Bioorganic & Medicinal Chemistry 22 (2014) 1227–1235

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

Synthesis and structure–activity relationship of *p*-carborane-based non-secosteroidal vitamin D analogs

Shinya Fujii [a,b], Atsushi Kano [a], Chalermkiat Songkram [c], Hiroyuki Masuno [a], Yoshiyuki Taoda [d], Emiko Kawachi [a], Tomoya Hirano [a], Aya Tanatani [e], Hiroyuki Kagechika [a,*]

[a] Institute of Biomaterials and Bioengineering, Tokyo Medical and Dental University, 2-3-10 Kanda-Surugadai, Chiyoda-ku, Tokyo 101-0062, Japan
[b] Institute of Molecular and Cellular Biosciences, The University of Tokyo, 1-1-1 Yayoi, Bunkyo-ku, Tokyo 113-0032, Japan
[c] Department of Pharmaceutical Chemistry, Faculty of Pharmaceutical Sciences, Prince of Songkla University, Kho-Hong, Hat Yai, Songkhla 90112, Thailand
[d] Graduate School of Pharmaceutical Sciences, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan
[e] Department of Chemistry, Faculty of Science, Ochanomizu University, 2-1-1 Otsuka, Bunkyo-ku, Tokyo 112-8610, Japan

ARTICLE INFO

Article history:
Received 22 December 2013
Revised 8 January 2014
Accepted 10 January 2014
Available online 21 January 2014

Keywords:
Vitamin D
Nuclear receptor
Carborane
Non-secosteroid

ABSTRACT

1α,25-Dihydroxyvitamin D_3 [1α,25$(OH)_2D_3$: **1**] is a specific modulator of nuclear vitamin D receptor (VDR), and novel vitamin D analogs are therapeutic candidates for multiple clinical applications. We recently developed non-secosteroidal VDR agonists bearing a *p*-carborane cage (a carbon-containing boron cluster) as a hydrophobic core structure. These carborane derivatives are structurally quite different from classical secosteroidal vitamin D analogs. Here, we report systematic synthesis and activity evaluation of carborane-based non-secosteroidal vitamin D analogs. The structure–activity relationships of carborane derivatives are different from those of secosteroidal vitamin D derivatives, and in particular, the length and the substituent position of the dihydroxylated side chain are rather flexible in carborane derivatives. The structure–activity relationships presented here should be helpful in development of non-secosteroidal vitamin D analogs for clinical applications.

1. Introduction

Vitamin D receptor (VDR) is a ligand-inducible nuclear receptor specific for vitamin D,[1] and plays important roles in many physiological processes, including phosphate and calcium homeostasis, immune regulation, bone metabolism, cell proliferation and differentiation.[2] VDR is activated by binding of the endogenous VDR agonist 1α,25-dihydroxyvitamin D_3 [1α,25$(OH)_2D_3$: **1**] (Fig. 1), and regulates expression of specific target genes. Because VDR and its ligands have significant roles in the pathogenesis and therapy of diseases such as osteoporosis, arthritis, psoriasis and cancers, many 1α,25$(OH)_2D_3$ analogs bearing a secosteroidal skeleton have been developed as drug candidates. For example, maxacalcitol (**2**) was reported to potently suppress keratinocyte proliferation and has been approved for treatment of psoriasis.[3] On the other hand, the structural complexity, synthetic inconvenience and chemical instability of the secosteroidal compounds are disadvantageous for potential clinical application. Development of novel non-secosteroidal VDR ligands is therefore important, but until recently only one series of bisphenol derivatives, such as LG190178 (**3**),[4] had been developed as potent non-secosteroidal VDR ligands.

We recently reported development of a potent non-secosteroidal VDR ligand **4** using *p*-carborane (1,12-dicarba-*closo*-dodecaborane), in place of the CD ring of the secosteroid structure of **1**.[5,6] Carboranes are carbon-containing boron clusters with unusual chemicophysical characteristics, including spherical geometry and a hydrophobic B–H surface.[7,8] We have shown that carboranes can be used as the hydrophobic core of biologically active molecules, especially nuclear receptor ligands.[9] Though the overall structure of compound **4** is quite different from those of classical vitamin D analogs, X-ray crystallographic analysis using VDR ligand-binding domain (LBD) complexed with the (*S*)-isomer of **4** revealed that the binding mode of compound **4** to VDR is similar to that of **1**.[5] The terminal primary hydroxyl group and the secondary hydroxyl group of the 1,3-diol part of compound **4** correspond to the 1α-hydroxyl group and the 3-hydroxyl group of **1**, respectively. The tertiary alcohol of the other alkyl chain corresponds to the 25-hydroxyl group of **1**. These results suggested that structural modifications used in reported vitamin D analogs might also be useful for the development of novel non-secosteroidal VDR ligands. On the basis of these considerations, we planned to investigate the structure–activity relationship of a series of carborane-containing vitamin D analogs.

* Corresponding author. Tel.: +81 3 5280 8032; fax: +81 3 5280 8127.
E-mail address: kage.chem@tmd.ac.jp (H. Kagechika).

0968-0896/$ - see front matter © 2014 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.bmc.2014.01.015

2. Results and discussion

2.1. Design and synthesis

In order to uncover the structure–activity relationship of non-secosteroidal vitamin D analogs, we planned to investigate the activity of two series of carborane derivatives. One series has modifications in the mono-hydroxylated alkyl chain, which corresponds to the side-chain structure on the D ring of **1**. In this series, we introduced ether functionalities (**5**–**7**) based on the substructure of **2**. Neopentyl alcohol **8** and pinacolone derivative **9** were also designed based on structure–activity relationship studies of diphenylmethane derivatives such as **3**.[4] The other series has modifications in the dihydroxyalkyl chain, which corresponds to the A-ring attached to the conjugated triene structure of **1**. Our previous studies and structure–activity relationship analysis of diphenylmethane derivative **3** revealed that 1,2-diol substructure, as well as 1,3-diol (corresponding to the A-ring of **1**), could be a hydrophilic pharmacophore of VDR ligands. Therefore, various compounds bearing 1,2- or 1,3-diol substructure and/or with ether oxygen at various positions, including compounds reported previously (**10**–**13**, **15**, **16**),[5,6] were designed and synthesized to investigate their vitamin D activity (Fig. 2). Since we found that the stereochemistry of the secondary hydroxyl group of the carborane derivative **4** was not critical for the vitamin D activity,[5] these compounds were evaluated as racemic mixtures.

Syntheses of compounds **5**–**9** are summarized in Schemes 1 and 2. A benzyloxyethyl group was introduced into the carborane cage via C-lithiated form of *p*-carborane (**17**)[10] to afford benzyl ether **18**, and removal of the benzyl group by catalytic hydrogenation afforded alcohol **19**. Introduction of 1,3-diol substructure afforded **20**, and then a hydroxymethyl group was introduced to give **21**. Construction of the side chain moiety gave **22**, and removal of protective groups gave the target compound **5**. Compounds **6**, **8** and **9** were also synthesized from *p*-carborane. Hydrogenation of compound **23** afforded bis(hydroxyethyl)carborane **24**. Introduction of 1,3-diol substructure gave compound **25**, and construction of side chain moieties by reaction with ethyl bromoacetate and then Grignard reagent gave compound **27**. Finally, removal of the benzylidene protective group afforded compound **6**. Pinacolone derivative **9** was synthesized via compound **28**, and compound **8** was prepared by reduction of compound **9** (Scheme 1). Compound **7** was also synthesized from *p*-carborane as a starting material. Construction of the side chain moiety in the manner described for preparation of compound **6** gave compound **31**, and then protection of alcohol with TES gave compound **32**. 1,3-Diol substructure was constructed to afford compound **7**. Introduction of a hydroxyethyl moiety gave alcohol **34**, and introduction of 1,3-diol substructure gave compound **35**. Removal of protective groups under acidic conditions gave compound **7**.

Synthesis of compounds **12** and **14** is illustrated in Scheme 3. Introduction of the side chain moiety into compound **18** gave **36**, and then catalytic hydrogenation afforded alcohol **37**. Introduction of 1,2-diol substructure gave **38**, and removal of protective groups afforded compound **12**. Compound **14** was also synthesized from *p*-carborane. Reaction of lithiated carborane and trimethylene oxide gave 3-hydroxypropylcarborane **39**. Introduction of 1,3-diol substructure into **39** gave **40**, and then introduction of the side chain moiety gave **41**. Removal of protective groups under acidic conditions afforded compound **14**. Preparation of compounds **10**, **11**, **13**, **15** and **16** was reported previously.[5,6]

2.2. Biological evaluation

Vitamin D activity of carborane derivatives was evaluated in terms of cell differentiation-inducing activity toward human acute promyelocytic leukemia cell line HL-60.[11] Table 1 shows structure–activity relationship data for the mono-hydroxylated alkyl chain

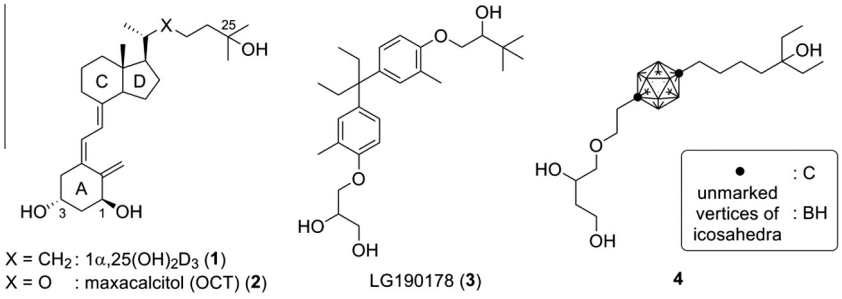


Figure 1. Structures of developed VDR ligands.

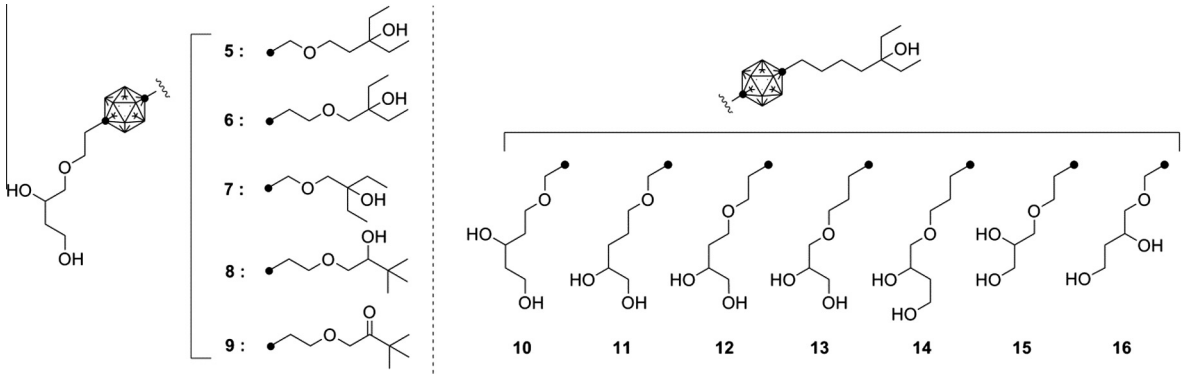
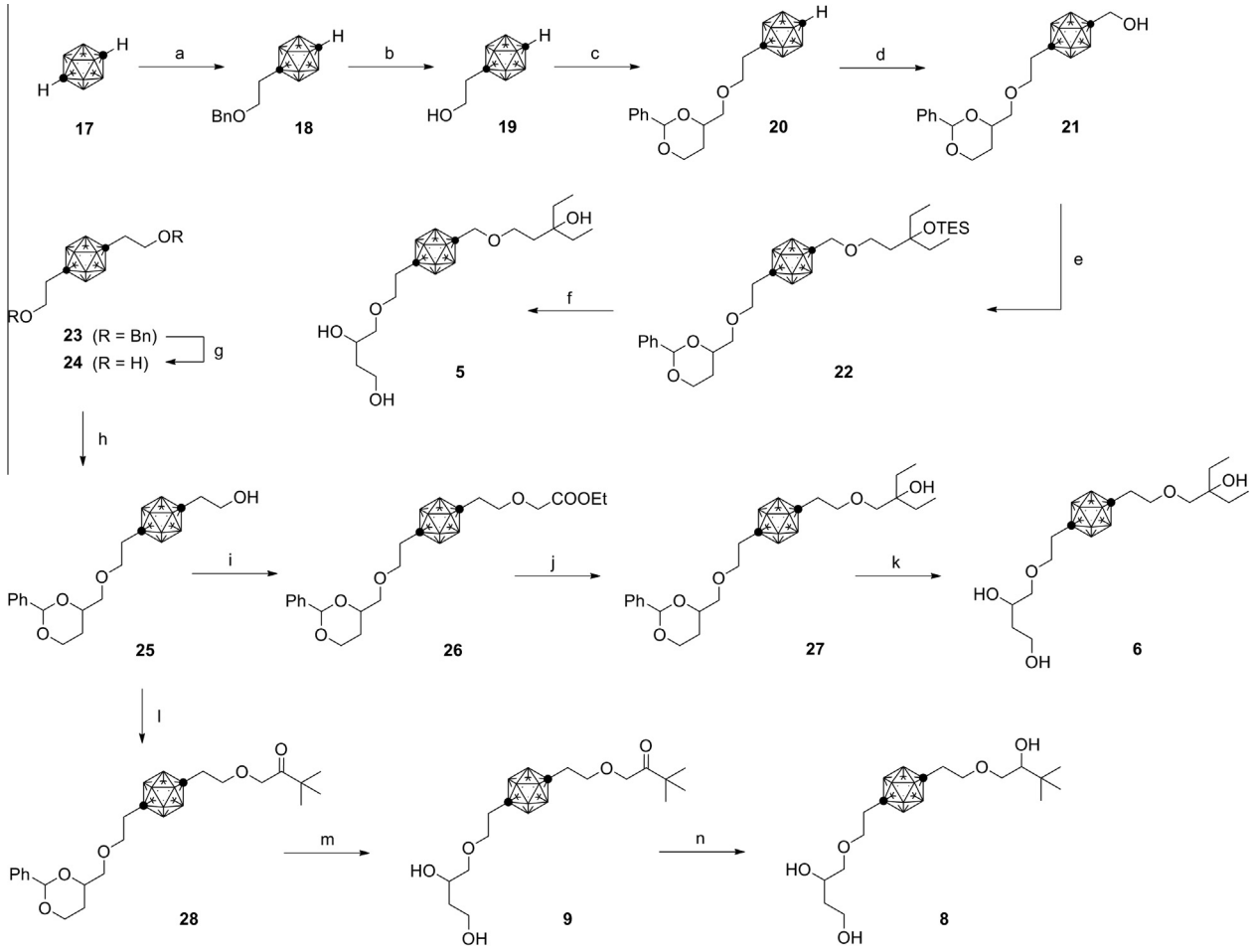
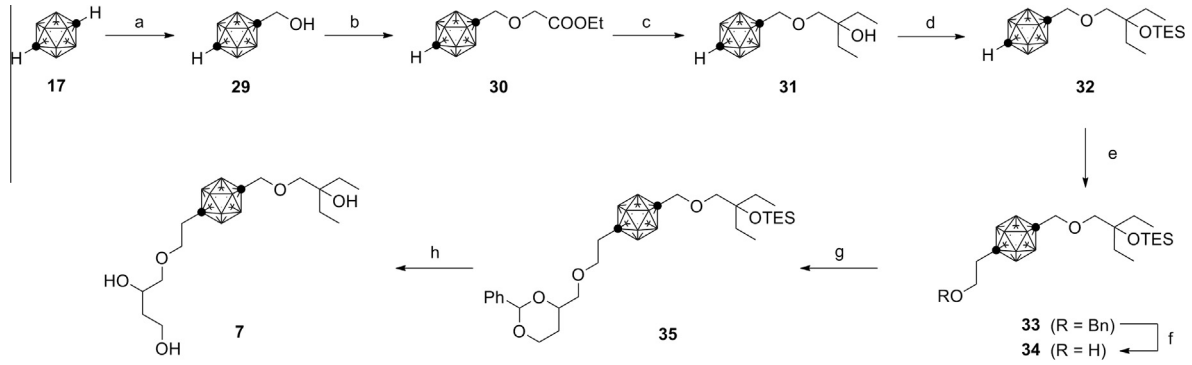


Figure 2. Structures of carborane-based vitamin D analogs investigated in this study.

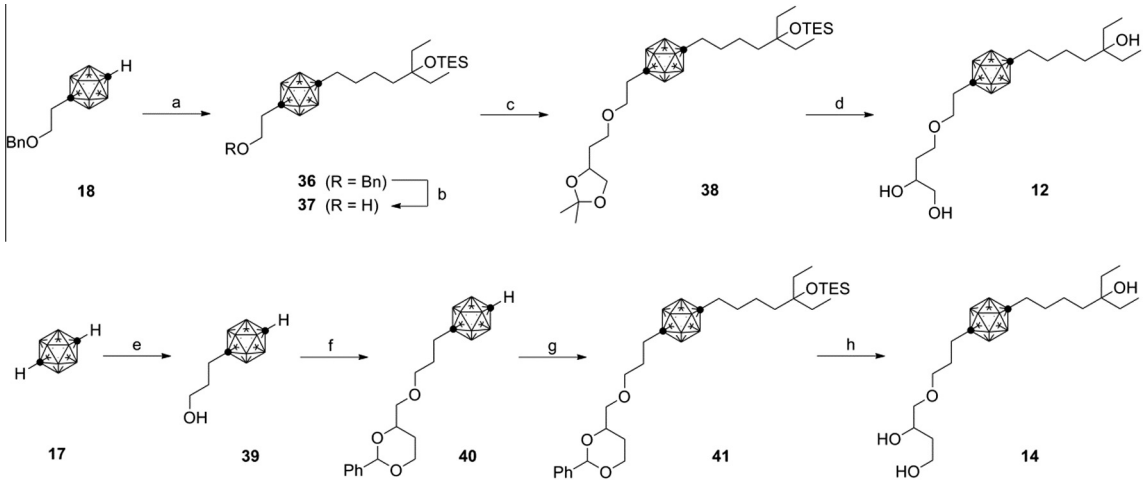


Scheme 1. Synthesis of designed carborane derivatives **5**, **6**, **8** and **9**. Reagents and conditions: (a) *n*-BuLi, benzyl 2-bromoethyl ether, ether, THF, 46%; (b) H_2, Pd/C, EtOH; (c) NaH, 4-(*p*-toluenesulfonyloxymethyl)-2-phenyl-1,3-dioxane, DMF, 32%; (d) *n*-BuLi, paraformaldehyde, benzene–ether, 70%; (e) NaH, 1-bromo-3-ethyl-3-(triethylsilyloxy)pentane, DMF, 15%; (f) HCl, H_2O, MeOH, THF, 25%; (g) H_2, Pd/C, EtOH, 87%; (h) NaH, 4-(*p*-toluenesulfonyloxymethyl)-2-phenyl-1,3-dioxane, DMF, 29%; (i) NaH, ethyl bromoacetate, DMF, 36%; (j) EtMgBr, THF, 42%; (k) HCl, H_2O, MeOH, THF, 44%; (l) NaH, 1-chloropinacolone, DMF, 17%; (m) HCl, H_2O, MeOH, THF, 44%; (n) $LiAlH_4$, Et_2O, quant.



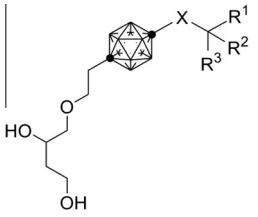
Scheme 2. Synthesis of designed carborane derivative **7**. Reagents and conditions: (a) *n*-BuLi, paraformaldehyde, benzene, ether, 66%; (b) NaH, ethyl bromoacetate, DMF, 75%; (c) EtMgBr, THF, 96%; (d) TESOTf, 2,6-lutidine, CH_2Cl_2, 46%; (e) *n*-BuLi, benzyl 2-bromoethyl ether, ether, THF, 66%; (f) H_2, Pd/C, EtOH, 79%; (g) NaH, 4-(*p*-toluenesulfonyloxymethyl)-2-phenyl-1,3-dioxane, DMF, 24%; (h) HCl, H_2O, MeOH, THF, 33%.

corresponding to the side chain of $1\alpha,25(OH)_2D_3$ (**1**). Compounds **5** and **6** bearing an ether oxygen atom in place of a methylene group of compound **4** exhibited moderate HL-60 cell differentiation-inducing activity. Ether derivative **7** bearing a shorter side chain moiety exhibited lower potency than **5** and **6**. Compound **8** bearing a *tert*-butyl group exhibited moderate potency similar to that of the diethyl derivative **5**. Ketone **9** exhibited lower potency than that of alcohol **8**. Thus, introduction of ether oxygen into the side chain moiety of the parent compound **4** decreased the HL-60 cell differentiation-inducing activity. In the case of secosteroidal compounds, it was expected that the less hindered oxa tethering chain would result in lower steric repulsion between the side chain and the CD ring moiety, and therefore **2** might exhibit potent vitamin D activity.[12] On the other hand, our previous X-ray crystallography



Scheme 3. Synthesis of carborane derivatives **12** and **14**. Reagents and conditions: (a) *n*-BuLi, 7-bromo-3-ethyl-3-triethylsilyloxyheptane, THF, ether, 96%; (b) H_2, Pd/C, EtOH, 87%; (c) NaH, 4-{2-(*p*-toluenesulfonyloxy)ethyl)}-2,2-dimethyl-1,3-dioxolane, DMF, 54%; (d) HCl, H_2O, MeOH, THF, 81%; (e) *n*-BuLi, trimethylene oxide, ether, 36%; (f) NaH, 4-(*p*-toluenesulfonyloxymethyl)-2-phenyl-1,3-dioxane, DMF, 22%; (g) *n*-BuLi, 7-bromo-3-ethyl-3-triethylsilyloxyheptane, THF, ether, 48%; (h) HCl, H_2O, MeOH, THF, 54%.

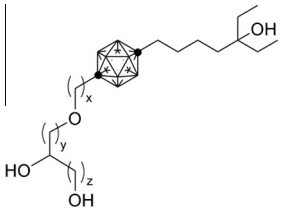
Table 1
HL-60 cell differentiation-inducing potency of carborane derivatives with modification in the mono-hydroxylated alkyl chain



Compound	X	R^1	R^2	R^3	EC_{50}[a] (nM)
4	$-(CH_2)_4-$	Et	Et	OH	47
5	$-(CH_2)_2-O-CH_2-$	Et	Et	OH	230
6	$-CH_2-O-(CH_2)_2-$	Et	Et	OH	460
7	$-CH_2-O-CH_2-$	Et	Et	OH	850
8	$-(CH_2)_2-O-CH_2-$	*t*-Bu	H	OH	310
9	$-(CH_2)_2-O-CH_2-$	*t*-Bu	=O		860

[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**.

Table 2
HL-60 cell differentiation-inducing potency of carborane derivatives with modification in the diol moiety



Compound	*x*	*y*	*z*	EC_{50}[a] (nM)
4	2	1	2	47
10	1	2	2	110
11	1	3	1	150
12	2	2	1	180
13	3	1	1	580
14	3	1	2	350
15	2	1	1	250
16	1	1	2	2900

[a] HL-60 cell differentiation-inducing potency was evaluated in the concentration range of 10^{-9} to 10^{-5} M. Cell differentiation was determined as the ratio of NBT-positive cells. EC_{50} value was calculated as the concentration of compound exhibiting 50% of the activity induced by 10^{-7} M **1**.

study of the complex of the (*S*)-isomer of **4** and the VDR-LBD showed that the methylene side chain of compound **4** adopts straight, continuous anti conformation in the complex. Based on these observations, a possible explanation of the low activity of ether compounds **5** and **6** is that the comparative flexibility of the ether side chain is unfavorable for adopting a straight conformation. The polar property of the ether moiety could also be unfavorable for hydrophobic interaction in the ligand-binding pocket. In addition, insertion of ether oxygen yields highly symmetrical structure, therefore the compounds also could induce weaker binding mode with upside-down direction. The low potency of compound **9** suggested that a hydroxyl group at the terminal of the side chain is required for potent vitamin D activity of both carborane derivatives and secosteroidal VDR ligands. Comparison of compounds **5** and **8** indicates that a *tert*-butyl group and geminal diethyl substructure are suitable hydrophobic substructures of the side chain, and hydrophobicity corresponding to C4 hydrocarbon is reasonable for the terminal region (Table 1).

The structure–activity relationship for the diol moiety is summarized in Table 2. Comparison of compounds **4** and **10**, which are isomers concerning the position of the ether oxygen atom, indicated that compound **4** exhibited higher HL-60 cell differentiation-inducing potency than did compound **10**. Regarding compounds **11**, **12** and **13**, which are also isomers regarding the position of the ether oxygen atom, compounds **11** and **12** exhibited almost equal vitamin D potency, whereas compound **13** was less potent. On the basis of these results, it is suggested that a suitable distance between the carborane cage and ether oxygen atom (*x* in Table 2) is two atoms distance, though one atom distance is also acceptable, whereas three atoms distance is not suitable. Compound **10** bearing 1,3-diol and compound **11** bearing 1,2-diol exhibited similar activity. Compound **14**, which has the longest dihydroxyalkyl functionality (8 atoms distance between carborane and terminal hydroxyl group), exhibited moderate activity, and compound **15** bearing the shortest chain (5 atoms distance) also exhibited moderate activity. On the other hand, compound **16**, which has the shortest distance between the secondary hydroxyl group and carborane cage (4 atoms distance) exhibited quite low activity. These results

suggested that the position of the secondary hydroxyl group is more important than the position of the terminal primary hydroxyl group. The reason for this, at least in part, could be the less flexible nature of the secondary hydroxyl group as compared with the terminal hydroxyl group. These considerations suggest that both 1,2-diol and 1,3-diol derivatives bearing a secondary hydroxyl group at a suitable position could exhibit vitamin D activity.

The structure–activity relationship studies indicated that compound **4** was the most potent among the synthesized carborane-based triols. It is noteworthy that the compounds with different lengths of dihydroxylated side chain or a different position of the dihydroxyl group also showed activities comparable to that of compound **4**, whereas modification of the A ring, including change of stereochemistry of hydroxyl groups, in secosteroidal vitamin D analogs causes significant decrease or loss of activity. The bulky spherical structure of carborane appears to be an effective hydrophobic core structure that allows these flexible dihydroxylated side chains to be arranged at the proper spatial positions for interaction with amino acid residues of the VDR. On the other hand, structure–activity relationship study regarding the monohydroxylated alkyl chain of carborane derivatives, corresponding to the side chain of 1α,25$(OH)_2D_3$ (**1**), revealed that introduction of ether substructure reduced the vitamin D potency of compounds. This finding suggested that flexibility or polarity of the side chain moiety of carborane derivatives reduces the activity of the compounds. We previously reported a structural analysis of VDR ligand-binding domain complexed with carborane derivative **4**, and revealed that the three hydroxyl groups of compound **4** function as a hydrogen-bonding pharmacophore corresponding to the three hydroxyl groups of 1α,25$(OH)_2D_3$ (**1**). On the other hand, the structure–activity relationships obtained in this study seemed quite characteristic of carborane-based VDR ligands. This structure–activity relationship information and structural analyses of carborane derivatives are expected to be helpful in the development of non-secosteroidal VDR ligands.

3. Conclusion

We have investigated the structure–activity relationship of a series of novel non-secosteroidal VDR ligands bearing a carborane cage as a hydrophobic pharmacophore. The structure–activity relationships of the carborane derivatives described here are different from those of secosteroidal vitamin D derivatives, and there is greater flexibility concerning the length and the substituent position of the dihydroxylated side chain in the carborane derivatives. We consider that carborane is a key hydrophobic core structure upon which two acyclic side chains can be arranged so as to ensure effective hydrogen bonding interactions with VDR in the ligand-binding pocket. The structure–activity relationship information obtained here should be helpful in further development of non-secosteroidal VDR ligands, as well as in the development of novel carborane-based bioactive substances.

4. Experimental

4.1. General

All reagents were purchased from Sigma–Aldrich Chemical Co., Tokyo Kasei Kogyo Co., Wako Pure Chemical Industries, and Kanto Chemical Co., INC. *p*-Carborane was purchased from Katchem s.r.o. (Prague, Czech Republic). Silica gel for column chromatography was purchased from Kanto Chemical Co., INC. ^{1}H NMR spectra were recorded on at 500 MHz on a BRUCKER AVANCE 500 spectrometer or at 400 MHz on a BRUCKER AVANCE 400 spectrometer, JEOL JNM-LA-400 or JNM-FX-400 spectrometers.

4.2. Synthesis

4.2.1. 1-(2-Benzyloxyethyl)-1,12-dicarba-*closo*-dodecaborane (18)

Under Ar atmosphere, *n*-BuLi (1.58 M in *n*-hexane, 4.1 mL, 38.1 mmol) was added to a solution of *p*-carborane (5.00 g, 34.7 mmol) in ether (120 mL) at 0 °C and stirred for 1 h at room temperature. Then benzyl 2-bromoethyl ether (8.95 g, 41.6 mmol) was added to the reaction mixture, and stirred for 16 h at room temperature. The reaction was quenched with water at 0 °C and diluted with AcOEt. The organic layer was washed with water and brine, dried with Na_2SO_4 and concentrated, then purified by silica gel column chromatography (eluent; hexane/ethyl acetate, 20:1) to give 4.45 g of **18** (46%) as colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.30–7.20 (m, 5H), 4.35 (s, 2H), 3.22 (t, J = 7.1 Hz, 2H), 3.0–1.3 (br m, 10H), 2.59 (s, 1H), 1.91 (t, J = 7.0 Hz, 2 H).

4.2.2. 1-{2-[(2-Phenyl-1,3-dioxan-4-yl)methoxy]ethyl}-1,12-dicarba-*closo*-dodecaborane (20)

Catalytic hydrogenation of **18** using 5% Pd on carbon in EtOH gave alcohol **19**. NaH (234 mg, 5.84 mmol) was added to a solution of **19** (1.00 g, 5.84 mmol) in DMF (6.0 mL) at 0 °C, and stirred for 10 min at 0 °C. Then 4-(*p*-toluenesulfonyloxymethyl)-2-phenyl-1,3-dioxane (2.03 g, 5.84 mmol) was added to the reaction mixture and stirred for 2 day at 90 °C. The reaction was quenched with water at 0 °C, and then diluted with AcOEt. The organic layer was washed with water and brine, dried with Na_2SO_4 and concentrated, then purified by silica gel column chromatography (eluent; hexane/ethyl acetate, 8:1) to give 678 mg of **20** (32%) as colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.48–7.45 (m, 2H), 7.36–7.30 (m, 3H), 5.49 (s, 1H), 4.27 (dd, J = 11.4, 3.8 Hz, 1H), 4.02–3.92 (m, 2H), 3.47 (dd, J = 10.3, 5.9 Hz, 1H), 3.37 (dd, J = 10.4, 4.8 Hz, 1H), 3.3–1.3 (br m, 10H), 3.29–3.23 (m, 2H), 2.63 (s, 1H), 1.89 (t, J = 7.0 Hz, 2H), 1.82 (dq, J = 12.3, 5.1 Hz, 1H), 1.53 (m, 1H).

4.2.3. 1-Hydroxymethyl-12-{2-[(2-phenyl-1,3-dioxan-4-yl)methoxy]ethyl}-1,12-dicarba-*closo*-dodecaborane (21)

A 1.56 M solution of *n*-BuLi in *n*-hexane (1.38 mL, 2.16 mmol) was added to a solution of **20** (606 mg, 1.66 mmol) in benzene (2.0 mL) and ether (1.6 mL) at 0 °C, and the mixture was stirred at room temperature for 1 h. Paraformaldehyde (80 mg, 2.16 mmol) was added to the mixture at 0 °C in one portion, and then the stirring was continued at room temperature for 16 h. The reaction was quenched with saturated aqueous ammonium chloride and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate and then concentrated. Purification by silica gel column chromatography (eluent; hexane/ethyl acetate, 4:1) gave **21** (70%) as colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.47–7.45 (m, 2H), 7.36–7.30 (m, 3H), 5.49 (s, 1H), 4.27 (dd, J = 11.5, 4.0 Hz, 1H), 4.02–3.92 (m, 2H), 3.48 (dd, J = 10.3, 5.9 Hz, 1H), 3.45 (s, 2H), 3.36 (dd, J = 10.3, 5.9 Hz, 1H), 3.45 (s, 2H), 3.36 (dd, J = 10.3, 4.6 Hz, 1H), 3.3–1.3 (br m, 10H), 3.29–3.21 (m, 2H), 1.91 (t, J = 7.0 Hz, 2H), 1.82 (dq, J = 12.5, 5.1 Hz, 1H), 1.52 (m, 1H).

4.2.4. 1-{2-[(2-Phenyl-1,3-dioxan-4-yl)methoxy]ethyl}-12-(3-ethyl-3-triethylsilyloxylpentyloxy)-methyl-1,12-dicarba-*closo*-dodecaborane (22)

NaH (56.0 mg, 1.39 mmol) was added to a solution of **21** (457 mg, 1.16 mmol) in DMF (4.0 mL) at 0 °C, and stirred for 10 min a 0 °C. Then the reaction mixture was added (3-bromo-1,1-diethylpropoxy)-diethylsilane (467 mg, 1.51 mmol) in DMF (4.0 mL) and stirred for 18 h at room temperature. Then the reaction was quenched with water at 0 °C, and then diluted with AcOEt. The organic layer was washed with water and brine, dried with Na_2SO_4 and concentrated, then purified by silica gel column

chromatography (eluent; hexane/ethyl acetate, 8:1) to give 88.5 mg of **22** (15%) as colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.47–7.45 (m, 2H), 7.36–7.28 (m, 3H), 5.49 (s, 1H), 4.27 (dd, J = 11.5, 4.9 Hz, 1H), 4.00–3.92 (m, 2H), 3.47 (dd, J = 10.3, 6.1 Hz, 1H), 3.38–3.23 (m, 5H), 3.3–1.3 (br m, 10H), 3.24 (s, 2H), 1.89 (t, J = 7.1 Hz, 2H), 1.82 (dq, J = 12.6, 4.9 Hz, 1H), 1.62–1.35 (m, 7H), 0.91 (t, J = 8.1 Hz, 9H), 0.80 (t, J = 7.5 Hz, 6H), 0.53 (q, J = 7.9 Hz, 6H).

4.2.5. 1-[2-(2,4-Dihydroxybutoxy)ethyl]-12-(3-ethyl-3-hydroxylpentyloxy)methyl-1,12-dicarba-*closo*-dodeca-borane (5)

2 M HCl (2.0 mL) was added to a solution of **22** (100 mg, 0.161 mmol) in MeOH/THF (3.0 mL), and stirred for 7 days at room temperature. The reaction mixture was diluted with AcOEt The organic layer was washed with water and brine, dried with Na_2SO_4 and concentrated, then purified by silica gel column chromatography (eluent; hexane/ethyl acetate, 2:1) to give 16.8 mg of **5** (25%) as colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.94 (m, 1H), 3.80 (t, J = 5.9 Hz, 2H), 3.45 (t, J = 6.0 Hz, 2H), 3.31 (dd, J = 9.3, 3.7 Hz, 1H), 3.3–1.3 (br m, 10H), 3.26 (s, 2H), 3.24–3.17 (m, 3H), 1.88 (t, J = 6.6 Hz, 2H), 1.64 (t, J = 6.1 Hz, 4H), 1.52–1.37 (m, 4H), 0.82 (t, J = 7.5 Hz, 6H).

4.2.6. 1,12-Bis(2-hydroxyethyl)-1,12-dicarba-*closo*-dodecaborane (24)

A mixture of **23** (6.38 g, 15.5 mmol) and 10% palladium on carbon (1.0 g) in ethanol (150 mL) was stirred at room temperature for 24 h under atmospheric pressure of hydrogen. Insoluble materials were filtered off through Celite, then the filtrate was concentrated. Purification by silica gel column chromatography (eluent; hexane/ethyl acetate, 2:1) gave **24** (87%) as white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.40 (m, 4H), 3.3–1.3 (br m, 10H), 1.87 (t, J = 7.1 Hz, 4H), 1.31 (s, 2H).

4.2.7. 1-(2-Hydroxyethyl)-12-{2-[(2-phenyl-1,3-dioxan-4-yl)methoxy]ethyl}-1,12-dicarba-*closo*-dodecaborane (25)

NaH (207 mg, 5.17 mmol) was added to a solution of **24** (1.00 g, 4.30 mmol) in DMF (2.0 mL) at 0 °C, and stirred for 10 min at 0 °C. Then 4-(*p*-toluenesulfonyloxymethyl)-2-phenyl-1,3-dioxane (1.50 g, 4.30 mmol) was added to the reaction mixture, and then stirred for 18 h at room temperature. Then the reaction was quenched with water at 0 °C and the mixture was diluted with AcOEt. The organic layer was washed with water and brine, dried with Na_2SO_4 and concentrated, then purified by silica gel column chromatography (eluent; hexane/ethyl acetate, 4:1) to give 502 mg of **25** (29%) as colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.47–7.44 (m, 2H), 7.36–7.30 (m, 3H), 5.49 (s, 1H), 4.27 (dd, J = 11.5, 4.2 Hz, 1H), 3.99–3.92 (m, 2H), 3.47 (dd, J = 10.3, 5.9 Hz, 1H), 3.41 (t, J = 7.1 Hz, 2H), 3.36 (dd, J = 10.3, 4.6 Hz, 1H), 3.3–1.3 (br m, 10H), 3.27–3.22 (m, 2H), 1.89–1.76 (m, 5H), 1.54–1.48 (m, 3H).

4.2.8. 1-{2-[(2-Phenyl-1,3-dioxan-4-yl)methoxy]ethyl}-12-[2-(ethoxycarbonylmethoxy)ethyl]-1,12-dicarba-*closo*-dodecaborane (26)

NaH (39.0 mg, 0.979 mmol) was added to a solution of **26** (200 mg, 0.490 mmol) in DMF (2.0 mL) at 0 °C, and stirred for 10 min at 0 °C. Then ethyl bromoacetate (200 mg, 0.490 mmol) was added to the reaction mixture, and then stirred for 18 h at room temperature. Then the reaction was quenched with water and diluted with AcOEt. The organic layer was washed with water and brine, dried with Na_2SO_4 and concentrated. Purification by silica gel column chromatography (eluent; hexane/ethyl acetate, 4:1) gave 174 mg of **26** (36%) as colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.47–7.45 (m, 2H), 7.35–7.32 (m, 3H), 5.48 (s, 1H), 4.24–4.11 (m, 5H), 3.98–3.93 (m, 4H), 3.46 (dd, J = 10.4, 6.0 Hz, 1H), 3.36 (dd, J = 10.4, 4.5 Hz, 1H), 3.3–1.3 (br m, 10H), 3.25 (m, 2H), 2.03–1.87 (m, 5H), 1.52 (m, 1H), 1.25 (t, J = 7.1 Hz, 3H).

4.2.9. 1-{2-[(2-Phenyl-1,3-dioxan-4-yl)methoxy]ethyl}-12-[2-(2-ethyl-2-hydroxybutoxy)ethyl]-1,12-dicarba-*closo*-dodecaborane (27)

EtMgBr (0.89 M in THF 0.51 mL 0.460 mmol) was added to a solution of **26** (75.0 mg, 0.152 mmol) in THF (3.0 mL) at 0 °C, and stirred for 3 h at room temperature. The reaction was quenched with saturated aqueous NH_4Cl solution at 0 °C and diluted with ether. The organic layer was washed with water and brine, dried with Na_2SO_4 and concentrated. Purification by silica gel column chromatography (eluent; hexane/ethyl acetate, 3:1) gave 32.5 mg of **27** (42%) as colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.47–7.45 (m, 2H), 7.36–7.25 (m, 3H), 5.49 (s, 1H), 4.27 (dd, J = 11.4, 4.9 Hz, 1H), 3.95 (m, 2H), 3.47 (dd, J = 10.3, 5.7 Hz, 1H), 3.36 (dd, J = 10.3, 4.6 Hz, 1H), 3.3–1.3 (br m, 10H), 3.27–3.17 (m, 3H), 3.14 (s, 2H), 1.88 (t, J = 7.0 Hz, 4H), 1.80 (dq, J = 12.5, 7.3 Hz, 1H), 1.44 (m, 6H), 0.83 (t, J = 7.5 Hz, 6H).

4.2.10. 1-[2-(2,4-Dihydroxybutoxy)ethyl]-12-[2-(2-ethyl-2-hydroxylbutoxy)ethyl]-1,12-dicarba-*closo*-dodeca-borane (6)

2 M HCl (1.0 ml) was added to a solution of **27** (30 mg, 0.0590 mmol) in MeOH/THF (2.0 mL), and stirred for 7 days at room temperature. The reaction mixture was diluted with AcOEt The organic layer was washed with water and brine, dried with Na_2SO_4 and concentrated, then purified by silica gel column chromatography (eluent; hexane/ethyl acetate, 3:1) to give 11.9 mg of **6** (44%) as colorless solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.93 (m, 1H), 3.81 (t, J = 5.5 Hz, 2H), 3.31 (dd, J = 9.3, 3.6 Hz, 1H), 3.3–1.3 (br m, 10H), 3.26–3.14 (m, 5H), 3.07 (s, 2H), 1.88 (t, J = 6.6 Hz, 4H), 1.71–1.60 (m, 3H), 1.46 (q, J = 7.7 Hz, 4H), 0.82 (t, J = 7.5 Hz, 6H).

4.2.11. 1-{2-[(2-Phenyl-1,3-dioxan-4-yl)methoxy]ethyl}-12-[2-(3,3-dimethyl-2-oxobutoxy)ethyl]-1,12-dicarba-*closo*-dodecaborane (28)

NaH (22.0 mg, 0.540 mmol) was added to a solution of **28** (200 mg, 0.490 mmol) in DMF (2.0 mL) and stirred for 10 min at 0 °C. Then 1-chloropinacolin (132 mg, 0.980 mmol) was added to the mixture and stirred for 18 h at room temperature. Then the reaction was quenched with water and diluted with AcOEt. The organic layer was washed with water and brine, dried with Na_2SO_4 and concentrated, then purified by silica gel column chromatography (eluent; hexane/ethyl acetate, 4:1) to give 42.2 mg of **28** (17%) as colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.47–7.45 (m, 2H), 7.36–7.30 (m, 3H), 5.48 (s, 1H), 4.27 (dd, J = 5.1, 11.4 Hz, 1H), 4.19 (s, 2H), 3.97–3.88 (m, 2H), 3.46 (dd, J = 5.9, 10.4 Hz, 1H), 3.35 (dd, J = 4.6, 10.3 Hz, 1H), 3.26–3.19 (m, 4H), 1.97–1.79 (m, 6H), 1.12 (s, 9H), 2.80–1.50 (br m, 10H).

4.2.12. 1-[2-(2,4-Dihydroxybutoxy)ethyl]-12-[2-(3,3-dimethyl-2-oxobutoxy)ethyl]-1,12-dicarba-*closo*-dodeca-borane (9)

2 M HCl (1.0 ml) was added to a solution of **28** (39.0 mg, 0.0770 mmol) in MeOH/THF (2.0 mL), and stirred for 7 days at room temperature. The reaction mixture was diluted with AcOEt. The organic layer was washed with water and brine, dried with Na_2SO_4 and concentrated, then purified by silica gel column chromatography (eluent; hexane/ethyl acetate, 3:1) to give 14.2 mg of **9** (44%) as colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.19 (s, 2H), 3.93 (m, 1H), 3.80 (t, J = 6.1 Hz, 2H), 3.30 (dd, J = 3.7, 9.3 Hz, 1H), 3.23–3.17 (m, 5H), 1.94 (t, J = 7.3 Hz, 2H), 1.87 (t, J = 6.8 Hz, 2H), 1.65 (m, 2H), 1.11 (s, 9H), 2.80–1.50 (br m, 10H).

4.2.13. 1-[2-(2,4-Dihydroxybutoxy)ethyl]-12-[2-(3,3-dimethyl-2-hydroxylbutoxy)ethyl]-1,12-dicarba-*closo*-dodecaborane (8)

$LiAlH_4$ (excess) was added to **9** (10.0 mg, 0.024 mmol) in ether (1.0 mL) at 0 °C, and stirred for 3 h at room temperature. The reaction was quenched with saturated aqueous NH_4Cl at 0 °C, and the mixture was diluted with ether. The organic layer was washed with water and brine, dried with Na_2SO_4. Concentration gave 10.1 mg of **8** (quant.) as colorless oil. The two diastereomers could not be separated, and the ratio could not be determined by ^1H NMR. ^1H NMR ($CDCl_3$, 500 MHz) δ 3.94 (m, 1H), 3.81 (t, J = 5.3 Hz, 2H), 3.42–3.30 (m, 3H), 3.26–3.14 (m, 6H), 1.88 (*t*, J = 6.8 Hz, 4H), 1.72–1.62 (m, 2H), 0.88 (s, 9H), 2.80–1.50 (br m, 10H).

4.2.14. 1-Hydroxymethyl-1,12-dicarba-*closo*-dodecaborane (29)

A 1.60 M solution of *n*-BuLi in *n*-hexane (10.4 mL, 16.7 mmol) was added dropwise to a solution of *p*-carborane (2.00 g, 13.9 mmol) in benzene (10 mL) and diethyl ether (5 mL) at 0 °C under Ar. The mixture was stirred at room temperature for 30 min, and paraformaldehyde (620 mg, 20.8 mmol) was added in one portion. After 3 h, the reaction was quenched with 1 M hydrochloric acid and extracted with ethyl acetate. The organic layer was washed successively with saturated aqueous sodium bicarbonate, water and brine, dried over sodium sulfate, and then concentrated. Purification by silica gel column chromatography (eluent: hexane/ethyl acetate, 8:1) gave **29** (66%) as a colorless solid. ^1H NMR ($CDCl_3$, 400 MHz) δ 3.47 (d, J = 7.3 Hz, 2H), 3.5–1.5 (br m, 10H), 2.7 (br s, 1H), 1.55 (t, J = 7.3 Hz, 1H).

4.2.15. 1-Ethoxycarbonylmethoxymethyl-1,12-dicarba-*closo*-dodecaborane (30)

A solution of **29** (4.02 g, 23.1 mmol) in DMF (20 mL) was added to a suspension of NaH (60% in oil, 1.20 g, 30.0 mmol) in DMF (60 mL) at 0 °C and the mixture was stirred at room temperature for 1 h. Ethyl bromoacetate (15.4 g, 92.2 mmol) was added to the mixture and the mixture was heated at 60 °C for 18 h. The solvent was removed under reduced pressure, and the residue was poured into water and extracted with dichloromethane. The organic layer was washed with brine, dried over magnesium sulfate, and then concentrated. Purification by silica gel column chromatography (eluent; hexane/ethyl acetate, 16:1) gave **30** (75%) as colorless oil. ^1H NMR ($CDCl_3$, 400 MHz) δ 4.15 (q, J = 7.2 Hz, 2H), 3.3–1.4 (br m, 10H), 3.94 (s, 2H), 3.41 (s, 2H), 2.69 (s, 1H), 1.24 (t, J = 7.2 Hz, 3H).

4.2.16. 1-(2-Ethyl-2-hydroxylbutoxy)methyl-1,12-dicarba-*closo*-dodecaborane (31)

A 0.89 M solution of EtMgBr (63.9 mL, 56.9 mmol) was added to a solution of **30** (4.49 g, 17.2 mmol) in THF (250 mL) at 0 °C and the mixture was stirred at room temperature for 2 h. The reaction was quenched with saturated aqueous ammonium chloride and extracted with ether. The organic layer was washed with brine, dried over sodium sulfate and then concentrated. Purification by silica gel column chromatography (eluent; hexane/ethyl acetate, 6:1) gave **31** (96%) as colorless oil: ^1H NMR ($CDCl_3$, 400 MHz) δ 3.36 (s, 2H), 3.3–1.3 (br m, 10H), 3.15 (s, 2H), 2.70 (s, 1H), 1.47 (q, J = 7.5 Hz, 4H), 0.83 (t, J = 7.5 Hz, 6H).

4.2.17. 1-(2-Ethyl-2-triethylsilyloxylbutoxy)methyl-1,12-dicarba-*closo*-dodecaborane (32)

Triethylsilyl trifluoromethanesulfonate (2.64 g, 9.99 mmol) and 2,6-lutidine (1.65 g, 15.4 mmol) were added to a solution of **31** (2.11 g, 7.68 mmol) at 0 °C and the mixture was stirred at room temperature for 16 h. The mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate and then concentrated. Purification by silica gel column chromatography (eluent; hexane) gave **32** (46%) as colorless oil; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.3–1.3 (br m, 10H) 3.22 (s, 2H), 3.09 (s, 2H), 1.43 (q, J = 7.5 Hz, 4H), 0.90 (t, J = 8.1 Hz, 9H), 0.78 (t, J = 7.5 Hz, 6H), 0.52 (q, J = 8.1 Hz, 6H).

4.2.18. 1-(2-Benzyloxyethyl)-12-(2-ethyl-2-triethylsilyloxylbutoxy)methyl-1,12-dicarba-*closo*-dodecaborane (33)

Under Ar atmosphere, *n*-BuLi (1.58 M in *n*-hexane, 0.64 mL, 1.00 mmol) was added to a solution of **32** (300 mg, 0.773 mmol) in ether (10 mL) at 0 °C, and stirred for 1 h at room temperature. Then benzyl 2-bromoethyl ether (249 mg, 1.16 mmol) was added to the mixture and stirred for 18 h at room temperature. Then the reaction was quenched with water, and the reaction mixture was diluted with AcOEt. The organic layer was washed with water and brine, dried with Na_2SO_4 and concentrated. Purification by silica gel column chromatography (eluent; hexane/ethyl acetate, 20:1) gave 265 mg (66%) of **33** as colorless oil. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.33–7.25 (m, 5H), 4.37 (s, 2H), 3.3–1.3 (br m, 10H), 3.23 (t, J = 7.1 Hz, 2H), 3.23 (s, 2H), 3.08 (s, 2H), 1.93 (t, J = 7.1 Hz, 2H), 1.42 (q, J = 7.5 Hz, 4H), 0.89 (t, J = 8.1 Hz, 9H), 0.78 (t, J = 7.5 Hz, 6H), 0.51 (q, J = 7.7 Hz, 6H).

4.2.19. 1-(2-Hydroxyethyl)-12-(2-ethyl-2-triethylsilyloxylbutoxy)methyl-1,12-dicarba-*closo*-dodecaborane (34)

Under H_2 atmosphere, 10% Pd/C (30 mg) was added to a solution of **33** (265 mg, 0.509 mmol) in EtOH (6.0 mL), and stirred for 18 h at room temperature. Insoluble materials were filtrated off and the filtrate was concentrated. Purification by silica gel column chromatography (eluent; hexane/ethyl acetate, 6:1) gave 173 mg (79%) of **34** as colorless oil. ^1H NMR ($CDCl_3$, 500 MHz) δ 3.42 (t, J = 7.0 Hz, 2H), 3.24 (s, 2H), 3.08 (s, 2H), 1.88 (t, J = 7.0 Hz, 2H), 1.41 (q, J = 7.5 Hz, 4H), 0.89 (t, J = 8.0 Hz, 9H), 0.77 (t, J = 7.5 Hz, 6H), 0.51 (q, J = 8.0 Hz, 6H), 2.80–1.50 (br m, 10H).

4.2.20. 1-[2-(2,4-Dihydroxybutoxy)ethyl]-12-(2-ethyl-2-hydroxylbutoxy)methyl-1,12-dicarba-*closo*-dodeca-borane (7)

NaH (48.3 mg, 1.20 mmol) was added to a solution of **34** (400 mg, 0.925 mmol) in DMF (2.0 mL) and stirred for 10 min at 0 °C. Then 4-(*p*-toluenesulfonyloxymethyl)-2-phenyl-1,3-dioxane (322 mg, 0.925 mmol) was added to the reaction mixture, and stirred for 1.5 h at room temperature. Then the reaction was quenched with water, and the mixture was diluted with CH_2Cl_2. The organic layer was washed with water and brine, dried with Na_2SO_4 and concentrated. Purification by silica gel column chromatography (eluent; hexane/ethyl acetate, 10:1) gave 135 mg of **35** (24%) as colorless oil. Then 2 M HCl (1.0 mL) was added to a solution of obtained **35** (132 mg, 0.217 mmol) in MeOH/THF (1.0 mL), and stirred for 4 h at room temperature. The reaction mixture was diluted with AcOEt. The organic layer was washed with water and brine, dried with Na_2SO_4 and concentrated. Purification by silica gel column chromatography (eluent; hexane/ethyl acetate, 2:1) gave 29.1 mg of **7** (33%) as colorless oil. ^1H NMR ($CDCl_3$, 400 MHz) δ 3.94 (m, 1H), 3.82 (t, J = 5.5 Hz, 2H), 3.32 (dd, J = 9.3, 3.5 Hz, 1H), 3.3–1.3 (br m, 10H), 3.28 (s, 2H), 3.22 (m, 3H), 3.12 (s, 2H), 2.28 (s, 3H), 1.89 (t, J = 6.8 Hz, 2H), 1.64 (m, 2H), 1.42 (q, J = 7.5 Hz, 4H), 0.80 (t, J = 7.5 Hz, 6H).

4.2.21. 1-(2-Benzyloxyethyl)-12-(5-triethylsilyloxy-5-ethylheptyl)-1,12-dicarba-*closo*-dodecaborane (36)

A 1.6 M solution of *n*-BuLi in n-hexane (4.08 mL, 6.54 mmol) was added to a solution of **18** (1.60 g, 5.75 mmol) in THF (20 mL) at 0 °C, and the mixture was stirred at room temperature for 15 min under Ar. Then, 7-bromo-3-ethyl(3-triethylsilyloxy)-heptane (1.70 g, 5.04 mmol) was added to the mixture at 0 °C, and

stirring was continued at room temperature for 40 h. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, and then concentrated. Purification by silica gel column chromatography (eluent; hexane/ethyl acetate, 100/1 to 20/1) gave **36** (2.60 g, 4.86 mmol, 96%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.31–7.25 (m, 5H), 4.37 (s, 2H), 3.3–1.3 (br m, 10H), 3.23 (t, J = 7.3 Hz, 2H), 1.93 (t, J = 7.3 Hz, 2H), 1.56 (m, 2H), 1.37 (q, J = 7.5 Hz, 4H), 1.25 (m, 3H), 1.07 (m, 4H), 0.90 (t, J = 7.9 Hz, 9H), 0.76 (t, J = 7.3 Hz, 6H), 0.52 (q, J = 7.9 Hz, 6H).

4.2.22. 1-(2-Hydroxyethyl)-12-(5-triethylsilyloxy-5-ethylheptyl)-1,12-dicarba-*closo*-dodecaborane (37)

A mixture of **36** (1.84 g, 3.44 mmol) and 10% palladium on carbon (200 mg) in ethanol (40 mL) was stirred at room temperature for 20 h under atmospheric pressure of hydrogen. Insoluble materials were filtered off through Celite, then the filtrate was concentrated. Purification by silica gel column chromatography (eluent; hexane/ethyl acetate, 8:1) gave **37** (87%) as white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.42 (t, J = 7.1 Hz, 2H), 3.3–1.3 (br m, 10H), 1.87 (t, J = 7.1 Hz, 2H), 1.58 (m, 2H), 1.37 (q, J = 7.7 Hz, 4H), 1.25 (m, 3H), 1.07 (m, 4H), 0.90 (t, J = 7.7 Hz, 9H), 0.76 (t, J = 7.3 Hz, 6H), 0.52 (q, J = 8.1 Hz, 6H).

4.2.23. 1-{2-[2-(2,2-Dimethyl-1,3-dioxolan-4-yl)ethoxy]ethyl}-12-(5-triethylsilyloxy-5-ethylheptyl)-1,12-dicarba-*closo*-dodecaborane (38)

NaH (46.8 mg, 1.17 mmol) was added to a solution of **37** (400 mg, 0.900 mmol) in DMF (2.0 mL) and stirred for 10 min at 0 °C. Then 4-{2-(*p*-toluenesulfonyloxy)ethyl}-2,2-dimethyl-1,3-dioxolane (270 mg, 0.900 mmol) in DMF (2.0 mL) was added to the reaction mixture, and stirred for 18 h at room temperature. Then the reaction was quenched with water, and the reaction mixture was diluted with AcOEt. The organic layer was washed with water and brine, dried with Na_2SO_4 and concentrated. Purification by silica gel column chromatography (eluent; hexane/ethyl acetate, 10:1) gave 277 mg of **38** (54%) as colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.12 (quint, J = 6.1 Hz, 1H), 4.00 (dd, J = 8.1, 5.9 Hz, 1H), 3.49 (t, J = 7.9 Hz, 1H), 3.36 (dd, J = 7.0, 5.5 Hz, 2H), 3.3–1.3 (br m, 10H), 3.13 (t, J = 6.2 Hz, 2H), 1.84 (t, J = 7.0 Hz, 2H), 1.81–1.66 (m, 2H), 1.56 (m, 2H), 1.37 (s, 3H), 1.32 (s, 3H), 1.24 (m, 2H), 1.04 (m, 4H), 0.89 (t, J = 8.1 Hz, 9H), 0.75 (t, J = 7.5 Hz, 6H), 0.50 (q, J = 7.9 Hz, 6H).

4.2.24. 1-[2-(3,4-Dihydroxybutoxy)ethyl]-12-(5-ethyl-5-hydroxyheptyl)-1,12-dicarba-*closo*-dodecaborane (12)

2 M HCl (4.0 mL) was added to a solution of **38** (290 mg, 0.480 mmol) in MeOH/THF (6.0 mL), and the mixture was stirred for 18 h at room temperature. The mixture was diluted with AcOEt, and then the organic layer was washed with water and brine, dried with Na_2SO_4 and concentrated. Purification by silica gel column chromatography (eluent; hexane/ethyl acetate, 2:1) gave 163 mg of **12** (81%) as colorless solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.84 (m, 1H), 3.59 (dd, J = 11.2, 3.5 Hz, 1H), 3.50 (m, 2H), 3.46 (dd, J = 11.2, 4.8 Hz, 1H), 3.3–1.3 (br m, 10H), 3.18 (m, 2H), 1.87 (t, J = 7.1 Hz, 2H), 1.78–1.57 (m, 4H), 1.38 (q, J = 7.5 Hz, 4H), 1.27 (m, 2H), 1.09 (m, 4H), 0.80 (t, J = 7.3 Hz, 6H).

4.2.25. 1-(3-Hydroxypropyl)-1,12-dicarba-*closo*-dodecaborane (39)

A 1.57 M solution of *n*-BuLi in *n*-hexane (24.3 mL, 38.1 mmol) was added to a solution of *p*-carborane (5.00 g, 34.7 mmol) in ether (120 mL) at 0 °C, and the mixture was stirred at room temperature for 1 h. Then trimethylene oxide (2.21 g, 38.1 mmol) was added to the mixture and stirring was continued at room temperature for 16 h. The reaction mixture was poured into water and extracted with ether. The organic layer was washed with brine, dried over magnesium sulfate, and then concentrated. Purification by silica gel column chromatography (eluent; hexane/ethyl acetate, 8:1) gave **39** (36%) as white wax. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.45 (t, J = 6.3 Hz, 2H), 3.0–1.4 (br m, 10H), 2.75 (s, 1H), 1.72–1.68 (m, 2H), 1.44–1.36 (m, 2H).

4.2.26. 1-{3-[(2-Phenyl-1,3-dioxan-4-yl)methoxy]propyl}-1,12-dicarba-*closo*-dodecaborane (40)

NaH (60% in oil, 46.8 mg, 1.17 mmol) was added to a solution of **39** (500 mg, 2.47 mmol) in DMF (4.0 mL) and stirred for 1.0 h at room temperature. Then 4-(*p*-toluenesulfonyloxymethyl)-2-phenyl-1,3-dioxane (861 mg, 2.47 mmol) in DMF (4.0 mL) was added to the reaction mixture, and stirred for 20 h at room temperature. Then the reaction was quenched with water, and the reaction mixture was diluted with AcOEt. The organic layer was washed with water and brine, dried with Na_2SO_4 and concentrated. Purification by silica gel column chromatography (eluent; hexane/ethyl acetate, 10:1) gave **38** (22%) as colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.46–7.44 (m, 2H), 7.35–7.30 (m, 3H), 5.49 (s, 1H), 4.27 (dd, J = 11.5, 5.1 Hz, 1H), 4.01–3.92 (m, 2H), 3.49 (dd, J = 10.4, 5.9 Hz, 1H), 3.38 (dd, J = 10.4, 4.8 Hz, 1H), 3.3–1.3 (br m, 10H), 3.31 (t, J = 6.2 Hz, 2H), 2.61 (s, 1H), 1.80 (dq, J = 12.8, 5.3 Hz, 1H), 1.71–1.67 (m, 2H), 1.48–1.38 (m, 3H).

4.2.27. 1-{3-[(2-Phenyl-1,3-dioxan-4-yl)methoxy]propyl}-12-(5-triethylsilyloxy-5-ethylheptyl)-1,12-dicarba-*closo*-dodecaborane (41)

Under Ar atmosphere, *n*-BuLi (1.57 M in *n*-hexane, 0.71 mL, 1.12 mmol) was added to a solution of **18** (326 mg, 0.86 mmol) in ether (8.0 mL) at 0 °C, and stirred for 30 min at room temperature. Then 7-bromo-3-ethyl-3-triethylsilyloxyheptane (786 mg, 2.33 mmol) was added to the reaction mixture and stirred for 16 h at room temperature. Then the reaction was quenched with water, and the mixture was diluted with AcOEt. The organic layer was washed with water and brine, dried with Na_2SO_4 and concentrated. Purification by silica gel column chromatography (eluent; hexane/ethyl acetate, 20:1) gave 452 mg of **36** (48%) as colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.46–7.44 (m, 2H), 7.36–7.30 (m, 3H), 5.49 (s, 1H), 4.27 (dd, J = 11.4, 4.0 Hz, 1H), 4.02–3.95 (m, 1H), 3.95 (dt, J = 11.9, 2.4 Hz, 1H), 3.49 (dd, J = 10.4, 6.1 Hz, 1H), 3.37 (dd, J = 10.3, 4.8 Hz, 1H), 3.30 (t, 6.2 Hz, 2H), 1.80 (dq, 12.6, 5.1 Hz, 1H), 3.3–1.3 (br m, 10H), 1.59–1.40 (m, 7H), 1.36 (q, J = 7.5 Hz, 4H), 1.27–1.23 (m, 2H), 1.07–1.05 (m, 4H), 0.90 (t, J = 7.7 Hz, 9H), 0.76 (t, J = 7.3 Hz, 6H), 0.52 (q, J = 7.7 Hz, 6H).

4.2.28. 1-[3-(2,4-Dihydroxybutoxy)propyl]-12-(5-ethyl-5-hydroxyheptyl)-1,12-dicarba-*closo*-dodecaborane (14)

2 M HCl (3.0 mL) was added to a solution of **41** (317 mg, 0.499 mmol) in MeOH/THF (12 mL), and the mixture was stirred for 4 h at room temperature. The mixture was diluted with AcOEt, and then the organic layer was washed with water and brine, dried with Na_2SO_4 and concentrated. Purification by silica gel column chromatography (eluent; hexane/ethyl acetate, 1:1) gave 116 mg of **14** (54%) as colorless solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.94 (s, 1H), 3.80 (q, J = 5.7 Hz, 2H), 3.34–3.20 (m, 4H), 3.3–1.3 (br m, 10H), 2.60 (d, J = 3.1 Hz, 1H), 2.36 (t, J = 3.1 Hz, 1H), 1.68–1.57 (m, 6H), 1.45–1.35 (m, 2H), 1.38 (q, J = 7.5 Hz, 4H), 1.29–1.24 (m, 2H), 1.10–1.09 (m, 4H), 1.00 (s, 1H), 0.80 (t, J = 7.7 Hz, 6H).

4.3. Biology

4.3.1. Assay of HL-60 cell differentiation-inducing activity

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 cell/mL with RPMI-1640

(5% FBS), and ethanol solution of a test compound was added to give 10^{-9} to 10^{-6} M final concentration. Control cells were treated with the same volume of ethanol alone. 1α,25(OH)$_2$D$_3$ was always assayed at the same time as a positive control. The cells were incubated at 37 °C under 5% CO_2 in air for 4 days. The percentage of differentiated cells was determined by 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). The percentage of cells containing blue-black formazan was determined in a minimum of 200 cells.

References and notes

1. (a) Evans, R. M. *Science* **1988**, *240*, 889; (b) Mangelsdorf, D. J.; Thummel, C.; Beato, M.; Herrlich, P.; Schütz, G.; Umesono, K.; Blumberg, B.; Kastner, P.; Mark, M.; Chambon, P.; Evans, R. M. *Cell* **1995**, *83*, 835.
2. *Vitamin D*; Feldman, D., Pike, J. W., Glorieux, F. H., Eds.; Elsevier Academic Press: New York, 2005. 2nd ed..
3. Kubodera, N. Development of OCT and ED-71. In *Vitamin D*; Feldman, D., Pike, J. W., Glorieux, F. H., Eds.; Elsevier Academic Press: New York, 2005; p 1525. 2nd ed..
4. (a) Boehm, M. F.; Fitzgerald, P.; Zou, A.; Elgort, M. G.; Bischoff, E. D.; Mere, L.; Mais, D. E.; Bissonnette, R. P.; Heyman, R. A.; Nadzan, A. M.; Reichman, M.; Allegretto, E. A. *Chem. Biol.* **1999**, *6*, 265; (b) Hosoda, S.; Tanatani, A.; Wakabayashi, K.; Makishima, M.; Imai, K.; Miyachi, H.; Hashimoto, Y. *Bioorg. Med. Chem.* **2006**, *14*, 5489.
5. Fujii, S.; Masuno, H.; Taoda, Y.; Kano, A.; Wongmayura, A.; Nakabayashi, M.; Ito, N.; Shimizu, M.; Kawachi, E.; Hirano, T.; Endo, Y.; Tanatani, A.; Kagechika, H. *J. Am. Chem. Soc.* **2011**, *133*, 20933.
6. Wongmayura, A.; Fujii, S.; Ito, S.; Kano, A.; Taoda, Y.; Kawachi, E.; Kagechika, H.; Tanatani, A. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 1756–1760.
7. *Carboranes*; Grimes, R. N., Ed., 2nd ed.; Academic Press: Elsevier, 2011.
8. For reviews of carboranes: (a) Bregadze, V. I. *Chem. Rev.* **1992**, *92*, 209; (b) Hawthorne, M. F. *Angew. Chem., Int. Ed.* **1993**, *32*, 950; (c) Soloway, A. H.; Tjarks, W.; Barnum, J. G. *Chem. Rev.* **1998**, *98*, 1515.
9. (a) Fujii, S.; Goto, T.; Ohta, K.; Hashimoto, Y.; Suzuki, T.; Ohta, S.; Endo, Y. *J. Med. Chem.* **2005**, *48*, 4654; (b) Fujii, S.; Yamada, A.; Tomita, K.; Nagano, M.; Goto, T.; Ohta, K.; Harayama, T.; Endo, Y.; Kagechika, H. *Med. Chem. Commun.* **2011**, *2*, 877; (c) Endo, Y.; Iijima, T.; Yamakoshi, Y.; Yamaguchi, M.; Fukasawa, H.; Shudo, K. *J. Med. Chem.* **1999**, *42*, 1501; (d) Endo, Y.; Iijima, T.; Yamakoshi, Y.; Fukasawa, H.; Miyaura, C.; Inada, M.; Kubo, A.; Itai, A. *Chem. Biol.* **2001**, *8*, 341; (e) Iijima, T.; Endo, Y.; Tsuji, M.; Kawachi, E.; Kagechika, H.; Shudo, K. *Chem. Pharm. Bull.* **1999**, *47*, 398; (f) Ohta, K.; Iijima, T.; Kawachi, E.; Kagechika, H.; Endo, Y. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5913.
10. Review of reactions of carboranes Kaszynski, P. *Collect. Czech. Chem. Commun.* **1999**, *64*, 895.
11. Mangelsdorf, D. J.; Koeffler, H. P.; Donaldson, C. A.; Pike, J. W.; Haussler, M. R. *J. Cell Biol.* **1984**, *98*, 391.
12. (a) Yamada, S.; Yamamoto, K.; Masuno, H.; Ohta, M. *J. Med. Chem.* **1998**, *41*, 1467; (b) Sussman, F.; Rumbo, A.; Villaverde, M. C.; Mouriño, A. *J. Med. Chem.* **2004**, *47*, 1613.