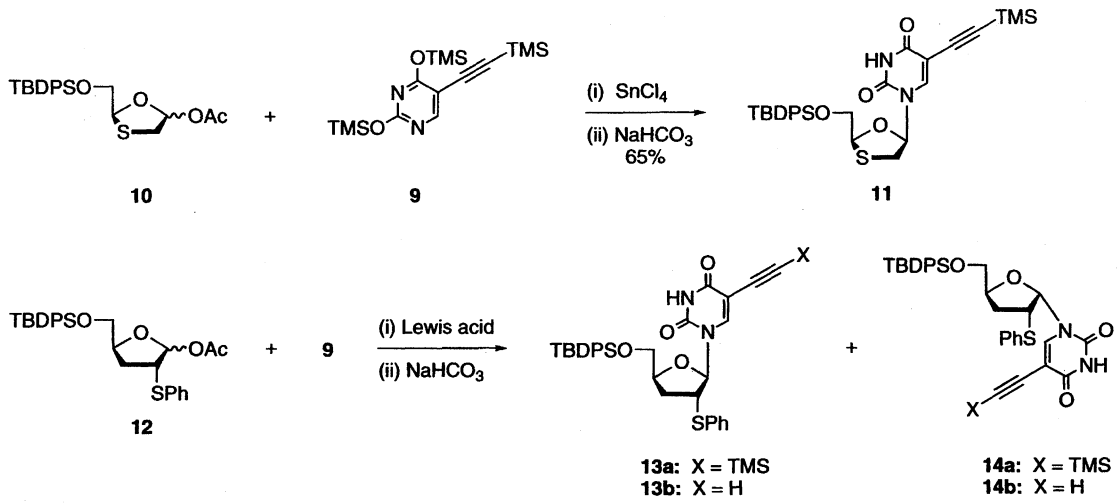
For initial trial, we chose **10** and **12** as sugar parts, because it is known that they may decrease toxicity[13] and exhibit high β selectivity in the Lewis acid-mediated nucleoside synthesis.[13,14] The structure unit **10** can be seen in the sugar moiety of antiretroviral agent 3TC, and **12** is involved as a sugar moiety of intermediate of antiretroviral agent d4T synthesis.[14] The condensation reaction of **9** and **10** using $SnCl_4$ gave the β anomer **11** as a sole product. The $SnCl_4$-mediated reaction of **9** with **12** afforded the β anomer **13a** with very high selectivity, along with small amounts of **14a** (**13a/14a** = 93/7), but the yield of the condensation products was ca. 50%. The use of TMSOTf instead of $SnCl_4$ led to a higher yield of β products with lower stereoselectivity; **13a** and **13b** were isolated in 66% combined yield and the ratio of **13** to **14** was 84 : 16. Partial removal of TMS group took place by using TMSOTf as a Lewis acid. Although it was reported that catalytic amounts of TMSOTf worked well in certain cases,[15] in our system the use of catalytic amounts of the reagent did not give a satisfactory result. We used stoichiometric amounts of the reagent in order to afford higher reaction rates. It was thought that exess amounts of TMSOTf might induce the anomerization at the anomeric carbon of **13**,[16] leading to lower selectivities. In fact, when we used two molar amounts of TMSOTf, the selectivity became even worse; α anomers **14** became a major product. Treatment of **13a** with NaOMe gave **13b** in essentially quantitative yield. The reaction of **13b** with $B_{10}H_{12}(EtCN)_2$, formed in situ from $B_{10}H_{14}$ and EtCN, gave carboranyluridine **15** in which a hydroxy group was protected by TBDPS group. Removal of TBDPS group from **15** using TBAF afforded the desired compound **6** in 57% overall yield from **13** (Scheme 3).

In the case of **11**, the silyl groups (TMS and TBDPS) were removed once and the 5′OH group was protected by



7 **8** **9**

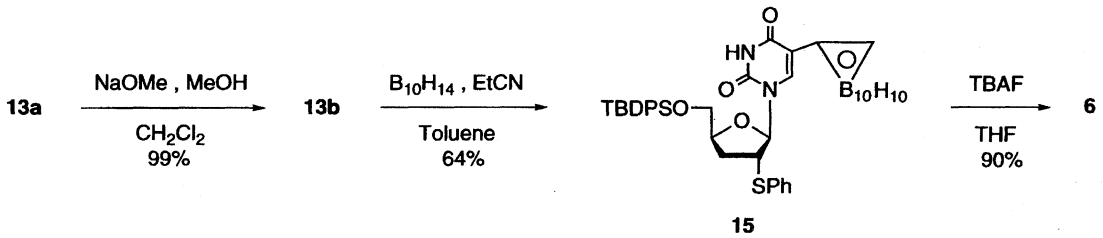
Scheme 1. Synthesis of 5-alkynylated uracil.



10 **9** **11**

12 **13a**: X = TMS **13b**: X = H **14a**: X = TMS **14b**: X = H

Scheme 2. Coupling of base and sugar-parts.



Scheme 3. Synthesis of *closo*-orthocarboranyluridine **6**.

a benzoyl group. The resulting acetylene derivative with a free acetylenic C–H bond was treated with $B_{10}H_{12}(EtCN)_2$ to give the corresponding carborane compound. Removal of the benzoyl group afforded the desired uridine **5**[17] in 40% overall yield from **11**.

(2) *nido*-Orthocarboranyluridines 17, 18, and 19. Water-soluble *nido* compounds were obtained by degradation of the *closo*-carborane cage unit using pyrrolidine as a base[18] (Scheme 4). Treatment of **1** with pyrrolidine under Ar atmosphere at room temperature gave the pyrrolidinium salt of *nido*-type **16**. Hydrogen gas evolved during the course of the reaction. The pyrrolidinium cation was then replaced by a sodium cation using ion exchange resin Dowex 50W-X8 (Na^+ form), affording the desired *nido*-orthocarboranyluridine **17**. Sugar-modified *closo*-types **5** and **6** were converted also to the corresponding *nido* derivatives **18** and **19** by using the same procedure as above.

nido-Structures of the newly synthesized carboranyluridines **17**, **18**, and **19** were confirmed by their ^1H and ^{11}B NMR spectra and IR spectra as shown below. A slightly broad peak appeared around 1.7 ppm in their ^1H NMR spectra, which was characteristic of a proton bonded to the carbon of the *nido* carborane anion.[19] The broad signal which appeared around −2 ppm could be assigned to the "extra" hydrogen which bridges two boron atoms on the open pentagonal face of the cage. ^{11}B-signals of **17** appeared at higher fields than that of the corresponding *closo*-carborane, clearly indicating the *nido*-framework of the newly synthesized carborane. Broad B–H stretching bands observed in the IR spectra of **17**, **18**, and **19** appeared at lower frequencies by about 60 cm^{-1} than those of the corresponding *closo* derivatives, which was also characteristic of the *nido*-framework.[19] It should be noted that *nido*-carboranyluridines **17**, **18**, and **19** are a mixture of diastereomers. This is understandable, because a boron atom abstraction of the *closo*-carborane cage takes place either at B-3 or at B-6 position (see **20**, Chart 2) and these two positions are diastereotopic to each other owing to the chiral substituent (uridine) at the C-1 position. In ^1H and ^{13}C NMR spectra, two sets of peaks were observed. Diastereomer ratios of these *nido*-carboranyluridines were in the range of 53—54 : 47—46, judging from the ratio of peak hights at 1′-proton.

In Vitro Evaluation. (1) Water Solubility. Water solubilities of *closo*-orthocarboranyluridines (**1**,[20] **5**, and **6**), and *nido*-orthocarboranyluridines (**17**, **18**, and **19**) are shown

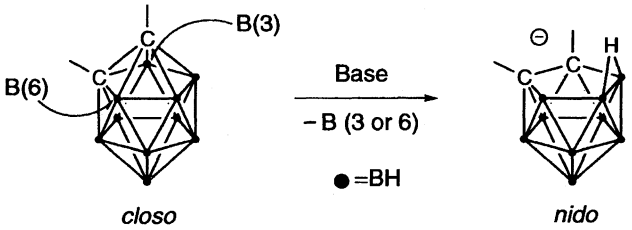
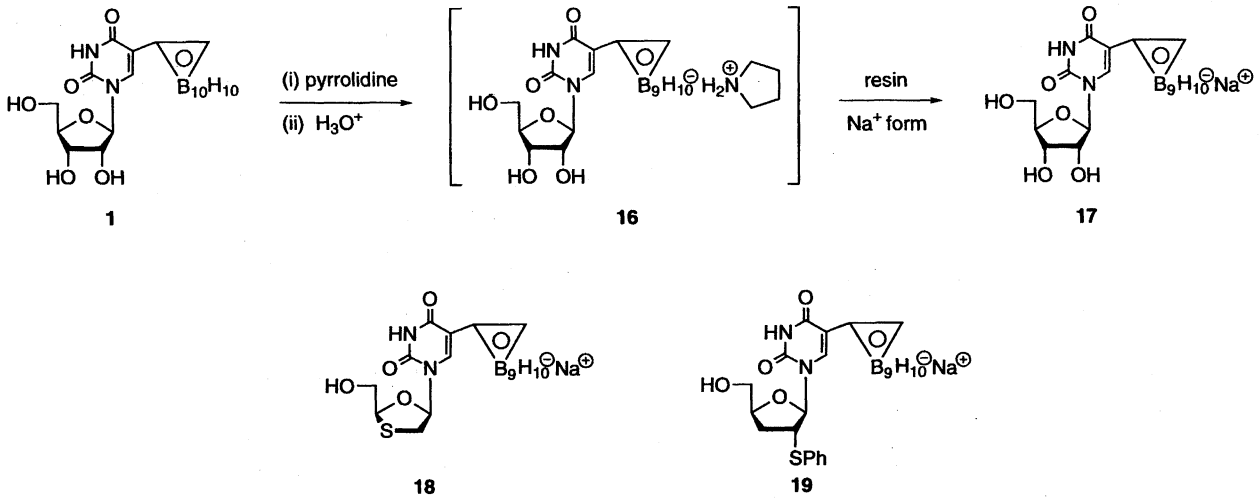


Chart 2.



Scheme 4. Conversion of orthocarboranyluridines to their *nido*-derivatives.

in Table 1. It is apparent that *nido*-type **17** is about 100 times, and sugar-modified *nido*-types **18** and **19** are about 1000 times more water-soluble than their *closo* counterparts. The water solubilities of these *nido*-types are of the order of 10^{-2} M (1 M=1 mol dm^{-3}), which seems enough for in vivo experiments.

(2) Cytotoxicity. Cytotoxicities of *closo*- and *nido*-carboranyluridines toward B-16 melanoma cells and TIG-1-20 fibroblast cells (human fetal lung normal cells) were evaluated in terms of IC_{50} values (Table 2). B-16 cells are a representative cancer cell and TIG-1-20 cells have been used as a model of normal cells.[9] It is clear that, on going from *closo*-types to *nido*-types, toxicities dramatically decrease by more than 10 times on IC_{50} values.

(3) Cellular Uptake. The comparison of cellular uptake between the *closo* (**1** and **6**) and *nido* (**17** and **19**) types is made in this section. Incorporation of each ^{10}B carrier into the cells was measured by using the ICP-AES method.[10] The cells [$(4.5—5.0)\times10^6$] were incubated for 1—24 h with Eagle-MEM medium containing each carrier at the concentration of IC_{50} value. Therefore injection does of *nido* compounds are about 10 times higher than their *closo* counterparts. At 3, 12, and 24 h, the cells were washed three times with PBS-(−) (Ca- and Mg-free phosphate-buffered saline, 4 mL) and processed for boron measurement by ICP. The results are summarized in Figs. 1 and 2. Very interestingly, cellular uptake levels of *anionic nido* derivatives **17** and **19** reached to the same values as those of neutral lipophilic *closo* counterparts **1** and **6**, respectively. As with the case of *closo*-type **6**,[8] *nido*-type **19** exhibited a markedly high boron concentration in TIG-1-20 cells (Fig. 2). The mechanism of this specific incorporation into TIG-1-20 cells presented by the sugar modification is unknown. It should be noted that we assumed that the boron concentration determined by the ICP method would be roughly similar to the intracellular concentration; therefore, further investigation will be needed for determining whether these *nido* compounds were really in the intracellular matrix or remained still in the cell membrane matrix. The latter case would be the result of inhibition of receptors in a plasma membrane.

Table 1. Water-Solubilities of Orthocarboranyluridines

Compound	Water-solubility/M, mol dm^{-3}	
	closo	*nido*
1 (**17**)	4.9×10^{-4}	5.8×10^{-2}
5 (**18**)	2.5×10^{-5}	1.5×10^{-2}
6 (**19**)	1.0×10^{-5}	2.6×10^{-2}

Table 2. Cytotoxicities of Orthocarboranyluridines

Compound	IC_{50}/M/10^{-5}	
	B-16	TIG-1-20
1	3.8	2.5
5	2.0±0.4	1.0±0.1
6	0.67±0.11	0.47±0.06
17	52±2	56±2
19	9.8±1.4	9.0±0.6

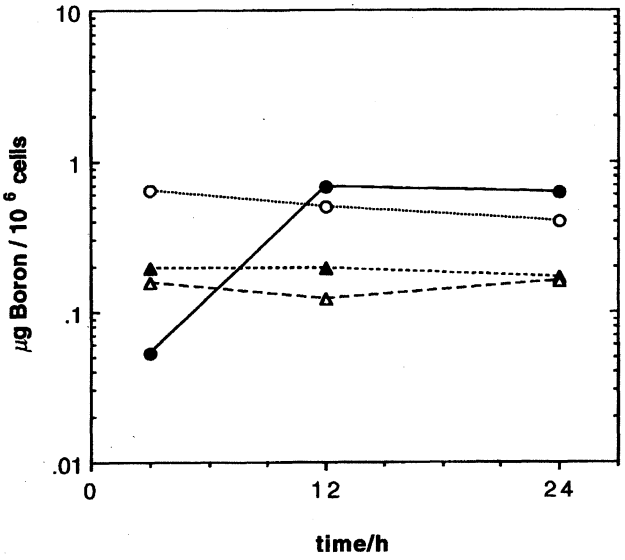
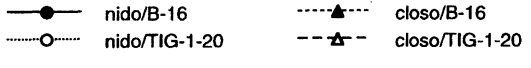


Fig. 1. Cellular uptake of *nido* **17** and *closo* **1**.



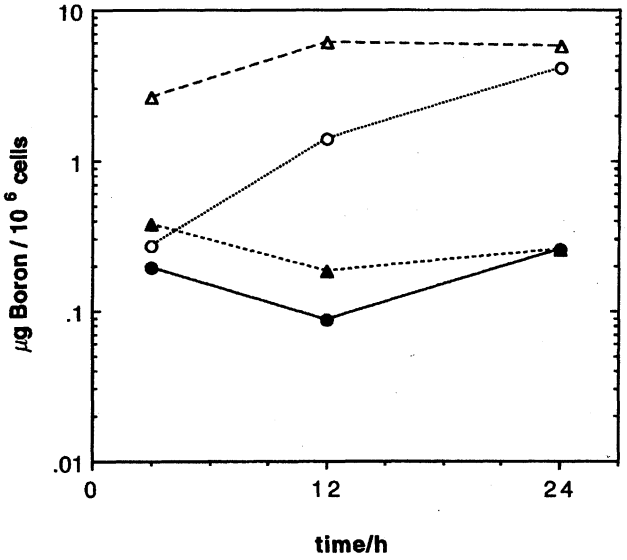
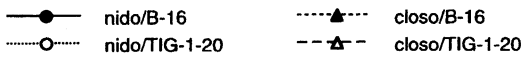


Fig. 2. Cellular uptake of *nido* **19** and *closo* **6**.



Conclusion

In clinical applications, water-soluble boron carriers would be injected more easily into blood than lipophilic ones, and would be kept in blood for longer periods, which might lead to highly selective accumulation into mitotically active cancer cells rather than normal cells. *nido*-Orthocarboranyluridine **17** seems to be promising compound as a practical ^{10}B carrier, because its water solubility is very high, its toxicity is very low, and it has relatively high performance in

cellular uptake. On the other hand, we have demonstrated that selective delivery of water-soluble boron compounds to some specific cell lines will be possible, as with the case of uridine derivative **19** which has a modified sugar-part and ionic *nido*-orthocarborane unit.

Experimental

Materials. All melting points were uncorrected. ^{1}H, ^{13}C, and ^{11}B NMR spectra were recorded on a JEOL GSX-270 spectrometer. The chemical shifts are reported in δ units, parts per million downfield from tetramethylsilane (^{1}H, ^{13}C) as an internal standard, or BF_3·OEt_2 (^{11}B) as an external standard, or in ppm relative to quintet at 3.30 (^{1}H) and septet at 49.0 (^{13}C) ppm for CD_3OD. IR spectra were taken with a Shimadzu FTIR-8200A spectrometer. Optical rotations were measured on a JASCO DIP-1000 spectrometer. High-resolution mass spectra were measured with a JEOL HX-110 spectrometer. Elemental analyses were carried out at the Analytical Center of Tohoku University. Perfect removal of water from carborane derivatives was not easy. Accordingly, some elemental analysis data are based on the molecular formula containing $(H_2O)_x$. Column chromatography was performed on Merck Kiesel gel 60 (230—400 mesh). THF was distilled under Ar from sodium/benzophenone ketyl before use. Pyridine was distilled over Ninhydrin and dried over KOH. CuI was purified by the literature procedure.[21] All other reagents were commercially available and were used without further purification. Preparation of **1** was carried out according to the method previously reported.[4b] Preparation of the sugar parts **10**[22] and **12**[14a,23] was carried out according to the known procedure.

Source of Cells. B-16 melanoma cells and TIG-1-20 fibroblast cells were obtained from Cancer Cell Repository, Research Institute for Tuberculosis and Cancer, Tohoku University.

5-[2-(Trimethylsilyl)ethynyl]uracil (8). To a suspension of 5-iodouracil (4.76 g, 20 mmol), $PdCl_2$ (354 mg, 2.0 mmol), Ph_3P (1.05 g, 4.0 mmol), and CuI (380 mg, 2.0 mmol) in THF (100 mL) was added Et_3N (5.58 mL, 40 mmol), followed by (trimethylsilyl)-acetylene (4.14 mL, 30 mmol), and the suspension was stirred at 40 °C for 3 h under Ar. The mixture was filtered though a Celite pad and the filtrate was concentrated under reduced pressure. The residue was suspended in CH_2Cl_2 (100 mL), filtered, and washed with CH_2Cl_2. The resulting residue was dissolved in acetone (100 mL) and filtered, and the filtrate was evaporated to dryness to give **8** as a white solid (86% yield). This product was recrystallized from acetone to give pure **8**: IR (KBr) 3181, 3069, 2958, 2904, 2822, 2164, 1716, 1688, 1623, 1446, 1423, 1254, 1231, 865, 843, 765 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ = 11.33 (br, 2H), 7.79 (s, 1H,), 0.18 (s, 9H); ^{13}C NMR (DMSO-d_6) δ = 162.5, 150.4, 146.7, 98.3, 96.9, 96.6. HRMS(EI) Calcd for $C_9H_{12}O_2N_2Si$: (M^+), 208.0668. Found: *m/z* 208.0661.

2,4-Bis[*O*-(trimethylsilyl)]-5-[2-(trimethylsilyl)ethynyl]uracil (9). A mixture of **8** (1.03 g, 4.9 mmol), hexamethyldisilazane (15 mL), and NH_4SO_4 (7 mg) was refluxed overnight. The mixture was concentrated in vacuo, and the residue was coevaporated with toluene (2.5 mL) to afford **9** as an oil, which was stored under Ar atmosphere and used for the next step without purification.

5-[2-(Trimethylsilyl)ethynyl]-5′-*O*-(*t*-butyldiphenylsilyl)-2′, 3′-dideoxy-3′-thiauridine (11). To **9** (0.74 mmol) prepared above was added a solution of the acetate **10** (154 mg, 0.37 mmol) in dry CH_2Cl_2 (2.3 mL), and the mixture was cooled to 0 °C. $SnCl_4$ (86 μL, 0.74 mmol) was slowly added, and the mixture was stirred for 40 min. The mixture was poured into an ice-cold mixture of saturated $NaHCO_3/H_2O$ solution (5 mL), ether (5 mL), and AcOEt (10 mL). The organic layer was washed with brine, dried over $MgSO_4$, and filtered through a Celite pad. Following solvent removal, the crude product was purified by column chromatography (hexane/AcOEt, 2.5 : 1) to give **11** as a white solid (135 mg, 65% yield): IR (KBr) 3191, 3074, 2953, 2929, 2900, 2855, 2161, 1714, 1694, 1456, 1277, 1113, 850, 705 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 8.59 (br, 1H), 7.84 (s, 1H), 7.72—7.67 (m, 4H), 7.46—7.37 (m, 6H), 6.27 (dd, *J* = 5.5, 5.5 Hz, 1H), 5.26 (dd, *J* = 4.8, 4.0 Hz, 1H), 4.00 (dd, *J* = 11.4, 4.0 Hz, 1H), 3.93 (dd, *J* = 11.4, 4.4 Hz, 1H), 3.44 (dd, *J* = 11.7, 5.5 Hz, 1H), 3.03 (dd, *J* = 11.7, 5.5 Hz, 1H), 1.09 (s, 9H), 0.18 (s, 9H). Anal. Calcd for $C_{29}H_{36}O_4N_2SSi_2$: C, 61.66; H, 6.42; N, 4.95%. Found: C, 61.28; H, 6.25; N, 4.94%.

5-[2-(Trimethylsilyl)ethynyl]-5′-*O*-(*t*-butyldiphenylsilyl)-2′, 3′-dideoxy-2′α-phenylthio-β-uridine (13a). To **9** (4.9 mmol, prepared from **8**) was added a solution of the acetate **12** (2.00 g, 3.9 mmol) in dry CH_2Cl_2 (25 mL), and the mixture was cooled to 0 °C. TMSOTf (801 μL, 4.1 mmol) was slowly added, and the mixture was stirred for 10 min. The mixture was poured into an ice-cold mixture of saturated $NaHCO_3/H_2O$ solution (20 mL) and ether (50 mL). The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The crude products were purified by column chromatography (hexane/AcOEt, 4 : 1) to give **13a** (1.12 g, 43% yield), **13b** (521 mg, 23%), **14a** (216 mg, 8%), and **14b** (96 mg, 4%) as white solids.

13a: IR (KBr) 3179, 3069, 2962, 2930, 2856, 2160, 1706, 1699, 1445, 1428, 1278, 1266, 1249, 1089, 1069, 842, 760, 743, 702, 690 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 8.30 (br, 1H), 7.73 (s, 1H), 7.69—7.64 (m, 4H), 7.46—7.38 (m, 8H), 7.29—7.26 (m, 3H), 6.02 (d, *J* = 7.3 Hz, 1H), 4.26—4.20 (m, 1H), 3.97 (dd, *J* = 11.3, 2.2 Hz, 1H), 3.78 (ddd, *J* = 8.8, 7.7, 7.3 Hz, 1H), 3.61 (dd, *J* = 11.5, 2.7 Hz, 1H), 2.42 (ddd, *J* = 12.6, 8.2, 4.4 Hz, 1H), 2.07 (ddd, *J* = 13.9, 9.1, 9.1 Hz, 1H), 1.13 (s, 9H), 0.08 (s, 9H); ^{13}C NMR ($CDCl_3$) δ = 160.6, 148.9, 142.4, 135.5, 133.5, 132.5, 132.3, 131.8, 130.1, 130.0, 129.2, 128.4, 128.0, 127.9, 127.8, 101.0, 100.0, 94.5, 89.5, 78.2, 65.5, 50.2, 32.4, 27.2, 19.3, −0.3. Anal. Calcd for $C_{36}H_{42}O_4N_2SSi_2$: C, 66.01; H, 6.46; N, 4.27%. Found: C, 66.04; H, 6.42; N, 4.40%.

5-Ethynyl-5′-*O*-(*t*-butyldiphenylsilyl)-2′,3′-dideoxy-2′α-phenylthio-β-uridine (13b): IR (KBr) 3281, 3193, 3075, 2930, 2856, 2118, 1694, 1626, 1456, 1427, 1281, 1113, 743, 702 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 8.27 (br, 1H), 7.84 (s, 1H), 7.67—7.64 (m, 4H), 7.45—7.39 (m, 8H), 7.29—7.27 (m, 3H), 6.03 (d, *J* = 7.0 Hz, 1H), 4.29—4.23 (m, 1H), 4.00 (dd, *J* = 11.3, 2.2 Hz, 1H), 3.81 (ddd, *J* = 8.8, 7.7, 7.3 Hz, 1H), 3.64 (dd, *J* = 11.5, 2.7 Hz, 1H), 2.94 (s, 1H), 2.43 (ddd, *J* = 12.6, 8.2, 4.4 Hz, 1H), 2.09 (ddd, *J* = 13.9, 9.1, 9.1 Hz, 1H), 1.12 (s, 9H). HRMS(EI) Calcd for $C_{29}H_{25}O_4N_2SSi$: ([M − *t*-Bu]$^+$), 525.1304. Found: *m/z* 525.1296.

5-[2-(Trimethylsilyl)ethynyl]-5′-*O*-(*t*-butyldiphenylsilyl)-2′, 3′-dideoxy-2′α-phenylthio-α-uridine (14a): IR (KBr) 3200, 3070, 2959, 2932, 2857, 2162, 1716, 1695, 1616, 1456, 1428, 1279, 1250, 1113, 845, 743, 702 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 7.76 (s, 1H), 7.66—7.63 (m, 4H), 7.59 (s, 1H), 7.45—7.38 (m, 8H), 7.27—7.24 (m, 3H), 6.19 (d, *J* = 4.8 Hz, 1H), 4.62—4.54 (m, 1H), 4.47—4.42 (m, 1H), 3.88 (dd, *J* = 11.4, 3.3 Hz, 1H), 3.66 (dd, *J* = 11.4, 3.3 Hz, 1H), 2.66 (ddd, *J* = 13.9, 7.7, 7.7 Hz, 1H), 2.20 (ddd, *J* = 13.9, 6.2, 3.3 Hz, 1H), 1.07 (s, 9H), 0.27 (s, 9H). HRMS(EI) Calcd for $C_{32}H_{33}O_4N_2SSi_2$: ([M − *t*-Bu]$^+$), 597.1699. Found: *m/z* 597.1704.

5-Ethynyl-5′-*O*-(*t*-butyldiphenylsilyl)-2′,3′-dideoxy-2′α-phenylthio-α-uridine (14b): IR (KBr) 3272, 3169, 3070, 2956, 2930, 2855, 2117, 1716, 1689, 1620, 1463, 1429, 1398, 1276, 1113, 1082, 742, 703, 688 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 7.84 (s, 1H), 7.66—7.63 (m, 4H), 7.58 (s, 1H), 7.45—7.36 (m, 8H), 7.24

(s, 3H), 6.20 (d, J = 4.4 Hz, 1H), 4.60—4.52 (m, 1H), 4.49—4.44 (m, 1H), 3.88 (dd, J = 11.4, 3.3 Hz, 1H), 3.66 (dd, J = 11.4, 3.3 Hz, 1H), 3.21 (s, 1H), 2.67 (ddd, J = 13.9, 7.7, 7.7 Hz, 1H), 2.19 (ddd, J = 13.9, 6.2, 3.3 Hz, 1H), 1.07 (s, 9H).

5-Ethynyl-5′-*O*-(*t*-butyldiphenylsilyl)-2′,3′-dideoxy-2′α-phenylthio-β-uridine (13b). To an ice-cold solution of **13a** (400 mg, 0.61 mmol) in MeOH (10 mL)/CH_2Cl_2 (5 mL) was added sodium methoxide 28 wt% in dry MeOH (492 mg, 2.6 mmol), and this mixture was stirred at room temperature for 7 h. The solution was neutralized by adding Dowex 50W-X8 (50—100 mesh, H^+ form) resin until the pH value of moistened pH paper reached 6. The mixture was filtered, and the resin was washed with MeOH. The combined filtrate was concentrated, and the residue was purified by column chromatography (hexane/AcOEt, 2 : 1) to give **13b** as a white solid (352 mg, 99% yield).

5-(*o*-Carboran-1-yl)-5′-*O*-(*t*-butyldiphenylsilyl)-2′,3′-dideoxy-2′α-phenylthiouridine (15). To a solution of **13b** (2.04 g, 3.5 mmol) and $B_{10}H_{14}$ (513 mg, 4.2 mmol) in toluene (100 mL) was added EtCN (12.5 mL, 175 mmol) at 80 °C, and the mixture was refluxed under Ar for 2.5 h. The mixture was evaporated in vacuo, and purified by column chromatography (hexane/AcOEt, 5 : 1) to give **15** as a white solid (1.57 g, 64% yield): IR (KBr) 3202, 3073, 2958, 2932, 2857, 2591 (ν(BH)), 1729, 1684, 1464, 1428, 1290, 1114, 1074, 741, 702 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 7.84 (br, 1H), 7.69—7.64 (m, 4H), 7.44—7.39 (m, 8H), 7.30—7.28 (m, 3H), 5.90 (d, J = 5.9 Hz, 1H), 5.58 (br, 1H), 4.38—4.30 (m, 1H), 3.82 (dd, J = 11.3, 5.8 Hz, 1H), 3.77 (dd, J = 11.0, 5.1 Hz, 1H), 3.61 (ddd, J = 7.7, 7.1, 7.1 Hz, 1H), 2.33 (ddd, J = 13.2, 7.3, 5.5 Hz, 1H), 2.08, (ddd, J = 13.2, 7.7, 7.7 Hz, 1H), 1.10 (s, 9H). Anal. Calcd for $C_{33}H_{44}O_4N_2SSiB_{10}(H_2O)_{1.0}$: C, 55.12; H, 6.44; N, 3.89%. Found: C, 55.21; H, 6.23; N, 3.65%.

5-(*o*-Carboran-1-yl)-2′,3′-dideoxy-2′α-phenylthiouridine (6). To a solution of **15** (800 mg, 1.1 mmol) in THF (40 mL), 1.0 M Bu_4NF in THF (3.6 mL, 3.6 mmol) was added, and the mixture was stirred at room temperature for 5 h. The mixture was poured into a mixture of H_2O (20 mL) and CH_2Cl_2 (40 mL), and the organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by column chromatography (CH_2Cl_2/EtOH, 40 : 1) to give **6** as a white solid (473 mg, 90% yield): $[\alpha]_D^{23}$ −74.6 (c 1.00, CH_3OH); IR (KBr) 3442, 3200, 3081, 2932, 2834, 2587, (ν(BH)), 1716, 1683, 1464, 1440, 1290, 1107, 1074, 747, 691, 651 cm^{-1}; ^1H NMR (CD_3OD) δ = 8.25 (s, 1H), 7.44—7.41 (m, 2H), 7.28—7.24 (m, 3H), 6.02 (d, J = 6.6 Hz, 1H), 5.86 (br, 1H), 4.34—4.31 (m, 1H), 3.95 (ddd, J = 8.8, 6.9, 6.9 Hz, 1H), 3.81 (dd, J = 11.7, 2.6 Hz, 1H), 3.63 (dd, J = 11.7, 2.6 Hz, 1H), 2.44 (ddd, J = 13.2, 8.4, 5.1 Hz, 1H), 2.14 (ddd, J = 13.2, 9.0, 9.0 Hz, 1H). Anal. Calcd for $C_{17}H_{26}O_4N_2SB_{10}$: C, 44.14; H, 5.66; N, 6.05%. Found: C, 44.43; H, 5.84; N, 5.89%.

5-(*o*-Carboran-1-yl)-2′,3′-dideoxy-3′-thiauridine (5). **5** was obtained from **11** according to the procedures below ((a)—(d)). (a) To a solution of **11** (79 mg, 0.14 mmol) in THF (0.7 mL), 1.0 M Bu_4NF in THF (0.42 mL, 0.42 mmol) was added, and the mixture was stirred at room temperature for 1.5 h. The mixture was evaporated to dryness, and the residue was triturated with Et_2O (3 mL). The resulting powder was purified by column chromatography (CH_2Cl_2/EtOH, 20 : 1) to give 5-ethynyl-2′,3′-dideoxy-3′-thiauridine **21** as a white solid (37 mg, quantitative yield): IR (KBr) 3453, 3247, 3167, 3083, 3037, 2840, 2559, 2111, 1701, 1676, 1613, 1466, 1433, 1281, 1073 cm^{-1}; ^1H NMR (CD_3OD) δ = 8.51 (s, 1H), 6.27 (dd, J = 5.5, 3.3 Hz, 1H), 5.28 (dd, J = 3.3, 3.3 Hz, 1H), 3.99 (dd, J = 12.8, 3.3 Hz, 1H), 3.85 (dd, J = 12.8, 3.6 Hz, 1H), 3.54 (s, 1H), 3.51 (dd, J = 12.1, 5.5 Hz, 1H), 3.26 (dd, J = 12.1, 3.7 Hz, 1H); ^{13}C NMR (CD_3OD) δ = 164.5, 151.1, 146.3, 99.3, 88.9, 88.1, 82.8, 76.0, 63.4, 38.6. (b) A stirred solution of **21** (352 mg, 1.4 mmol) in CH_2Cl_2 (7 mL) and pyridine (448 μL, 5.5 mmol) was cooled to 0 °C and treated with benzoyl chloride (177 μL, 1.5 mmol). After stirring for 2 h at 0 °C, the mixture was poured into a cold mixture of 1 M HCl/H_2O (5.5 mL) and ether (30 mL). The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The resulting residue was purified by column chromatography (hexane/AcOEt, 4 : 3) to give 5-ethynyl-5′-*O*-benzoyl-2′,3′-dideoxy-3′-thiauridine **22** as a white solid (373 mg, 75% yield): IR (KBr) 3283, 3175, 3071, 2891, 2842, 2118, 1716, 1664, 1624, 1469, 1450, 1434, 1270, 1121, 1060, 709 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 8.16 (br, 1H), 8.10—8.06 (m, 2H), 7.99 (s, 1H), 7.63—7.44 (m, 3H), 6.31 (dd, J = 5.5, 4.4 Hz, 1H), 5.49 (dd, J = 4.8, 3.7 Hz, 1H), 4.77 (dd, J = 12.4, 4.8 Hz, 1H), 4.72 (dd, J = 12.4, 3.3 Hz, 1H), 3.57 (dd, J = 12.5, 5.5 Hz, 1H), 3.16 (dd, J = 12.5, 4.4 Hz, 1H), 3.07 (s, 1H). HRMS(EI) Calcd for $C_{17}H_{14}O_5N_2S$: (M^+), 358.0623. Found: m/z 358.0611. (c) To a solution of **22** (340 mg, 0.95 mmol) and $B_{10}H_{14}$ (139 mg, 1.1 mmol) in toluene (28 mL) was added EtCN (2.03 mL, 29 mmol) at 80 °C, and the mixture was refluxed under Ar for 3.5 h. The mixture was evaporated in vacuo, and purified by column chromatography (hexane/AcOEt, 2 : 1) to give 5-(*o*-carboran-1-yl)-5′-*O*-benzoyl-2′,3′-dideoxy-3′-thiauridine **23** as a white solid (281 mg, 62% yield): IR (KBr) 3203, 3083, 2582 (ν(BH)), 1717, 1674, 1464, 1269, 1167, 1093, 709 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 8.20 (br, 1H), 8.09—8.04 (m, 2H), 8.05 (s, 1H), 7.63—7.44 (m, 3H), 6.32 (dd, J = 5.5, 4.0 Hz, 1H), 5.67 (br, 1H), 5.52 (dd, J = 5.5, 4.8 Hz, 1H), 4.72 (d, J = 5.1 Hz, 2H), 3.59 (dd, J = 12.5, 5.5 Hz, 1H), 3.15 (dd, J = 12.5, 4.0 Hz, 1H). Anal. Calcd for $C_{17}H_{24}O_5N_2SB_{10}(H_2O)_{0.81}$: C, 41.57; H, 5.25; N, 5.70%. Found: C, 41.31; H, 4.85; N, 5.61%. (d) To an ice-cold solution of **23** (265 mg, 0.56 mmol) in MeOH (7 mL)/CH_2Cl_2 (3.5 mL) was added sodium methoxide 28w% in dry MeOH (130 mg, 0.67 mmol), and this mixture was stirred at room temperature for 1.5 h. The solution was neutralized by adding Dowex 50W-X2 (50—100 mesh, H^+ form) resin until pH value of moistened pH paper reached 6. The mixture was filtered, and the resin was washed with MeOH. The combined filtrate was concentrated, and the residue was purified by column chromatography (CH_2Cl_2/EtOH, 30 : 1) to give **5** as a white solid (178 mg, 86% yield): $[\alpha]_D^{25}$ +0.82 (c 0.50, CH_3OH); IR (KBr) 3420, 3203, 3083, 2932, 2832, 2591 (ν(BH)), 1716, 1683, 1464, 1290, 1161, 1108, 1059, 809, 771, 726, 645 cm^{-1}; H NMR ($CDCl_3$) δ = 8.42 (s, 1H), 6.33 (dd, J = 5.5, 2.6 Hz, 1H), 5.93 (br, 1H), 5.29 (dd, J = 4.0, 4.0 Hz, 1H), 4.00 (dd, J = 12.5, 3.7 Hz, 1H), 3.91 (dd, J = 12.5, 4.0 Hz, 1H), 3.57 (dd, J = 12.8, 5.5 Hz, 1H), 3.29 (dd, J = 12.8, 2.2 Hz, 1H). Anal. Calcd for $C_{10}H_{20}O_4N_2SB_{10}(H_2O)_{0.25}$: C, 31.86; H, 5.48; N, 7.43%. Found: C, 32.02; H, 5.28; N, 7.40%.

Sodium 7-(Uridin-5-yl)dodecahydro-7,8-dicarba-*nido*-undecaborate (17). Orthocarboranyluridine **1** (100 mg, 0.26 mmol) was treated with pyrrolidine (540 μL, 6.5 mmol) under Ar. After stirring at room temperature for 3 h, the mixture was treated with CH_2Cl_2 (540 μL) and stirred for 2 h. The mixture was evaporated in vacuo, washed with saturated NH_4Cl/H_2O solution, and the resulting residue was subjected to cation exchange on Dowex 50W-X8 (50—100 mesh, Na^+ form) in MeOH (15 mL)/H_2O (15 mL). After vigorous stirring at room temperature for 72 h, the mixture was filtered and the resin was washed with MeOH. The combined filtrate was concentrated, and the product was purified by column chromatography (CH_2Cl_2/EtOH, 4 : 1) to give **17** as a translucent film (57 mg, 55% yield): IR (KBr) 3434, 2532 (ν(BH)), 1688, 1472, 1385, 1269, 1102, 1056 cm^{-1}; ^1H NMR (CD_3OD) δ = 7.50 (m, 1H), 5.88—5.84 (m, 1H), 4.18—4.12 (m, 1H), 4.10—4.05 (m, 1H),

4.01—3.96 (m, 1H), 3.83—3.68 (m, 2H), 1.73 (br, 1H); ^{11}B NMR (CD_3OD) δ = −9.3, −15.9, −17.4, −20.4, −32.4, −33.4, −36.1, −37.7. Anal. Calcd for $C_{11}H_{22}O_6N_2B_9Na(H_2O)_{2.0}$: C, 30.39; H, 6.02; N, 6.44%. Found: C, 30.61; H, 5.84; N, 6.16%.

Sodium 7-(2′,3′-Dideoxy-3′-thiauridin-5-yl)dodecahydro-7,8-dicarba-*nido*-undecaborate (18). Orthocarboranyluridine **5** (40 mg, 0.11 mmol) was treated with pyrrolidine (224 μL, 2.7 mmol) under Ar. After stirring at room temperature for 7 h, the mixture was treated with CH_2Cl_2 (224 μL) and stirred for 15 min. The mixture was evaporated in vacuo, washed with saturated NH_4Cl/H_2O solution, and the resulting residue was subjected to cation exchange on Dowex 50W-X8 (50—100 mesh, Na^+ form) in MeOH (20 mL). After vigorous stirring at room temperature for 72 h, the mixture was filtered and the resin was washed with MeOH. The combined filtrate was concentrated, and the product was purified by column chromatography (CH_2Cl_2/EtOH, 6 : 1) to give **18** as a translucent film (36 mg, 89% yield): IR (KBr) 3414, 3222, 2524 (ν(BH)), 1699, 1469, 1385, 1270, 1161, 1038, 785 cm^{-1}; ^{1}H NMR (CD_3OD) δ = 7.57 (m, 1H), 6.32—6.28 (m, 1H), 5.26—5.21 (m, 1H), 4.00—3.81 (m, 2H), 3.50—3.43 (m, 1H), 3.13—3.05 (m, 1H), 1.73 (br, 1H). Anal. Calcd for $C_{10}H_{20}O_4N_2SB_9Na(H_2O)_{2.3}$: C, 28.19: H, 5.81; N, 6.57%. Found: C, 28.16; H, 5.60; N, 6.58%.

Sodium 7-(2′,3′-Dideoxy-2′ α-phenylthiouridin-5-yl)dodecahydro-7,8-dicarba-*nido*-undecaborate (19). Orthocarboranyluridine **6** (70 mg, 0.15 mmol) was treated with pyrrolidine (316 μL, 3.8 mmol) under Ar. After stirring at room temperature for 6 h, the mixture was treated with CH_2Cl_2 (316 μL) and stirred for 30 min. The mixture was evaporated in vacuo, washed with saturated NH_4Cl/H_2O solution, and the resulting residue was subjected to cation exchange on Dowex 50W-X8 (50—100 mesh, Na^+ form) in MeOH (20 mL)/H_2O (5 mL). After vigorous stirring at room temperature for 72 h, the mixture was filtered and the resin was washed with MeOH. The combined filtrate was concentrated, and the product was purified by column chromatography (CH_2Cl_2/EtOH, 6 : 1) to give **19** as a translucent film (65 mg, 90% yield): IR (KBr) 3628—3110, 3055, 2936, 2527 (ν(BH)), 1683, 1472, 1385, 1269, 1069, 1040, 785, 751, 692 cm^{-1}; ^{1} NMR (CD_3OD) δ = 7.38—7.17 (m, 6H), 5.95—5.89 (m, 1H), 4.27—4.21 (m, 1H), 3.98—3.78 (m, 1H), 3.76—3.60 (m, 1H), 2.43—2.33 (m, 1H), 2.15—2.07 (m, 1H), 1.65 (br, 1H). Anal. Calcd for $C_{17}H_{26}O_4N_2SB_9Na(H_2O)_{2.0}$: C, 39.97; H, 5.92; N, 5.48%. Found: C, 39.60; H, 5.80; N, 5.55%.

Water Solubility. Suitable amounts of each boron compound were added to pure water to give a saturated solution. The mixture was stirred for 12 h at 20 °C, and a saturated solution of each boron compound was obtained. Undissolved boron compounds were filtered through a membrane filter (Millipore; 0.22 μm). The concentration of boron atom of each saturated solution was obtained by using ICP-AES (Shimadzu, ICP-1000-III).

Determination of IC_{50}. Different doses of the boron compound **17** (1.4, 0.68, 0.34, and 0.17 mg) were dissolved in DMSO (20 μL) and diluted with Eagle-MEM medium (3.0 mL) respectively. Each of the resulting solutions and the suspensions of the cells, which were preincubated in Eagle-MEM medium (10% FCS) for 4 d at 37 °C under a 5% carbon dioxide atmosphere to achieve confluency, in fresh Eagle-MEM medium (10% FCS, 1×10^5 cells/mL, 1.0 mL) were placed in a Falcon 3002 culture dish (60 mm diameter), and incubated for 3 d at 37 °C under a 5% carbon dioxide atmosphere. It is known that DMSO is nontoxic at the concentration lower than 0.5%. The medium was removed in order to exclude dead cells from the dish. The remaining cells were treated by trypsin, and the number of living cells (B-16 and TIG-1-20) was counted by using a hemocytometer. We assessed cell viability under a micrometer. The observed value was divided by the number of the standard system, in which no boron compounds were added. Three replications of each experiment were carried out. Values are represented as mean ± SE. In the case of **5**, **6**, and **19**, the same procedure was used.

Boron Incorporation into B-16 and TIG-1-20. B-16 cells were cultured in Falcon 3025 dishes (150 mm diameter). When the cells were grown to fill the dish, the cell number was counted (5.0×10^6 cells/dish). One dish was for a control experiment. The boron compounds **6**, **17**, and **19** were added to the dishes. The concentration was adjusted to each IC_{50} value. The cells were incubated for 3, 12, and 24 h at 37 °C under a 5% carbon dioxide atmosphere. After the medium was removed, the remaining cells were washed with three portions of Ca- and Mg-free phosphate-buffered saline (PBS-(−); 4 mL), collected by a rubber policeman, digested with 4 mL of 60% $HClO_4$–30% H_2O_2 solution, and decomposed for 3 h at 75 °C. After the filtration with a membrane filter, the boron concentration was determined by using ICP-AES. Control experiments were carried out. In the case of TIG-1-20 cells, a similar procedure was used.

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