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SYNTHESIS AND STRUCTURE-ACTIVITY RELATIONSHIP STUDY OF 1,12-DICARBA-CLOSO-DODECABORANE-BASED TRIOL DERIVATIVES AS NONSECOSTEROIDAL VITAMIN D ANALOGS

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Abstract – The secosteroidal hormone 1α,25-dihydroxyvitamin D_3 [1α,25$(OH)_2D_3$] is a specific ligand of nuclear vitamin D receptor (VDR), and novel vitamin D analogs are promising candidates for multiple clinical applications. We previously developed a series of 1,12-dicarba-*closo*-dodecaborane (*p*-carborane) derivatives as nonsecosteroidal VDR agonists. Here, we report the synthesis and structure-activity relationship of *p*-carborane-based nonsecosteroidal vitamin D analogs bearing a nitrogen or a sulfur atom in the linker structure. Biological evaluation revealed that the structure–activity relationships of amine derivatives and sulfide derivatives are different, and therefore the choice of the linker structure significantly affects the activity. We also found that benzylamine structure could be a lead scaffold for novel vitamin D analogs. The structure–activity relationships presented here should be helpful in further development of nonsecosteroidal vitamin D analogs.

INTRODUCTION

Vitamin D receptor (VDR) is the ligand-inducible nuclear receptor specific for vitamin D,[1] and plays important roles in many physiological processes, including bone metabolism and immune response. It is therefore a promising target for drug discovery for diseases such as osteoporosis, psoriasis, arthritis and cancers.[2] VDR is activated by binding of the endogenous agonist, 1α,25-dihydroxyvitamin D_3 [1α,25$(OH)_2D_3$; **1**], a metabolically activated form of vitamin D_3, and regulates the expression of specific target genes. Thousands of secosteroidal derivatives of **1** have been synthesized, and several, such as

maxacalcitol and eldecalcitol, are in clinical use.[3] On the other hand, in contrast to the conventional derivatives, vitamin D analogs without secosteroid structure, namely, nonsecosteroidal derivatives, have been less investigated, though they would be useful as clinical drug candidates and as tools for investigation of VDR function.[4]

We previously reported the development of nonsecosteroidal vitamin D analogs such as **2** and **3** by using a 1,12-dicarba-*closo*-dodecaborane (*p*-carborane) as the hydrophobic core structure.[5,6] *p*-Carborane is a carbon-containing boron cluster with unusual chemicophysical characteristics, including spherical geometry and a hydrophobic B–H surface,[7] and we have shown that hydrophobic boron clusters can be used as the hydrophobic core of biologically active molecules.[8] Though the overall structure of *p*-carborane-based vitamin D analogs is quite different from those of classical secosteroid VDR ligands, including **1**, X-ray crystallographic analysis of the VDR ligand-binding domain (LBD) complexed with **3** revealed that the binding mode of **3** is similar to that of **1**, and the carborane cage functions as a hydrophobic anchor for binding with the receptor, like the CD-ring of **1** (Figure 1).[5] The results also suggested that the length and flexibility of the dihydroxyalkyl chain are important for the activity. In this study, we designed, synthesized and evaluated the biological activity of compounds bearing sulfur or nitrogen functionalities in the dihydroxyalkyl chain in order to explore the structure-activity relationship (SAR) of the dihydroxyalkyl moiety of *p*-carborane-based vitamin D analogs and to develop novel vitamin D analogs.

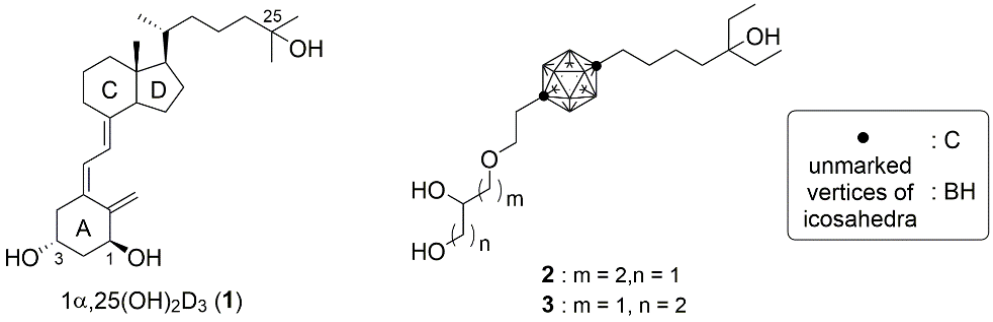
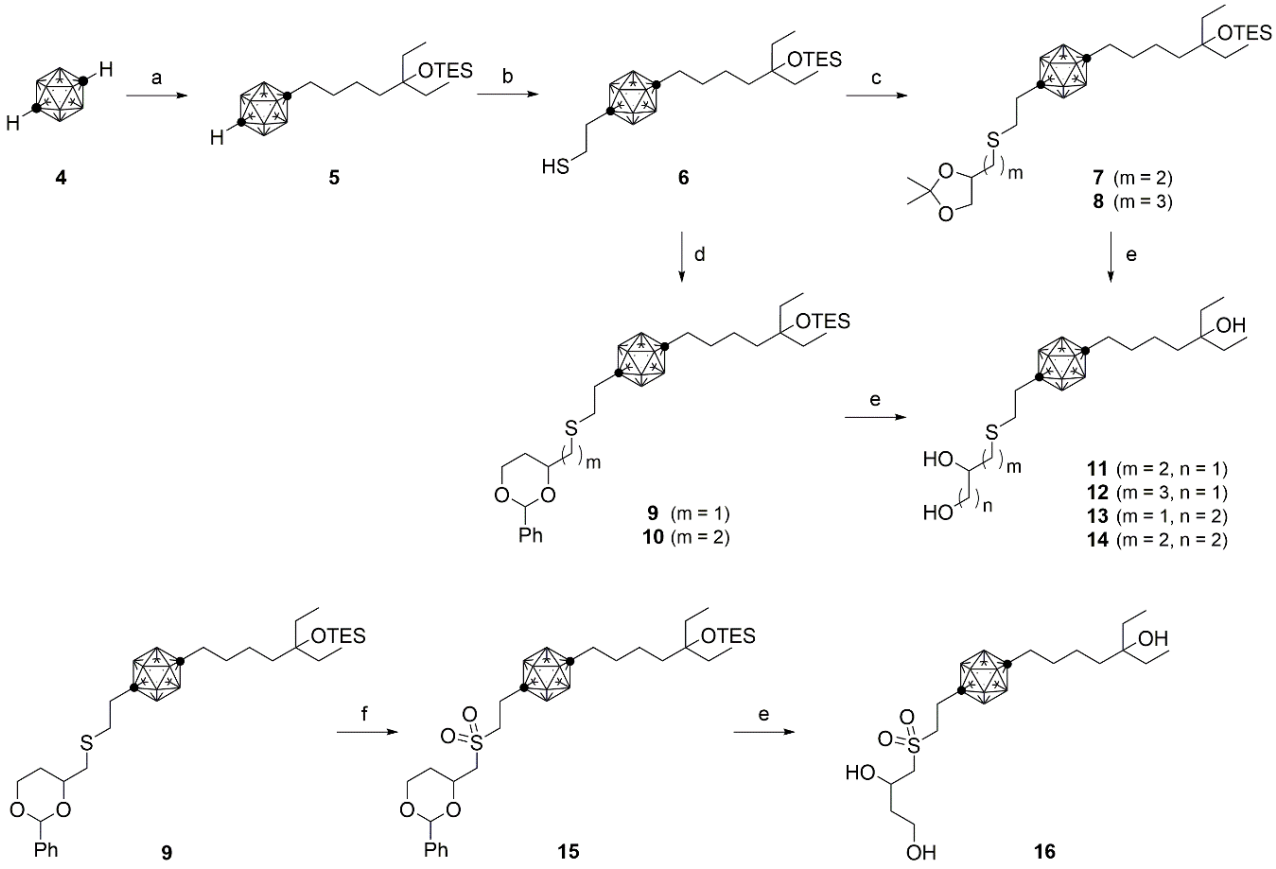


Figure 1. Structures of endogenous VDR ligand **1** and our synthesized carborane derivatives **2** and **3**

RESULTS AND DISCUSSION

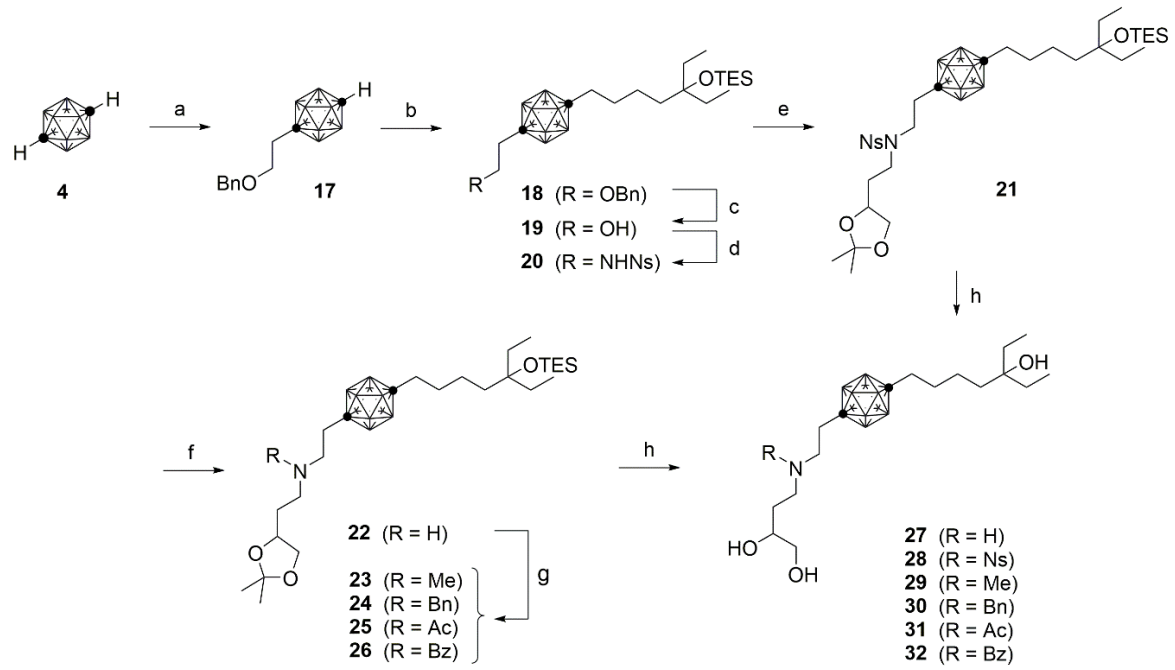
First, we designed the sulfur-containing compounds **11**-**14**, with different chain lengths and positions of the hydroxy groups, and sulfone derivative **16**. The synthetic routes are illustrated in Scheme 1. Introduction of the monohydroxy side-chain moiety into *p*-carborane gave **5**, and the reaction of *C*-lithiated **5** with ethylene sulfide afforded thiol **6**. Introduction of 1,2-diol or 1,3-diol substructure using the corresponding tosylate gave **7**-**10**. Removal of the protecting groups afforded triol derivatives **11**-**14**.

Oxidation of **9** using mCPBA afforded sulfone **15**, and removal of the protecting groups afforded sulfone-containing triol **16**.



Scheme 1. Synthesis of sulfur-containing *p*-carborane-based vitamin D analogs **11**-**14** and **16**. Conditions and reagents: (a) *n*-BuLi, 7-bromo-3-ethyl-3-triethylsilyloxyheptane, THF, 46%; (b) *n*-BuLi, ethylene sulfide, THF, 22%; (c) NaH, 2-(2,2-dimethyl-1,3-dioxolan-4-yl)ethyl *p*-toluenesulfonate, DMF, 41% for **7**; NaH, 3-(2,2-dimethyl-1,3-dioxolan-4-yl)propyl *p*-toluenesulfonate, DMF, 41% for **8**; (d) NaH, (2-phenyl-1,3-dioxan-4-yl)methyl *p*-toluenesulfonate, DMF, 22%, for **9**; NaH, 2-(2-phenyl-1,3-dioxan-4-yl)ethyl *p*-toluenesulfonate, DMF, 64%, for **10**; (e) HCl, H_2O, MeOH, THF, 38-75%; (f) mCPBA, CH_2Cl_2, 61%; mCPBA: *m*-chloroperbenzoic acid.

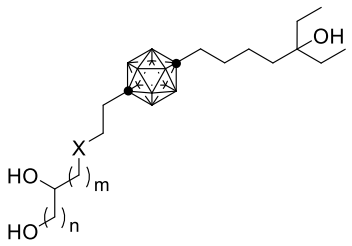
Synthesis of the nitrogen-containing compounds **27**-**32** is illustrated in Scheme 2. In this case, we fixed the chain length, and examined the effect of the *N*-substituent. Serial alkylation on the carbon atoms of *p*-carborane gave compound **18**, and then catalytic hydrogenation afforded alcohol **19**. The hydroxy group of **19** was converted to a 2-nitrobenzenesulfonylamino (NsNH)[9] group by Mitsunobu reaction using TMAD[10] to afford **20**, and introduction of 1,2-diol substructure by *N*-alkylation reaction gave **21**. The nitrobenzenesulfonyl group of **21** was removed with thiophenol to give secondary amine derivative **22**, and alkylation or acylation of **22** afforded compounds **23**-**26**. Finally, removal of the protective groups of **21**-**26** gave the designed triols **27**-**32** (Scheme 2).



Scheme 2. Synthesis of nitrogen-containing *p*-carborane-based vitamin D analogs **27-32**. Conditions and reagents: (a) *n*-BuLi, benzyl 2-bromoethyl ether, Et_2O, THF, 46%; (b) *n*-BuLi, 7-bromo-3-ethyl-3-triethylsilyloxyheptane, THF-Et_2O, 96%; (c) H_2, Pd/C, EtOH, 87%; (d) TMAD, PBu_3, $NsNH_2$, THF, 60%; (e) $CsCO_3$, 2-(2,2-dimethyl-1,3-dioxolan-4-yl)ethyl *p*-toluenesulfonate, DMF, 99%, (f) $CsCO_3$, PhSH, MeCN, 81%; (g) RX, K_2CO_3, DMF, or RX, pyridine, CH_2Cl_2; (h) HCl, H_2O, MeOH, THF, 69% (**27**), 75% (**28**), 17-65% (**29-32**, for 2 steps); TMAD: *N*,*N*,*N*',*N*'-tetramethylazodicarboxamide, Ns: 2-nitrobenzenesulfonyl.

The vitamin D activity of carborane derivatives was evaluated in terms of differentiation-inducing activity toward human acute promyelocytic leukemia cell line HL-60.[11] Vitamin D_3 is one of the most potent inducers of the differentiation of HL-60 cells, and our previously developed carborane-based analogs exhibited potent differentiation-inducing activity.[5,6] Table 1 shows structure–activity relationship data for carborane derivatives bearing a sulfur atom in the dihydroxylated side chain. Sulfide derivative **11** exhibited differentiation-inducing activity with an EC_{50} value of 2.7×10^{-7} M. The potency was only slightly less than that of the corresponding ether derivative **2** (EC_{50}: 1.8×10^{-7} M), indicating that exchange of the ether to sulfide can be considered as an isosteric exchange. The other sulfide derivatives **12** – **14** also exhibited differentiation-inducing activity similar to that of **11** with EC_{50} values of $2.1–2.6 \times 10^{-7}$ M. The distance to the sulfur atom and the nature of the diol moiety, i.e., 1,2-diol or 1,3-diol, did not markedly affect the activity. These results suggested that the sulfur atom in the dihydroxylated side chain of these carborane-based vitamin D analogs does not have a critical interaction with the receptor, in accordance with the conclusion in the case of the oxygen atom of **3**, based on the co-crystal structure determination of **3** with the VDR ligand-binding domain (LBD). On the other hand, in contrast to the sulfide derivatives, sulfone derivative **15** was completely inactive, suggesting that the highly polar character of the sulfone substructure is unfavorable for binding to the receptor.

Table 1. HL-60-cell-differentiation-inducing potency of carborane derivatives bearing a sulfur atom in the dihydroxylated side chain

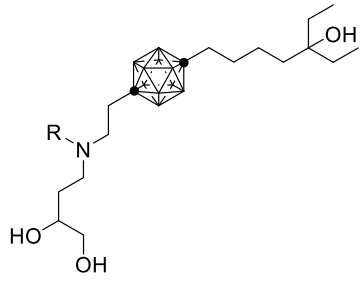


compound	X	m	n	EC_{50} [M] [a]
2	O	2	1	1.8×10^{-7}.[b]
11	S	2	1	2.7×10^{-7}
12		3	1	2.2×10^{-7}
13		1	2	2.1×10^{-7}
14		2	2	2.6×10^{-7}
16	SO_2	1	2	N.A.

[a]HL-60-cell-differentiation-inducing potency was evaluated over the concentration range of 10^{-9} to 10^{-5} M. Cell differentiation was determined as the ratio of NBT-positive cells. The EC_{50} value was calculated as the concentration of each compound exhibiting 50% of the activity induced by 10^{-7} M **1**. [b]Taken from our previous report.[6] N.A.: no activity.

Table 2 shows structure–activity relationship data for carborane derivatives bearing a nitrogen functionality in the dihydroxylated side chain. In contrast to the sulfide derivatives, these compounds did not exhibit differentiation-inducing activity, except for *N*-benzyl derivative **30** (EC_{50} value of 4.4×10^{-7} M). Secondary amine derivative **27** as well as tertiary amine derivative **29** were inactive. These results suggest that the amine functionality is unsuitable for the linking substructure because of its high polarity compared with ether and sulfide. Compounds bearing sulfonamide (**28**) and amide (**31** and **32**) structure also did not exhibit activity. Suhara et al. also reported that introduction of an amide group as the linking moiety in secosteroid derivatives resulted in the complete loss of activity.[12] The rigid nature of the amide substructure may prevent the molecule from adopting a suitable conformation for binding to the receptor.

Table 2. HL-60-cell-differentiation-inducing potency of carborane derivatives bearing a nitrogen functionality in the dihydroxylated side chain



compound	R	EC_{50} [M] [a]
2	-	1.8×10^{-7}.[b]
27	H-	N.A.
28	2-NO_2-C_6H_4-SO_2-	N.A.
29	Me-	N.A.
30	$C_6H_5CH_2$-	4.4×10^{-7}
31	MeCO-	N.A.
32	C_6H_5CO-	N.A.

[a]HL-60-cell-differentiation-inducing potency was evaluated over the concentration range of 10^{-9} to 10^{-5} M. Cell differentiation was determined as the ratio of NBT-positive cells. The EC_{50} value was calculated as the concentration of each compound exhibiting 50% of the activity induced by 10^{-7} M **1**. [b]Taken from our previous report.[6] N.A.: no activity.

It is interesting that benzylamine derivative **30** exhibited differentiation-inducing activity with comparable potency to the oxygen- or sulfur-containing derivatives. In order to estimate the binding mode of benzylamine derivative **30** to VDR, docking simulation using the crystal structure of VDR BD was performed. Because **30** has a stereocenter at the secondary hydroxy group, we conducted the docking simulation with both the *R* and *S* isomers of **30**. Figure 2A shows the docking model of *R*-**30** with the VDR LBD, with the co-crystal structure of **1** superimposed. In the calculated structure, the 1,2-diol moiety of the *R*-form of **30** is located in the region where the A ring of **1** is located, and the tertiary alcohol on the other side chain interacts with His301 and His393, which interact with the 25-hydroxy group of **1**. The carborane moiety of *R*-**30** binds at the hydrophobic region of the VDR LBD, where the D ring of **1** is located. Interestingly, the phenyl group of *R*-**30** occupies the hydrophobic region where the C ring of **1** is located. Figure 2B shows the docking model of compound *S*-**30**. Though the carbon backbone in the region of the terminal diol is located at a different position from that in the case of *R*-**30**, the calculated binding form of *S*-**30** is essentially similar to that of *R*-**30**, namely, the three hydroxy groups of *R*-**30** and *S*-**30** are placed at similar locations in the ligand-binding pocket, and the carborane cage and phenyl group occupy the hydrophobic cavity. The calculation implies that the additional hydrophobic interaction involving the phenyl ring could compensate for the disadvantageous amine substructure, so that **30** exhibits biological activity. The results suggest that increasing the hydrophobic volume near the hydrophobic core structure could be a new design strategy to enhance the vitamin D activity of nonsecosteroidal analogs.

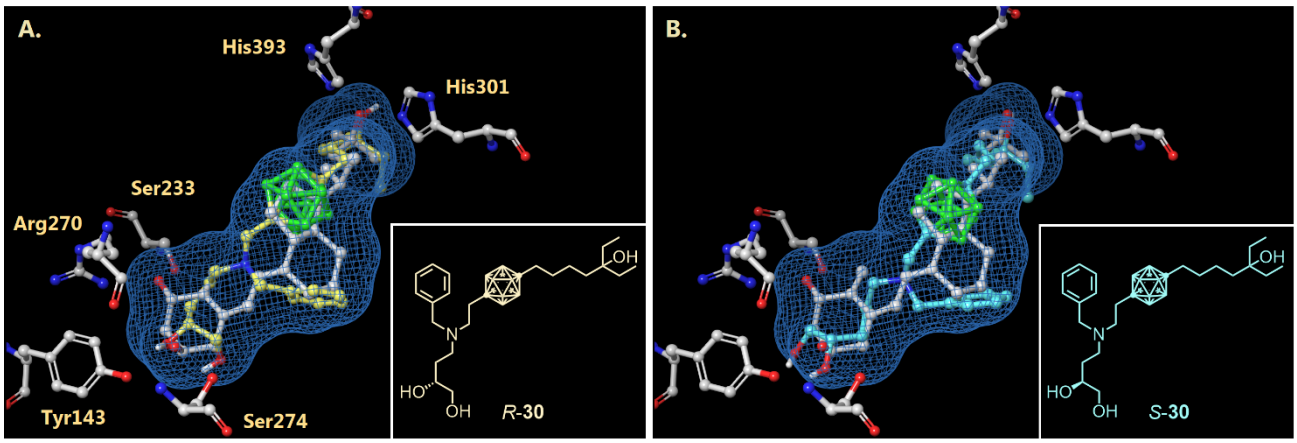


Figure 2. Docking simulation of benzylamine derivative **30** with rat VDR LBD (PDB ID: 1RK3)[13] using AutoDock[14]. A) The docking model of the *R*-form of **30** (carbon in yellow) is superimposed on the VDR LBD bound to 1α,25(OH)$_2$D$_3$ (**1**) (carbon in gray). The protein surface is indicated as a blue mesh. B) The docking model of *S*-form of **30** (carbon in light blue) is superimposed on the VDR LBD complex with **1**.

In summary, in this study we investigated the structure-activity relationship of *p*-carborane-based nonsecosteroidal vitamin D analogs bearing a nitrogen or a sulfur functionality in the linker structure. We found that sulfide could be used in the linker structure as well as ether, whereas sulfone was not suitable. Amine (except for benzylamine **30**), amide and sulfonamide derivatives were inactive. These results suggested that a polar and rigid substructure in the linker moiety is disadvantageous for receptor binding. Docking simulation of the active benzylamine derivative **30** suggested that the benzyl group enhances the hydrophobic interaction between the receptor and compound. The structure–activity relationships presented here should be helpful in the further development of nonsecosteroidal vitamin D analogs.

EXPERIMENTAL

Synthesis

General: All reagents were purchased from Sigma-Aldrich Chemical Co., Tokyo Kasei Kogyo Co., Wako Pure Chemical Industries, or Kanto Chemical Co., Inc. Silica gel for column chromatography was purchased from Kanto Chemical Co., Inc. ^{1}H NMR spectra were recorded at 500 MHz on a Bruker AVANCE 500 spectrometer or 400 MHz on a Bruker AVANCE 400 spectrometer. Chemical shifts are reported as parts per million (ppm). Data are reported as follows: chemical shift, multiplicity (s, singlet; d, doublet; t, triplet; br, broad; m, multiplet), coupling constants (Hz), integration. The purity of the final compounds was determined by ^{1}H NMR, and was ≥95% in all cases.

1-(5-Ethyl-5-triethylsilyloxyheptyl)-1,12-dicarba-*closo*-dodecaborane (5): A solution of *n*-BuLi (1.55 M in *n*-hexane, 1.0 mL, 1.55 mmol) was added to a solution of *p*-carborane (0.21 g, 1.39 mmol) in THF (14 mL) at 0 °C and the mixture was stirred at room temperature for 15 min under an argon atmosphere. Then, 7-bromo-3-ethyl-(3-triethylsilyloxy)heptane (0.57 g, 1.67 mmol) was added to the mixture at 0°C, and stirring was continued at room temperature for 4 h. The reaction mixture was poured into water and extracted with AcOEt. The organic layer was washed with brine, dried over sodium sulfate, and concentrated. Purification by silica gel column chromatography (eluent; hexane) gave **5** (0.26 g, 46%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.80–1.50 (br m, 11 H), 1.60–1.58 (m, 2 H), 1.38 (q, J = 7.9 Hz, 4 H), 1.30–1.26 (m, 2 H), 1.11–1.06 (m, 4 H) 0.92 (t, J = 7.9 Hz, 9 H), 0.78 (t, J = 7.3 Hz, 6 H), 0.54 (q, J = 7.9 Hz, 6 H).

1-(2-Mercaptoethyl)-12-(5-ethyl-5-triethylsilyloxyheptyl)-1,12-dicarba-*closo*-dodecaborane (6): A solution of *n*-BuLi (1.60 M in *n*-hexane, 0.30 mL, 0.48 mmol) was added to a solution of **5** (177 mg, 0.44 mmol) in THF (5.0 mL) at 0 °C, and then ethylene sulfide (0.030 ml, 0.49 mmol) was added and stirring was continued at 0 °C for 15 min. The reaction mixture was poured into saturated aqueous NH_4Cl solution and extracted with AcOEt. The organic layer was washed with brine, dried over sodium sulfate, and concentrated. Purification by silica gel column chromatography (eluent; hexane/CH_2Cl_2 = 20/1) gave

6 (44 mg, 22%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.80–1.50 (br m, 10 H), 2.31–2.25 (m, 2 H), 1.92–1.88 (m, 2 H), 1.59–1.56 (m, 2 H), 1.37 (q, *J* = 7.4 Hz, 4 H), 1.31–1.25 (m, 3 H), 1.08–1.06 (m, 4 H), 0.91 (t, *J* = 8.0 Hz, 9 H), 0.77 (t, *J* = 7.4 Hz, 6 H), 0.53 (q, *J* = 8.0 Hz, 6 H).

1-(5-(2,2-Dimethyl-1,3-dioxolan-4-yl)-3-thiapentyl)-12-(5-ethyl-5-triethylsilyloxyheptyl)-1,12-dicarba-*closo*-dodecaborane (7): Compound **6** (44.0 mg, 0.096 mmol) and 4-{2-(*p*-toluenesulfonyloxy)ethyl}-2,2-dimethyl-1,3-dioxolane (35.0 mg, 0.11 mmol) were added to a suspension of NaH (60% in oil, 6.0 mg, 0.15 mmol) in THF (1.0 mL) at 0 °C. The mixture was stirred at room temperature for 2 h, then poured into saturated aqueous NH_4Cl solution and extracted with AcOEt. The organic layer was washed with brine, dried over sodium sulfate, and concentrated. Purification by silica gel column chromatography (eluent; hexane/AcOEt = 20/1) gave **7** (23 mg, 41%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.15–4.12 (m, 1 H) 4.04 (dd, *J* = 8.0 Hz, 6.1 Hz, 1 H) 3.52 (dd, *J* = 8.0 Hz, 7.0 Hz, 1 H), 2.80–1.50 (br m, 10 H), 2.57–2,52 (m, 1 H), 2.48–2,42 (m, 1 H), 2.20-2.26 (m, 2 H), 1.89–1.85 (m, 2 H), 1.81–1.76 (m, 1 H), 1.72–1.69 (m, 1 H), 1.68–1.57 (m, 2 H), 1.41 (s, 3 H), 1.37 (q, *J* = 7.5 Hz, 4 H) 1.34 (s, 3 H), 1.31–1.25 (m, 2 H), 1.09–1.06 (m, 4 H), 0.92 (t, *J* = 8.0 Hz, 9 H), 0.77 (t, *J* = 7.5 Hz, 6 H), 0.53 (q, *J* = 8.0 Hz, 6 H).

1-(6-(2,2-Dimethyl-1,3-dioxolan-4-yl)-3-thiahexyl)-12-(5-ethyl-5-triethylsilyloxyheptyl)-1,12-dicarba-*closo*-dodecaborane (8): Compound **6** (42.0 mg, 0.091 mmol) and 4-{3-(*p*-toluenesulfonyloxy)propyl}-2,2-dimethyl-1,3-dioxolane (32.0 mg, 0.10 mmol) were added to a suspension of NaH (60% in oil, 10 mg, 0.25 mmol) in THF (0.5 mL) at 0 °C. The mixture was stirred at room temperature for 1 h, then poured into saturated aqueous NH_4Cl solution and extracted with AcOEt. The organic layer was washed with brine, dried over sodium sulfate, and concentrated. Purification by silica gel column chromatography (eluent; hexane/AcOEt = 20/1) gave **8** (23 mg, 41%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.08–4.01 (m, 2 H), 3.50 (t, *J* = 7.0 Hz, 1 H), 2.80–1.50 (br m, 10 H), 2.44 (t, *J* = 6.9 Hz, 2 H), 2.28–2.23 (m, 2 H), 1.88–1.83, (m, 2 H), 1.68–1.52 (m, 6 H), 1.41 (s, 3 H), 1.37 (q, *J* = 7.5 Hz, 4 H) 1.34 (s, 3 H), 1.28–1.25 (m, 2 H), 1.11–1.06 (m, 4 H), 0.91 (t, *J* = 7.9 Hz, 9 H), 0.77 (t, *J* = 7.5 Hz, 6 H), 0.53 (q, *J* = 7.9 Hz, 6 H).

1-{4-(2-Phenyl-1,3-dioxan-4-yl)-3-thiabutyl}-12-(5-ethyl-5-triethylsilyloxyheptyl)-1,12-dicarba-*closo*-dodecaborane (9): Compound **6** (86 mg, 0.19 mmol) and 4-(*p*-toluenesulfonyloxymethyl)-2-phenyl-1,3-dioxane (74 mg, 0.213 mmol) were added to a suspension of NaH (60% in oil, 12 mg, 0.30 mmol) in THF (1.0 mL) at 0 °C. The mixture was stirred at room temperature for 3 h, then poured into saturated aqueous NH_4Cl solution and extracted with AcOEt. The organic layer was washed with brine, dried over sodium sulfate, and concentrated. Purification by silica gel column chromatography (eluent; hexane/AcOEt e = 20/1) gave **9** (26.0 mg, 22%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47–7.26 (m, 5 H), 5.50 (s, 1 H), 4.28 (dd, *J* = 11.5 Hz, 4.0 Hz, 1 H), 3.99–

3.92 (m, 2 H), 2.80–1.50 (br m, 10 H), 2.68 (dd, *J* = 13.8 Hz, 6.5 Hz, 1 H), 2.55 (dd, *J* = 13.8 Hz, 5.5 Hz, 1H), 2.41–2.37 (m, 2 H), 1.89–1.60 (m, 4 H), 1.63–1.57 (m, 2 H), 1.38 (q, *J* = 7.5 Hz, 4 H), 1.29–1.26, (m, 2 H), 1.11–1.07 (m, 4 H), 0.92 (t, *J* = 7.9 Hz, 9 H), 0.78 (t, *J* = 7.5 Hz, 6 H), 0.53 (t, *J* = 7.9 Hz, 6 H).

1-{5-(2-Phenyl-1,3-dioxan-4-yl)-3-thiapentyl}-12-(5-ethyl-5-triethylsilyloxyheptyl)-1,12-dicarba-*closo*-dodecaborane (10): Compound **6** (80 mg, 0.17 mmol) and 4-{2-(*p*-toluenesulfonyloxy)ethyl}-2-phenyl-1,3-dioxane (71 mg, 0.19 mmol) were added to a suspension of NaH (60% in oil, 8.0 mg, 0.20 mmol) in THF (1.0 mL) at 0 °C. The mixture was stirred at room temperature for 1 h, then poured into saturated aqueous NH_4Cl solution and extracted with AcOEt. The organic layer was washed with brine, dried over sodium sulfate, and concentrated. Purification by silica gel column chromatography (eluent; hexane/AcOEt = 20/1) gave **10** (74.0 mg, 64%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48–7.33 (m, 5 H), 5.49 (s, 1 H), 4.28–4.25 (dd, *J* = 11.5 Hz, 4.0 Hz, 1 H), 3.99–3.91 (m, 2 H), 2.80–1.50 (br m, 10 H), 2.66 (m, 2 H), 2.29–2.26 (m, 2 H), 1.93–1.77 (m, 5 H), 1.73–1.67 (m, 1 H), 1.60–1.57 (m, 2 H), 1.38 (q, *J* = 7.4 Hz, 4 H), 1.35–1.10, (m, 2 H), 1.09–0.95 (m, 4 H), 0.92 (t, *J* = 7.9 Hz, 9 H), 0.78 (t, *J* = 7.4 Hz, 6 H), 0.53 (t, *J* = 7.9 Hz, 6 H).

General Procedure A for removal of protective groups: synthesis of 1-(6,7-dihydroxy-3-thiaheptyl)-12-(5-ethyl-5-hydroxyheptyl)-1,12-dicarba-*closo*-dodecaborane (11): Compound **7** (23 mg, 0.044 mmol) was dissolved in MeOH (0.2 mL) and THF (0.8 mL), and then 2 M hydrochloric acid (0.25 mL) was added to the solution at 0 °C. The mixture was stirred for 3 h at room temperature, poured into saturated aqueous $NaHCO_3$ solution, and extracted with AcOEt. The organic layer was washed with brine, dried over sodium sulfate, and concentrated. Purification by silica gel column chromatography (eluent; hexane/AcOEt = 5/1) gave **11** (65 mg, 0.155 mmol, 96%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.81–3.79 (m, 1 H), 3.63 (dd, *J* = 11.0 Hz, 3.1 Hz, 1 H), 3.43 (dd, *J* = 11.0, 7.6, Hz, 1 H), 2.80–1.50 (br m, 10 H), 2.57–2.50 (m, 2 H), 2.47 (s, 1 H), 2.30–2.25 (m, 2 H), 2.04 (s, 1 H), 1.88–1.84 (m, 2 H), 1.67–1.58 (m, 4 H), 1.39 (q, *J* = 7.6 Hz, 4 H), 1.30–1.25 (m, 2 H), 1.14–1.09 (m, 5 H), 0.81 (t, *J* = 7.6 Hz, 6 H).

1-(7,8-Dihydroxy-3-thiaoctyl)-12-(5-ethyl-5-hydroxyheptyl)-1,12-dicarba-*closo*-dodecaborane (12): General Procedure A using compound **8** as a starting material. 68%, colorless oil, ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.70–3.67 (m, 1 H), 3.63 (dd, *J* = 11.0 Hz, 3.1 Hz, 1 H), 3.42 (dd, *J* = 11.0, 7.6, Hz, 1 H), 2.80–1.50 (br m, 10 H), 2.45 (t, *J* = 7.2 Hz, 2 H), 2.27–2.24 (m, 2 H), 1.87–1.84 (m, 2 H), 1.79 (br s, 3 H), 1.74–1.46 (m, 6 H), 1.39 (q, *J* = 7.5 Hz, 4 H), 1.30–1.25 (m, 2 H), 1.13–1.08 (m, 4 H), 0.81 (t, *J* = 7.5 Hz, 6 H).

1-(5,7-Dihydroxy-3-thiaheptyl)-12-(5-ethyl-5-hydroxyheptyl)-1,12-dicarba-*closo*-dodecaborane (13): General Procedure A using compound **9** as a starting material. 49%, colorless oil, ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.88–3.80 (m, 3 H), 2.80–1.50 (br m, 10H), 2.45–2.31 (m, 4 H), 1.89–1.85 (m, 2 H), 1.78–1.59 (m, 4 H), 1.39 (q, *J* = 7.5 Hz, 4 H), 1.31–1.25 (m, 2 H), 1.14–1.09 (m, 4 H), 0.81 (t, *J* = 7.5 Hz, 6 H).

1-(6,8-Dihydroxy-3-thiaoctyl)-12-(5-ethyl-5-hydroxyheptyl)-1,12-dicarba-*closo*-dodecaborane (14): General Procedure A using compound **10** as a starting material. 54%, colorless oil, ^{1}H NMR (500 MHz, MeOD) δ 3.84–3.78 (m, 1 H), 3.70 (t, *J* = 6.5 Hz, 2 H), 2.80–1.50 (br m, 10 H), 2.58–2.48 (m, 2 H), 2.38–2.34 (m, 2 H), 1.97–1.92 (m, 2 H), 1.84–1.75 (m, 2 H), 1.70–1.59 (m, 4 H), 1.43 (q, *J* = 7.5 Hz, 4 H), 1.35–1.29 (m, 2 H), 1.18–1.10 (m, 4 H), 0.84 (t, *J* = 7.5 Hz, 6 H).

1-{2-[(2-Phenyl-1,3-dioxan-4-yl)methyl]sulfonyl}ethyl-12-(5-ethyl-5-triethylsilyloxyheptyl)-1,12-dicarba-*closo*-dodecaborane (15): Compound **9** (50 mg, 0.078 mmol) was dissolved in CH_2Cl_2 (1.0 mL), and then *m*-chloroperbenzoic acid (70%, 39 mg, 0.17 mmol) was added to the solution at 0 °C. The mixture was stirred for 3 h at room temperature, and diluted with CH_2Cl_2. The organic layer was washed with aqueous 3 M NaOH solution and brine, dried over sodium sulfate, and concentrated. Purification by silica gel column chromatography (eluent; hexane/AcOEt = 2/1) gave **15** (32 mg, 61%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45–7.42 (m, 5 H), 5.54 (s, 1 H), 4.48–4.43 (m, 1 H), 4.30 (dd, *J* = 11.8 Hz, 4.2 Hz, 1 H), 3.99 (dt, *J* = 12.2 Hz, 2.4 Hz, 1 H), 3.24 (dd, *J* = 15.2 Hz, 9.8 Hz, 1 H), 2.94–2.83 (m, 3 H), 2.80–1.50 (br m, 10H), 2.13–2.02 (m, 2 H), 2.00–1.87 (m, 2 H), 1.58–1.54 (m, 2 H), 1.39 (q, *J* = 7.5 Hz, 4 H), 1.28–1.25, (m, 2 H), 1.10–1.03 (m, 4 H), 0.92 (t, *J* = 7.9 Hz, 9 H), 0.78 (t, *J* = 7.5 Hz, 6 H), 0.54 (t, *J* = 7.9 Hz, 6 H).

1-(2,4-Dihydroxybutylsulfonyl)ethyl-12-(5-ethyl-5-hydroxyheptyl)-1,12-dicarba-*closo*-dodecaborane (16): General Procedure A using compound **15** as a starting material. 38%, colorless oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.45–4.42 (m, 1 H), 3.94–3.86 (m, 2 H), 3.12 (dd, *J* = 14.6 Hz, 4,6 Hz, 1 H), 3.01–2.93 (m, 3 H), 2.80–1.50 (br m, 10 H), 2.15 (t, *J* = 8.5 Hz, 2 H), 1.86–1.69 (m, 2 H), 1.62–1.59 (m, 2 H), 1.39 (q, *J* = 7.5 Hz, 4 H), 1.36–1.25 (m, 2 H), 1.25 (br s 3 H), 1.15–1.10 (m, 4 H), 0.81 (t, *J* = 7.5 Hz, 6 H).

1-(2-(2-Nitrobenzenesulfonyl)aminoethyl)-12-(5-ethyl-5-triethylsilyloxyheptyl)-1,12-dicarba-*closo*-dodecaborane (20): Preparation of compound **19** was reported previously.[5,6] $NsNH_2$ (680 mg, 3.4 mmol), tributylphosphine (680 mg, 3.4 mmol) and TMAD (580 mg 3.4 mmol) were added to a solution of **19** (500 mg, 1.12 mmol) in THF (10 mL) at 0 °C. The mixture was stirred at room temperature for 2 h and at 50 °C for 2 h, then further TMAD (200 mg 1.12 mmol) was added at 0 °C, and stirring was continued at room temperature for 2 h and at 50 °C for 2 h. The reaction mixture was evaporated, and the residue was purified by silica gel column chromatography (eluent: hexane/AcOEt = 1/4) to give 422 mg (0.672 mmol, 60%) of **20** as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (m, 1 H), 7.85 (m, 1 H), 7.73 (m, 2 H), 5.21 (t, *J* = 6.1 Hz, 1 H), 2.88 (m, 2 H), 2.8–1.5 (br m, 10 H), 1.85 (t, *J* = 7.8 Hz, 2 H), 1.55 (m, 2 H), 1.35 (q, *J* = 7.4 Hz, 4 H), 1.24 (t, *J* = 7.1 Hz, 2 H), 1.04 (m, 4 H), 0.89 (t, *J* = 7.7 Hz, 9 H), 0.75 (t, *J* = 7.4 Hz, 6 H), 0.50 (q, *J* = 7.7 Hz, 6 H).

1-(2-((2,2-Dimethyl-1,3-dioxolan-4-yl)ethyl)(2-nitrobenzenesulfonyl)aminoethyl)-12-(5-ethyl-5-triethylsilyloxyheptyl)-1,12-dicarba-*closo*-dodecaborane (21): Compound **20** (300 mg 0.477 mmol)

was dissolved in DMF (6.0 mL), Cs_2CO_3 (310 mg, 0.95 mmol) was added to the solution at 0 °C, and the mixture was stirred for 10 min at room temperature. Then 4-{2-(*p*-toluenesulfonyloxy)ethyl}-2,2-dimethyl-1,3-dioxolane (220 mg 0.72 mmol) in DMF (1.5 mL) was added at 0 °C, and stirring was continued at room temperature for 2 h and at 50 °C for 2 h. Next, tributylammonium iodide (52 mg, 0.14 mmol) was added at 0 °C, and stirring was continued at 50 °C for 2 h. The reaction mixture was diluted with AcOEt, washed with water and brine, dried with Na_2SO_4 and evaporated. Purification by silica gel column chromatography (eluent: CH_2Cl_2) gave **21 (**340 mg , 95%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (m, 1 H), 7.67 (m, 2 H), 7.59 (m, 1 H), 4.00 (m, 2 H), 3.48 (m, 1 H), 3.25 (m, 2 H), 3.04 (m, 2 H), 2.8–1.5 (br m, 10 H), 1.80 (m, 2 H), 1.71 (m, 2 H), 1.57 (t, *J* = 7.8 Hz, 2 H), 1.36 (q, *J* = 7.4 Hz, 4 H), 1.36 (s, 3 H), 1.28 (s, 3 H), 1.24 (m, 2 H), 1.05 (m, 4 H), 0.89 (t, *J* = 7.9 Hz, 9 H), 0.75 (t, *J* = 7.4 Hz, 6 H), 0.51 (t, *J* = 7.9 Hz, 6 H).

1-(2-((2,2-Dimethyl-1,3-dioxolan-4-yl)ethyl)aminoethyl)-12-(5-ethyl-5-triethylsilyloxyheptyl)-1,12-dicarba-*closo*-dodecaborane (22): Compound **21** (340 mg 0.540 mmol) was dissolved in MeCN (5.0 mL), then Cs_2CO_3 (310 mg, 0.95 mmol) and thiophenol (180 mg 1.62 mmol) were added at 0 °C. The mixture was stirred at room temperature for 3 h, and diluted with AcOEt. The organic layer was washed with water and brine, dried with Na_2SO_4 and evaporated. Purification by silica gel column chromatography (eluent: CH_2Cl_2/MeOH = 10/1) gave **22** (250 mg, 81%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.07 (m, 1 H), 4.00 (m, 1 H), 3.48 (t, *J* = 7.5 Hz, 1 H), 2.8–1.5 (br m, 10 H), 2.58 (m, 2 H), 2.39 (t, *J* = 7.5 Hz, 2 H), 1.77 (t, *J* = 7.8 Hz, 2 H), 1.68 (m, 2 H), 1.59 (m, 2 H), 1.38 (q, *J* = 7.4 Hz, 4 H), 1.38 (s, 3 H), 1.32 (s, 3 H), 1.25 (t, *J* = 7.7 Hz, 2 H), 1.07 (m, 4 H), 0.90 (t, *J* = 7.9 Hz, 9 H), 0.76 (t, *J* = 7.4 Hz, 6 H), 0.52 (t, *J* = 7.9 Hz, 6 H).

1-(2-(3,4-Dihydroxybutyl)aminoethyl)-12-(5-ethyl-5-hydroxyheptyl)-1,12-dicarba-*closo*-dodecaborane (27): General Procedure A using compound **22** as a starting material. 67%, colorless oil, ^{1}H NMR(500 MHz, CD_2Cl_2) δ 3.68 (m, 1 H), 3.47 (dd, *J* = 11.1 Hz, 3.9 Hz, 1 H), 3.36 (dd, , *J* = 11.1 Hz, 5.4 Hz, 1 H), 2.81 (m, 1 H), 2.8–1.5 (br m, 10 H), 2.66 (m, 2 H), 2.42 (m, 2 H), 1.79 (m, 2 H), 1.62 (m, 2 H), 1.55 (m, 2 H), 1.36 (q, *J* = 7.5 Hz, 4 H), 1.26 (m, 2 H), 1.10 (m, 4 H), 0.79 (t, *J* = 7.5 Hz, 6 H); ^{13}C NMR (125 MHz, CH_2Cl_2) δ 80.4, 77.1, 74.4, 73.1, 66.8, 49.0, 47.7, 38.2, 38.1, 32.2, 31.3, 30.5, 23.3, 7.8; ^{11}B NMR (160 MHz, CH_2Cl_2) δ -12.9.

1-(2-(3,4-Dihydroxybutyl)(2-nitrobenzenesulfonyl)aminoethyl)-12-(5-ethyl-5-hydroxyheptyl)-1,12-dicarba-*closo*-dodecaborane (28): General Procedure A using compound **22** as a starting material. 75%, colorless oil, ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (m, 1 H), 7.68 (m, 2 H), 7.59 (m, 1 H), 3.71 (m, 1 H), 3.60 (m, 1 H), 3.43 (m, 2 H), 3.20 (m, 1 H), 3.04 (*t*, *J* = 8.7 Hz, 2 H), 2.8–1.5 (br m, 10 H), 1.87 (m, 2 H), 1.70 (m, 2 H), 1.59 (m, 2 H), 1.38 (q, *J* = 7.5 Hz, 4 H), 1.27 (m, 2 H), 1.08 (m, 4 H), 0.80 (t, *J* = 7.5 Hz, 6

H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149,37, 135.2, 134.2, 133.1, 132.2, 125.7, 75.7, 70.1, 67.8, 48.0, 46.2, 39.23, 39.1, 36.5, 33.0, 32.3, 31.4, 24.2, 9.1; ^{11}B NMR (160 MHz, $CDCl_3$) δ -12.1.

1-(2-(3,4-Dihydroxybutyl)(methyl)aminoethyl)-12-(5-ethyl-5-hydroxyheptyl)-1,12-dicarba-*closo*-dodecaborane (29): Compound **22** (40.0 mg 0.070 mmol) was dissolved in DMF (1.0 mL), then K_2CO_3 (15.0 mg, 0.105 mmol) and MeI (10.0 mg 0.070 mmol) were added. The mixture was stirred at 0 °C for 1 h, then diluted with AcOEt, washed with water and brine, dried with Na_2SO_4 and evaporated. Purification of the residue by silica gel column chromatography (eluent: hexane/AcOEt = 10/1) gave **23** (15 mg) as a colorless oil.

Compound **29** was prepared from the obtained **23** according to General Procedure A (5.0 mg, 17% for 2 steps). Colorless oil. ^{1}H NMR (500 MHz, CD_2Cl_2) δ 3.74 (m, 1 H), 3.47 (dd, *J* = 11.1 Hz, 3.9 Hz, 1 H), 3.36 (dd, *J* = 11.1 Hz, 5.4 Hz, 1 H), 2.8–1.5 (br m, 10 H), 2.58 (ddd, *J* = 13.5 Hz, 10.5 Hz, 3.5 Hz, 1 H), 2.40 (dt, *J* = 13.2 Hz, 3.8 Hz, 1 H), 2.25 (dt, *J* = 5.2 Hz, 12.4 Hz, 1 H), 2.15 (dt, *J* = 4.8 Hz, 13.2 Hz, 1 H), 2.12 (s, 3 H), 1.79 (m, 2 H), 1.63 (m, 3 H), 1.44 (m, 1 H), 1.37 (q, *J* = 7.4 Hz, 4 H), 1.27 (m, 2 H), 1.10 (m, 4 H), 0.79 (t, *J* = 7.4 Hz, 6 H); ^{13}C NMR(125 MHz, CD_2Cl_2) δ 80.4, 77.9, 74.2, 67.8, 58.2, 57.2, 42.7, 39.2, 39.1, 35.5, 32.3, 31.9, 31.4, 30.3, 24.2, 8.8; ^{11}B NMR(160 MHz, CD_2Cl_2) δ -12.1.

1-(2-Benzyl(3,4-dihydroxybutyl)aminoethyl)-12-(5-ethyl-5-hydroxyheptyl)-1,12-dicarba-*closo*-dodecaborane (30): Compound **22** (40.0 mg 0.070 mmol) was dissolved in DMF (1.0 mL), then K_2CO_3 (20 mg, 0.14 mmol) and benzyl bromide (18 mg 0.11 mmol) were added at 0 °C. The mixture was stirred at room temperature for 3 h, then diluted with AcOEt, washed with water and brine, dried with Na_2SO_4 and evaporated. Purification of the residue by silica gel column chromatography (eluent: hexane/AcOEt = 10/1) gave **24** (30 mg) as a colorless oil. Compound **30** was prepared from the obtained **24** according to General Procedure A (11 mg, 31% for 2 steps). Colorless oil. ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.34 (t, *J* = 7.5 Hz, 2 H), 7.29 (t, *J* = 7.5 Hz, 1 H), 7.23 (d, *J* = 7.5 Hz, 2 H), 3.67 (m, 1 H), 3.64 (d, *J* = 13.2 Hz, 1 H), 3.45 (dd, *J* = 11.0 Hz, 3.8 Hz, 1 H), 3.34 (dd, *J* = 11.1 Hz, 5.4 Hz, 1 H), 3.31 (d, *J* = 13.2 Hz, 1 H), 2.8–1.5 (br m, 10 H), 2.61 (ddd, *J* = 13.5 Hz, 10.5 Hz, 3.5 Hz, 1 H), 2.53 (dt, *J* = 5.2 Hz, 12.4 Hz, 1 H), 2.16 (dt, *J* = 5.2 Hz, 12.4 Hz, 1 H), 1.83 (dt, *J* = 4.8 Hz, 13.2 Hz, 1 H), 1.76 (dt, *J* = 4.8, 13.2Hz, 1 H), 1.65–1.59 (m, 3 H), 1.42 (m, 1 H), 1.38 (q, *J* = 7.4 Hz, 4 H), 1.20 (m, 2 H), 1.09 (m, 4 H), 0.78 (t, *J* = 7.4 Hz, 6 H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 130.5, 129.7, 128.82, 75.4, 74.0, 67.8, 59.7, 53.8, 53.6, 39.2, 39.1, 34.7, 32.3, 31.4, 30.2, 24.2, 8.8; ^{11}B NMR (160 MHz, CD_2Cl_2) δ -13.0.

1-(2-Aceto(3,4-dihydroxybutyl)aminoethyl)-12-(5-ethyl-5-hydroxyheptyl)-1,12-dicarba-*closo*-dodecaborane (31): Compound **22** (40.0 mg 0.070 mmol) was dissolved in CH_2Cl_2 (1.0 mL), then acetic anhydride (35 mg, 0.35 mmol) and pyridine (56 mg 0.70 mmol) were added at 0 °C. The mixture was stirred at room temperature for 2 h, then evaporated. The residue was purified by silica gel column chromatography (eluent: hexane/AcOEt = 10/1 to 1/4) to give **25** (41mg) as a colorless oil. Compound **31**

was prepared from the obtained **25** according to General Procedure A (21 mg, 65% for 2 steps). Colorless oil. ^{1}H NMR (500 MHz, CD_2Cl_2, 303K: conformers attributed to different conformations of amide were observed) δ 3.84 (m, 0.8 H), 3.61 (m, 0.4 H), 3.50 (m, 0.8 H), 3.38 (m, 1.6 H), 3.25 (m, 0.4 H), 3.06 (1.2 H, m), 2.93 (m, 0.8 H), 2.81 (m, 1 H), 2.8–1.5 (br m, 10 H), 2.00 (s, 0.6 H), 1.99 (s, 2.4 H) , 1.90 (dt, *J* = 13.2 Hz, 4.8 Hz, 1 H), 1.83 (dt, *J* = 4.8 Hz, 13.2 Hz, 1 H), 1.66 (m, 3 H) , 1.52 (m, 1 H), 1.39 (q, *J* = 7.4 Hz, 4 H), 1.28 (m, 2 H), 1.11 (m, 4 H), 0.80 (t, *J* = 7.4 Hz, 6 H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 172.9, 81.9, 76.3, 75.4, 70.6, 69.4,68.0, 67, 49.2, 46.7, 43,2, 39.2, 39.1, 35.4, 33.4, 32.8, 32.3, 31.9, 31.4, 24.2, 22.4, 22.1, 8.8; ^{11}B NMR (160 MHz, CD_2Cl_2) δ -12.9.

1-(2-Benzoyl(3,4-dihydroxybutyl)aminoethyl)-12-(5-ethyl-5-hydroxyheptyl)-1,12-dicarba-*closo*-dodecaborane (32): Compound **22** (25 mg 0.044 mmol) was dissolved in CH_2Cl_2 (2.0 mL), then benzoyl chloride (9.3 mg, 0.066 mmol) and pyridine (14.0 mg 0.17 mmol) were added at 0 °C. The mixture was stirred at room temperature for 1 h, then evaporated. The residue was purified by silica gel column chromatography (eluent: hexane/AcOEt = 1/4) to give of **26** (23 mg) as a colorless oil. Compound **32** was prepared from the obtained **26** according to General Procedure A (10 mg, 42% for 2 steps). Colorless oil. ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.48–7.36 (m, 3 H), 7.22 (m, 2 H), 3.96 (m, 1 H), 3.57 (m, 2 H), 3.45 (m, 1 H), 3.00 (m, 2 H), 2.90 (m, 1 H), 2.8–1.5 (br m, 10 H), 1.87 (dt, *J* = 5.2 Hz, 12.4Hz, 1 H), 1.78 (dt, *J* = 5.2 Hz, 12.4 Hz, 1 H), 1.59 (m, 3 H), 1.51 (m, 1 H), 1.36 (q, *J* = 7.4 Hz, 4 H), 1.26 (m, 2 H), 1.08 (m, 4 H), 0.79 (t, *J* = 7.4 Hz, 6 H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 174.2, 137.2, 131.0, 127.2, 81.7, 76.1, 75.4, 69.8, 67.7, 49.7, 43.0, 39.1, 39.0, 36.9, 32.8, 32.2, 31.4, 24.2, 8.8; ^{11}B NMR (160 MHz, CD_2Cl_2) δ -12.9.

HL-60 cell differentiation assay: HL-60 cell differentiation assay was performed as described in the previous report. Briefly, HL-60 cells were cultured in RPMI-1640 medium supplemented with 5% FBS and penicillin G and streptomycin at 37 °C under 5% CO_2 in air. The cells were diluted to 8.0×10^4 cells/mL with the medium, and an ethanol solution of a test compound was added. The cells were incubated at 37 °C for 4 days, and then the percentage of differentiated cells was determined by means of the nitro-blue tetrazolium (NBT) reduction assay. Cells were incubated at 37 °C for 20 min in RPMI-1640 (5% FBS) and an equal volume of phosphate-buffered saline (PBS) containing NBT (0.2%) and 12-*O*-tetradecanoylphorbol 13-acetate (TPA; 200 ng/mL) was added. The percentage of cells containing blue-black formazan was determined in a minimum of 200 cells.

Docking simulation: The structure of the rat VDR LBD was prepared from the Protein Data Bank accession No. 1RK3[13]. Polar hydrogens and partial atomic charges were assigned using AutoDockTools (ADT). Molecular docking was performed using AutoDock 4.2 with the Genetic Algorithm. AutoDock parameters for boron atom were Rii = 4.08 and eii = 0.180.

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