Bioorganic & Medicinal Chemistry 22 (2014) 5891–5901

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

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

Structural development of *p*-carborane-based potent non-secosteroidal vitamin D analogs

Shinya Fujii [a,b], Ryota Sekine [a], Atsushi Kano [a], Hiroyuki Masuno [a], Chalermkiat Songkram [c], Emiko Kawachi [a], Tomoya Hirano [a], Aya Tanatani [d], 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] Department of Chemistry, Faculty of Science, Ochanomizu University, 2-1-1 Otsuka, Bunkyo-ku, Tokyo 112-8610, Japan

ARTICLE INFO

Article history:
Received 30 July 2014
Revised 8 September 2014
Accepted 9 September 2014
Available online 16 September 2014

Keywords:
Vitamin D
Nuclear receptor
Carborane
Non-secosteroid

ABSTRACT

Non-secosteroidal vitamin D receptor (VDR) ligands are promising candidates for many clinical applications. We recently developed novel non-secosteroidal VDR agonists based on *p*-carborane (an icosahedral carbon-containing boron cluster) as a hydrophobic core structure. Here, we report the design, synthesis and biological evaluation of carborane-based vitamin D analogs bearing various substituents at the diol moiety. Among the synthesized compounds, methylene derivative **31** exhibited the most potent vitamin D activity, which was comparable to that of the natural hormone, 1α,25$(OH)_2D_3$. This compound is one of the most potent non-secosteroidal VDR agonists reported to date, and is a promising lead for development of novel drug candidates.

© 2014 Elsevier Ltd. All rights reserved.

1. Introduction

Vitamin D receptor (VDR), a ligand-inducible nuclear receptor for vitamin D,[1,2] plays important roles in many physiological processes, including calcium and phosphate homeostasis, bone metabolism, and immune regulation.[3] VDR is activated by binding of its endogenous agonist, 1α,25-dihydroxyvitamin D_3 [1α,25$(OH)_2D_3$: **1**] (Fig. 1), and regulates expression of specific target genes. Since VDR is involved in the pathogenesis of various diseases, many VDR ligands have been developed as candidate therapeutic agents, for example, for osteoporosis, arthritis, psoriasis and cancers. Thousands of 1α,25$(OH)_2D_3$ analogs have been synthesized, and the structure–activity relationships of secosteroidal compounds have been examined in detail. On the other hand, development of non-secosteroidal VDR ligands remains quite limited, and only a few non-secosteroidal VDR ligands exhibiting potent activity have been reported so far, even though they are anticipated to have fewer side effects than secosteroidal ligands.[4,5]

We have recently developed novel non-secosteroidal VDR ligands, such as compound **3**, bearing a *p*-carborane cage as the hydrophobic pharmacophore.[6–8] *p*-Carborane is a member of the class of polyhedral carbon-containing boron clusters with unique characteristics, such as highly symmetrical icosahedral structure, remarkable chemical and thermal stability, and high hydrophobicity.[9–11] Though the structure of **3** is quite different from that of the natural hormone, 1α,25$(OH)_2D_3$ (**1**), X-ray crystallographic analysis revealed that **3** induces the active conformation of VDR in a similar manner to 1α,25$(OH)_2D_3$ (**1**).[6] X-ray analysis also revealed that the two hydroxyl groups of the 1,3-diol substructure of **3** form hydrogen bonds to VDR similar to those of the 1α- and 3-hydroxyl groups of 1α,25$(OH)_2D_3$, and the tertiary hydroxyl group of **3** also forms hydrogen bonds like the 25-hydroxyl group of 1α,25$(OH)_2D_3$ (**1**, Fig. 2). These findings indicate that compound **3** functions as VDR ligand in a similar manner to 1α,25$(OH)_2D_3$ (**1**). Thus, we considered that structural modifications that potentiate the activity of secosteroidal VDR ligands could be also effective in carborane-based non-secosteroidal VDR ligands. We recently reported the development of tetraol-type vitamin D analogs such as **4** based on this idea.[12] Introduction of a ω-hydroxyalkoxy substituent into secosteroidal derivatives enhances the vitamin D potency, and we found that **4** exhibited potent activity equal to that of secosteroidal derivative **2**. Herein we report further structural development of carborane-based non-secosteroidal VDR ligands bearing various substituents at the 1,3-diol moiety, based on the structure of the complex of **3** with VDR.

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

http://dx.doi.org/10.1016/j.bmc.2014.09.020
0968-0896/© 2014 Elsevier Ltd. All rights reserved.

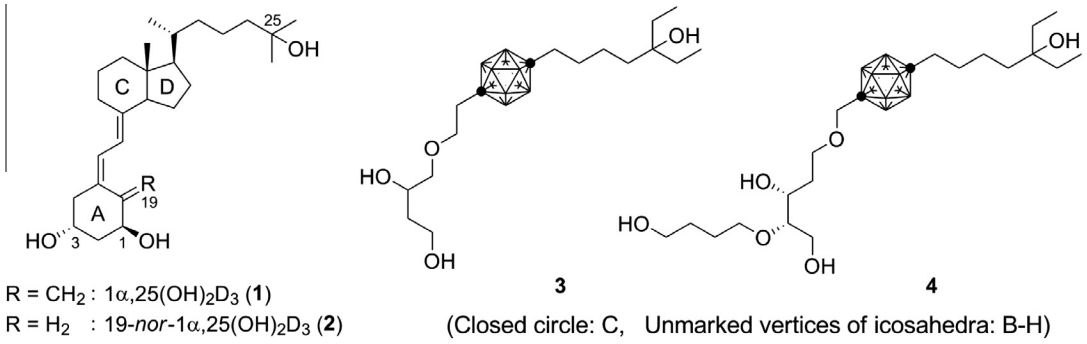


Figure 1. Structures of natural hormone, $1\alpha,25(OH)_2D_3$ (**1**), 19-nor derivative **2**, and our developed non-secosteroidal VDR ligands **3** and **4**. In carborane structures, closed circles indicate carbon atoms and other vertices of the icosahedra are B–H. Stereochemistry of **4** indicates relative configuration.

2. Results and discussion

2.1. Molecular design

Structure–activity relationship studies of secosteroidal VDR ligands revealed that introduction of a small hydrophobic substituent such as a methyl or methylene group at the 2-position enhances the ligand potency (Fig. 3).[13–16] Crystallographic analysis of the VDR ligand-binding domain (LBD) complexed with **3** revealed that there is a small hydrophobic pocket near the 1,3-diol moiety of **3** (Fig. 4a).[6] Therefore we designed compounds bearing various small substituents (R in Fig. 4b) at the carbon atom corresponding to the 2-position of secosteroid. The selected substituents were methyl, methylene, cyclopropyl and methoxy groups. The 1,3-diol substructures bearing these substituents were connected to the hydrophobic *p*-carborane cage by an ether tethering structure (Fig. 4b).

2.2. Synthesis

The substituted 1,3-diol substructures were prepared in the form of 4-(2-toluenesulfonyloxyethyl)-1,3-dioxanes (Scheme 1). The diol structure of tris(hydroxymethyl)aminomethane (**7**) was protected with acetonide and the 1,2-aminoalcohol moiety was oxidized to afford 1,3-dioxane **8**.[17] A 2-hydroxyethyl functionality

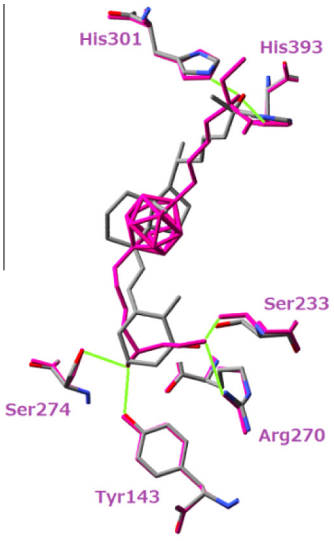


Figure 2. Superimposition of the structures of secosteroid $1\alpha,25(OH)_2D_3$ (**1**) in gray (PDBID: 1RK3), and carborane derivative (*S*)-**3** in purple (PDBID: 3VJS) in the complex with rat VDR ligand-binding domain (LBD).

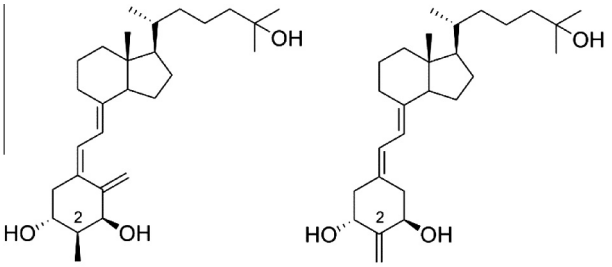


Figure 3. Structures of potent VDR ligands **5** and **6** bearing a small hydrophobic substituent at the location corresponding to the 2-position of secosteroid.

was introduced via the enamine form of **8** to give **9**.[17] The carbonyl group of **9** was converted into a methylene group using Wittig reaction to afford olefin **10**, and then the TBS group of **10** was converted to a tosyl group to give the desired 1,3-diol synthon **11**. Methylated 1,3-diol substructure was also prepared from olefin **10**. Catalytic hydrogenation of **10** gave *trans*- and *cis*-methyl compounds as a diastereo mixture, then the TBS group was removed under acidic conditions and diastereomers **12** and **13** were separated into racemic mixture. The relative configurations of compounds **12** and **13** were determined from the ^1H NMR coupling constants.[18] The primary alcohol **12** with *trans*-configuration was converted to tosylate **14** by means of a standard protocol. On the other hand, tosylation of *cis* compound **13** gave a complex mixture, because the relatively unstable acetonide with *cis*-configuration could be cleaved under the conditions of tosylation. Cyclopropyl derivative **15** was synthesized from olefin **10** using diazomethane, and the silyl ether of **15** was converted to tosylate to give **16**. Compounds **23** and **24** were synthesized as reported previously.[12] Briefly, ketone **9** was reduced with sodium borohydride to give alcohols **17** and **18**. The hydroxyl group of each compound was protected with a benzyl group to afford **19** and **20**, and the silyl ether was converted to tosylate to give **23** and **24**, respectively (Scheme 1).

The hydrophobic core with a side chain moiety was prepared from *p*-carborane **25**.[19] Reaction between C-lithiated *p*-carborane and paraformaldehyde gave alcohol **26**, and protection of the hydroxyl group with a benzyl group gave **27**. The 5-hydroxypentyl substructure corresponding to the side chain moiety of $1\alpha,25(OH)_2D_3$ (**1**) was introduced, and removal of the benzyl group of **28** afforded key intermediate **29**. Connection between **29** and diol moiety **11** bearing an *exo*-methylene group gave **30**, and removal of protecting groups afforded the desired compound **31**. Compound **33** was similarly synthesized from tosylate **14**. Since the tosylate of **13** could not be obtained, compound **30** was

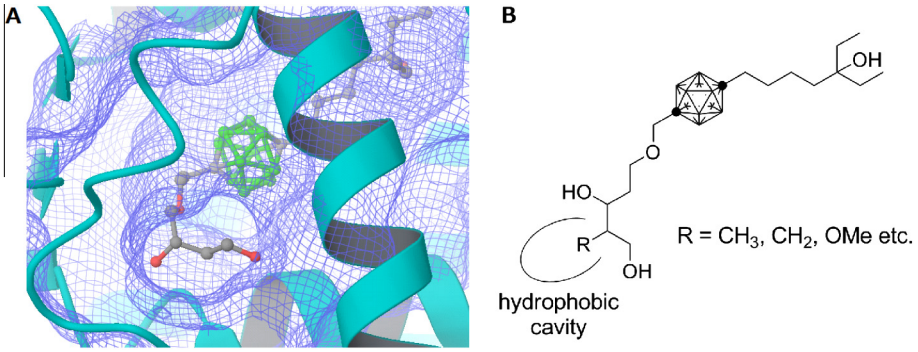
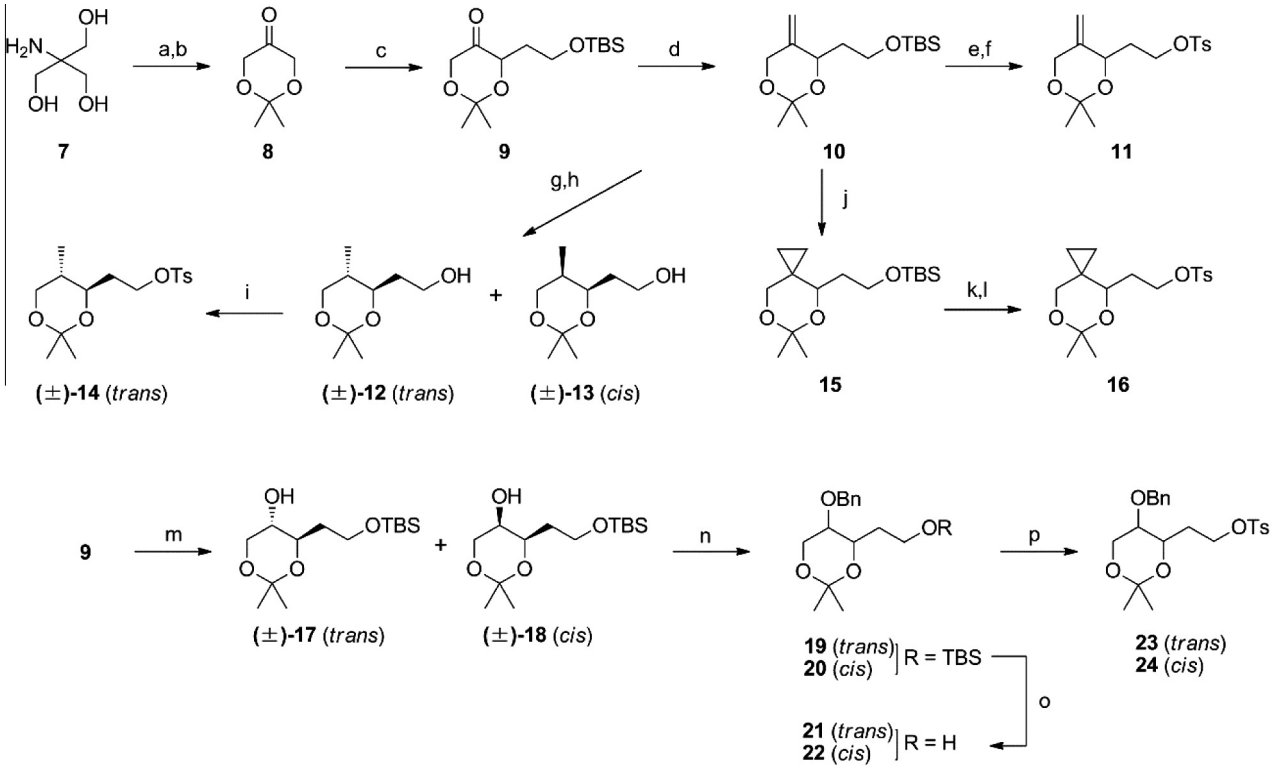


Figure 4. (A) A hydrophobic cavity near the 1,3-diol moiety of **3** in the crystal structure of the complex of **3** with rat VDR LBD. The protein surface is indicated by a light blue mesh. (B) Design scheme of novel carborane-based VDR ligands.



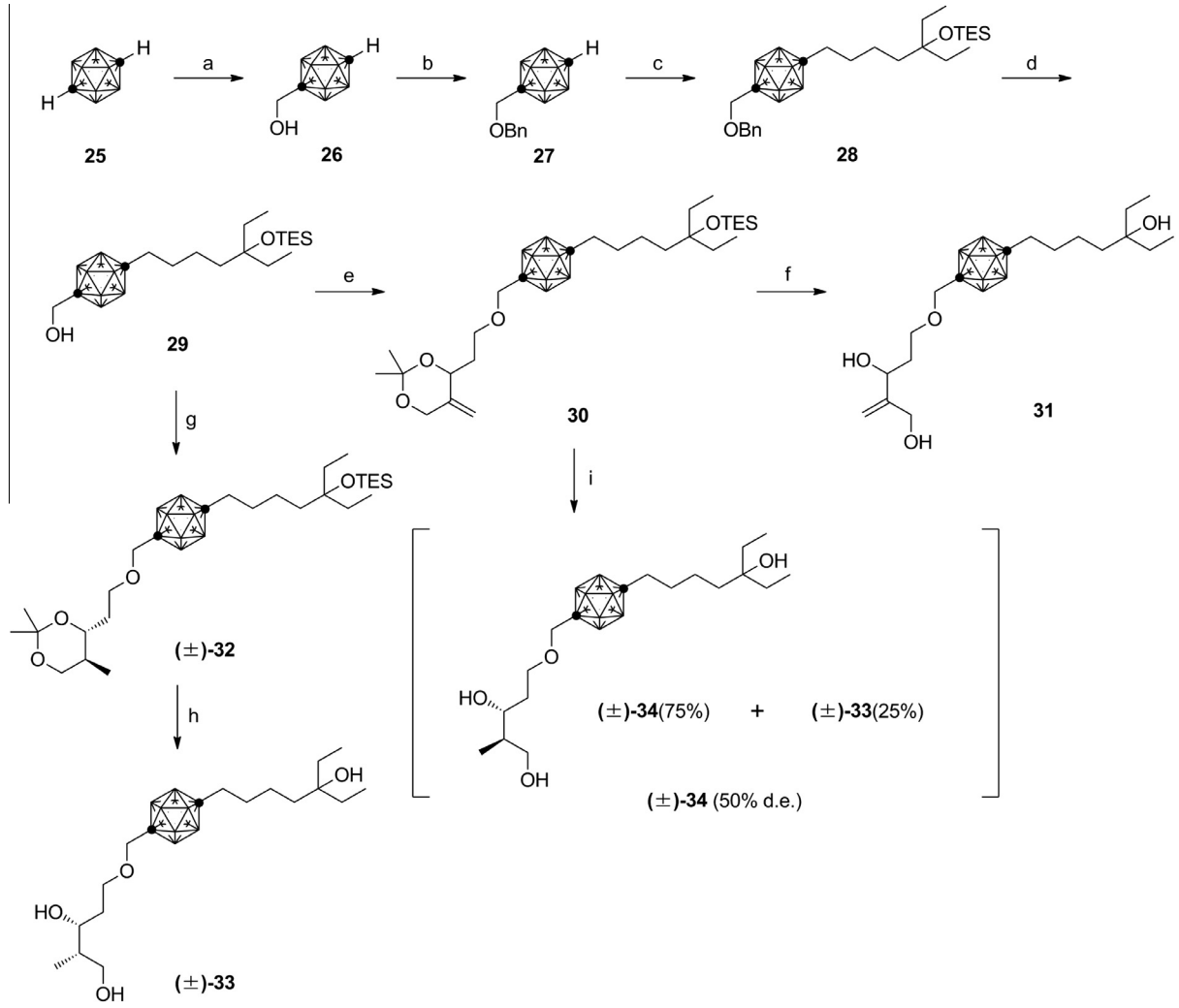
Scheme 1. Synthesis of the precursors for the diol moieties. Reagents and conditions: (a) 2,2-dimethoxypropane, TsOH–H_2O, DMF, rt, 78%; (b) $NaIO_4$, H_2O, rt, 91%; (c) (i) cyclohexyamine, benzene, rt; (ii) LDA, ICH_2CH_2OTBS, −78 °C, 40%; (d) CH_3PPh_3Br, *n*-BuLi, THF, rt, 70%; (e) TBAF, THF, rt, 69%; (f) TsCl, pyridine, DCM, rt, 50%; (g) H_2, Pd/C, MeOH, rt; (h) TBAF, THF, rt, 31% (**12**), 37% (**13**); (i) TsCl, pyridine, DCM, 41%; (j) CH_2N_2, $Pd(OAc)_2$, diethyl ether, rt, 60%; (k) TBAF, THF, rt, 70%; (l) TsCl, pyridine, DCM, 22%; (m) $NaBH_4$, MeOH, rt, 52% (**17**), 30% (**18**); (n) NaH, BnBr, DMF, rt, quant. (**19**), 87% (**20**); (o) TBAF, THF, rt, 86% (**21**) 94% (**22**); (p) TsCl, DMAP, DCM, rt, quant. (**23**), 73% (**24**).

hydrogenated with Pd/C in methanol to afford a diastereo mixture of deprotected **33** and **34** (**33**:**34** = 1:2). Although the diasteromers of **33** and **34** could not be separated, we used the mixture with 50% diasteromeric excess of **34** for biological evaluation in order to investigate the difference of potency of the diastereomers by means of comparison with pure compound **33**.

Scheme 3 shows synthesis of the cyclopropyl, hydroxyl and methoxy derivatives. Cyclopropane derivative **36** was synthesized in the same manner as described for **31** (shown in Scheme 2). Hydroxyl and methoxy derivatives were synthesized using diol fragments **23** or **24**. Connection between **29** and diol moieties bearing *trans* **23** or *cis*-configuration **24** gave compound **37** or **38**, respectively. Removal of the benzyl group of **37** and **38** afforded alcohols **39** and **40**, and then methylation afforded **41** and **42**, respectively. Finally, removal of the protecting groups afforded the desired compounds **43**–**46** as racemic mixtures.

2.3. Biological evaluation

Vitamin D activity of synthesized *p*-carborane derivatives was evaluated in terms of cell differentiation-inducing activity toward human acute promyelocytic leukemia cell line HL-60.[20] Table 1 summarizes the potency of the carborane derivatives. As we previously reported, compound **3** exhibited significant vitamin D activity, being approximately one-tenth as potent as 1α,25$(OH)_2D_3$ (**1**), and compound **47**,[8] an isomer of **3** and the parent compound for structural development in this study, exhibited slightly weaker activity than **3**. All the synthesized *p*-carborane derivatives bearing substituents at the 1,3-diol moiety exhibited vitamin D activity. Among the tested compounds, methylene derivative **31** exhibited the most potent vitamin D activity with an EC_{50} value of 6.1 nM, which is comparable to that of 1α,25$(OH)_2D_3$ (**1**). Introduction of a methylene group enhanced the potency by one order of magnitude.



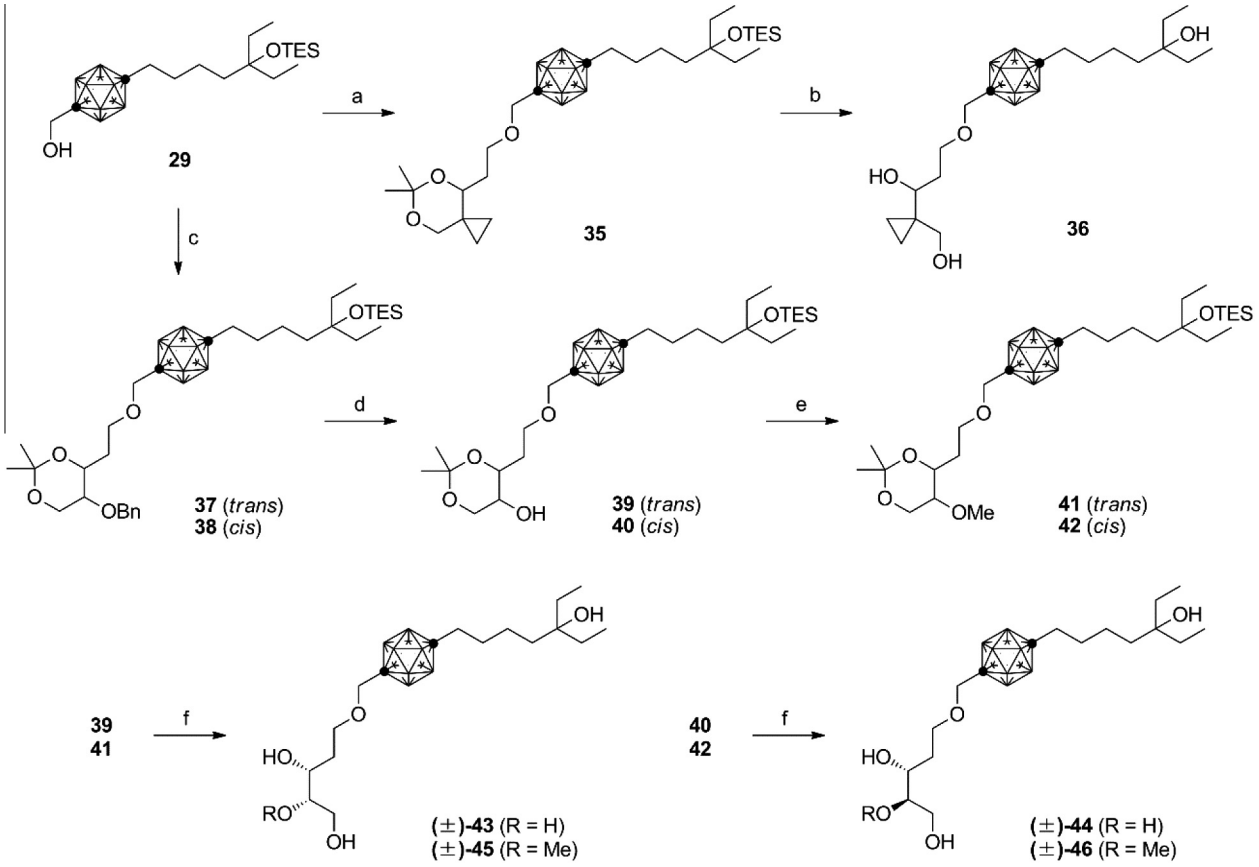
Scheme 2. Synthesis of carborane-based vitamin D analogs bearing methylene or methyl groups. Reagents and conditions: (a) *n*-BuLi, paraformaldehyde, benzene, rt, 66%; (b) NaH, BnBr, DMF, rt, quant.; (c) *n*-BuLi, $Br(CH_2)_4C(Et)_2OTES$, THF, rt, 82%; (d) H_2, $Pd(OH)_2/C$, MeOH, rt, quant.; (e) NaH, **11**, DMF, rt, 44%; (f) HCl, MeOH, THF, H_2O, rt, 77%; (g) NaH, **14**, DMF, rt, 52%; (h) HCl, MeOH, THF, H_2O, rt, 91%; (i) H_2, Pd/C, MeOH, 60%.

Activities of the methyl, methoxy and cyclopropane derivatives were higher than or equal to that of unsubstituted compound **47**. As recently reported, 1,2,3-triol derivatives **43** and **44** exhibited activity equal to or less potent than that of **47**. Methoxy derivative **45** exhibited potent activity with an EC_{50} value of 8.4 nM. Regarding the difference of potency between diastereomers, compounds derived from 1,3-dioxanes with *trans*-configuration, that is, compounds **33**, **43** and **45**, exhibited higher potency than the corresponding compounds **34**, **44** and **46** derived from 1,3-dioxanes with *cis*-configuration.

2.4. Discussion

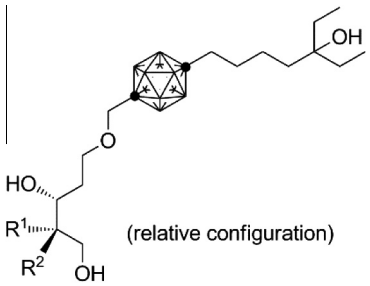
Based on the structure of the VDR LBD complex with carborane derivative **3**, we designed and synthesized novel carborane derivatives bearing substituents at the carbon atom corresponding to the 2-position of $1\alpha,25(OH)_2D_3$ (**1**). Methylene derivative **31**, methyl derivatives **33** and **34**, and methoxy derivatives **45** and **46** exhibited higher activity than the parent compound **47**, whereas compound **36** bearing a cyclopropane moiety exhibited activity equal to that of **47**. These results suggest that introduction of a small aprotic substituent is favorable for vitamin D activity of carborane derivatives, while introduction of two geminal substituents is not effective. In the case of secosteroidal vitamin D_3 derivatives, structure–activity relationship studies revealed that removal of the 19-methylene group of $1\alpha,25(OH)_2D_3$ (**1**), yielding 19-*nor*-$1\alpha,25(OH)_2D_3$ (**2**, Fig. 1), reduced the vitamin D activity by one order of magnitude,[21] whereas 2-methylene-19-*nor*-$1\alpha,25(OH)_2D_3$ (2MD: **5**, Fig. 3) exhibited potent vitamin D activity equal to that of $1\alpha,25(OH)_2D_3$ (**1**).[7] X-ray analysis of the VDR LBD complexed with **5** revealed that the methylene group at the 2-position enhanced hydrophobic and van der Waals (vdW) interactions with VDR at the cavity formed by Tyr143 and Phe150.[22] In the case of carborane-based VDR ligands that lack the interaction at the positions corresponding to C10 and C19 of $1\alpha,25(OH)_2D_3$ (**1**), hydrophobic and vdW interactions involving the methylene group could compensate for the loss, and this may be the reason why compound **31** shows potent activity comparable to that of $1\alpha,25(OH)_2D_3$ (**1**), despite the flexible nature of acyclic alkyl or alkoxy chains.

Structure–activity relationship study of the diastereomers revealed that the configuration of the substituent (R^1 or R^2 in Table 1) significantly affected the activity of these compounds. In the case of secosteroid-type derivatives, the stereochemistry of the substituent at the 2-position markedly influenced the activity, owing to not only increase of hydrophobic interaction, but also change of the conformational equilibrium of the A ring. The importance of the stereochemistry of substituents was also observed during structural development of tetraol derivatives, including



Scheme 3. Synthesis of carborane-based vitamin D analogs bearing cyclopropyl, hydroxyl or methoxy group. Reagents and conditions: (a) NaH, **16**, DMF, rt, 38%; (b) HCl, MeOH, THF, H_2O, rt, 53%; (c) NaH, **23** or **24**, DMF, rt, 98% (**37** using **23**), 90% (**38** using **24**); (d) H_2, $Pd(OH)_2/C$, MeOH, rt, 90% (**39**), 89% (**40**); NaH, MeI, DMF, rt, 89% (**41**), 97% (**42**); (f) HCl, MeOH, THF, H_2O, rt, 88% (**43**), 93% (**45**), 88% (**44**), 95% (**46**).

Table 1
HL-60 cell differentiation-inducing potency of *p*-carborane-based vitamin D analogs



Compound	R^1	R^2	EC_{50}[a] (nM)
$1\alpha,25(OH)_2D_3$	—		4.4
3	—		47
31	$=CH_2$		6.1
33	$-CH_3$	—H	27
34[b]	—H	$-CH_3$	53
36	$-CH_2-CH_2-$		78
43	—OH	—H	63
44	—H	—OH	200
45	$-OCH_3$	—H	8.4
46	—H	$-OCH_3$	34
47	—H	—H	74

[a] The EC_{50} value was calculated as the concentration of each compound exhibiting 50% of the activity of 10^{-7} M $1\alpha,25(OH)_2D_3$ (**1**). HL-60 cell differentiation was determined by measuring the ratio of nitroblue tetrazolium (NBT)-positive cells in the concentration range of 10^{-10} M to 10^{-6} M test compound.

[b] Compound **34** was prepared as a mixture with diastereomer **33**, with a diastereomeric excess of 50% (see Scheme 2).

4.[6] Though the 1,3-diol substructure of the carborane-based VDR ligands is quite flexible in comparison to the A ring, the conformation of the diol moiety could be affected by substituents introduced at the central carbon atom of the 1,3-diol moiety. The present studies were performed with racemic mixtures, and further investigations of the relationship between stereochemistry and activity are in progress.

3. Conclusion

We investigated structural development of non-secosteroidal vitamin D analogs containing a hydrophobic carborane cage by focusing on the diol moiety. Introduction of a small substituent at a carbon atom of **47** corresponding to the 2-position of $1\alpha,25(OH)_2D_3$ (**1**) increased the vitamin D potency, and the highly potent non-secosteroidal vitamin D analog **31** was developed. This compound is one of the most potent non-secosteroidal VDR ligands so far developed. These compounds and their SAR information should be helpful in the development of new-generation VDR ligands.

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. ^1H NMR spectra were

recorded on at 600 MHz on a BRUCKER AVANCE 600 spectrometer or at 500 MHz on a BRUCKER AVANCE 500 spectrometer or at 400 MHz on a BRUCKER AVANCE 400 spectrometer. ^{13}C NMR spectra were recorded on at 125 MHz on a BRUCKER AVANCE 500 spectrometer. Chemical shifts are reported in ppm as δ values from tetramethylsilane. Data are reported as follows: chemical shift, multiplicity (s, singlet; d, doublet; t, triplet; q quartet; br, broad; and m, multiplet), coupling constants (Hz), and integration. Mass spectra were collected on a Bruker Daltonics micrO TOF focus-II in the positive ion modes.

4.2. Synthesis

4.2.1. 2,2-Dimethyl-1,3-dioxane-5-one (8)

2,2-Dimethoxypropane (21.5 mL, 175 mmol) and *p*-toluenesulfonic acid monohydrate (1.58 g, 7.93 mmol) were added to a solution of tris(hydroxylmethyl)aminomethane (25.2 g, 159 mmol) in DMF (180 mL), and the mixture was stirred at room temperature for 22 h. The mixture was diluted with ethyl acetate, and then triethylamine was further added. The solvent was removed under reduced pressure, then the crude product was purified with silica gel column chromatography (eluent; *n*-hexane/ethyl acetate; 5:1) to give 2,2-dimethyl-5-amino-5-hydroxymethyl-1,3-dioxaone (20.9 g, 78%) as colorless solid. 2,2-Dimethyl-5-amino-5-hydroxymethyl-1,3-dioxaone: ^1H NMR (400 MHz, $CDCl_3$) δ 3.80 (d, J = 12.0 Hz, 2H), 3.60 (d, J = 12.0 Hz, 2H), 3.53 (s, 2H), 2.61 (s, 2H), 1.45 (s, 3H), 1.41 (s, 3H). The obtained intermediate (10.2 g, 62.1 mmol) was dissolved in water (60 mL), and KH_2PO_4 (8.51 g, 621 mmol) was added to the solution. Then aqueous solution of $NaIO_4$ (0.5 M, 125 mL, 63 mmol) was added dropwise during 3 h at 0 °C and then stirred for 1 h at room temperature. The mixture was extracted with dichloromethane and the organic layer was washed with 5% aqueous sodium thiosulfate and brine and dried with Na_2SO_4. The solvent was removed under reduced pressure to give compound **8** (7.35 g, 91%) as colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 4.15 (s, 4H), 1.45 (s, 6H).

4.2.2. 4-(2-*t*-Butyldimethylsilyloxyethyl)-2,2-dimethyl-1,3-dioxane-5-one (9)

Cyclohexylamine (2.70 mL, 23.1 mmol) was added to a mixture of compound **8** (1.54 g, 11.5 mmol) and molecular sieves 4 A (4.0 g) in benzene (50 mL) at 0 °C and then stirred for 1 h at room temperature. Insoluble materials were filtered off through Celite, then the filtrate was concentrated. The obtained intermediate was dissolved in THF (30 mL), then a solution of LDA in hexane–THF (10.1 mL, 11.5 mmol) and *t*-butyl(2-iodoethoxy)dimethylsilane (3.30 g, 11.5 mmol) was added at −78 °C. The mixture was stirred for 18 h at room temperature, then the reaction was quenched with saturated aqueous ammonium chloride. The mixture was extracted with ethyl acetate, washed with brine, dried with Na_2SO_4 and then concentrated. Purification by silica gel column chromatography (eluent; *n*-hexane/ethyl acetate; 30:1) gave compound **9** (1.32 g, 40%) as yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 4.44 (m, 1H), 4.28 (dd, J = 16.9 Hz, 1.4 Hz, 1H), 3.99 (d, J = 16.9 Hz, 2H), 3.74–3.70 (m, 2H), 2.16–2.08 (m, 1H), 1.70–1.58 (m, 1H), 1.46 (s, 3H), 1.43 (s, 3H), 0.88 (s, 9H), 0.05 (s, 6H).

4.2.3. 4-(2-*t*-Butyldimethylsilyloxyethyl)-2,2-dimethyl-5-methylene-1,3-dioxane (10)

A solution of *n*-BuLi (1.6 M in hexane, 12.5 mL, 21.2 mmol) was added to a solution of CH_3PPh_3Br (7.60 g, 21.2 mmol) in THF (200 mL) at 0 °C and then stirred for 1 h at room temperature. Then compound **9** (2.04 g, 7.08 mmol) was added to the mixture at 0 °C and stirred for 30 min at room temperature. The reaction was quenched with saturated aqueous ammonium chloride. The mixture was extracted with ethyl acetate, washed with brine, dried with Na_2SO_4 and then concentrated. Purification by silica gel column chromatography (eluent; *n*-hexane/ethyl acetate; 40:1) gave compound **10** (1.41 g, 70%) as colorless oil. ^1H NMR (600 MHz, $CDCl_3$) δ 4.84 (s, 2H), 4.53 (d, J = 9.3 Hz, 1H), 4.29 (d, J = 13.5 Hz, 1H), 4.24 (d, J = 13.5 Hz, 1H), 3.79–3.75 (m, 2H), 2.03–1.99 (m, 1H), 1.75–1.70 (m, 1H), 1.46 (s, 3H), 1.38 (s, 3H), 0.90 (s, 9H), 0.06 (s, 6H).

4.2.4. 2,2-Dimethyl-5-methylene-4-(2-*p*-toluenesulfonyloxy ethyl)-1,3-dioxane (11)

A solution of tetra-*n*-butylammonium fluoride (1.0 M in THF, 0.42 mL, 0.42 mmol) was added to a solution of compound **10** (106 mg, 0.35 mmol) in THF (3.5 mL) at 0 °C, and then the mixture was stirred for 2.5 h at room temperature. The reaction was quenched with saturated aqueous ammonium chloride, extracted with ethyl acetate, washed with brine and then concentrated. Purification by silica gel column chromatography (eluent; *n*-hexane/ethyl acetate = 2:1) gave intermediate alcohol (41.6 mg, 69%). Intermediate alcohol: ^1H NMR (600 MHz, $CDCl_3$) δ 4.88 (s, 1H), 4.83 (s, 1H), 4.62 (d, J = 8.6 Hz, 1H), 4.31 (d, J = 13.7 Hz, 1H), 4.26 (d, J = 13.7 Hz, 1H), 3.86–3.81 (m, 2H), 2.45 (dd, J = 7.0 Hz, 4.1 Hz, 1H), 2.06–2.03 (m, 1H), 1.94–1.92 (m, 1H), 1.50 (s, 3H), 1.40 (s, 3H). The obtained alcohol (200 mg, 1.16 mmol) was dissolved in dichloromethane, and pyridine (0.36 mL) and *p*-toluenesulfonyl chloride (360 mg, 1.74 mmol) were added to the solution at 0 °C. The mixture was stirred for 5 h at room temperature, the reaction was quenched with saturated aqueous ammonium chloride, extracted with ethyl acetate, washed with brine, dried with Na_2SO_4 and then concentrated. Purification by silica gel column chromatography (eluent; *n*-hexane/ethyl acetate; 5:1) gave compound **11** (190 mg, 50%) as colorless oil. ^1H NMR (600 MHz, $CDCl_3$) δ 7.80 (d, J = 8.2 Hz, 2H), 7.35 (d, J = 8.2 Hz, 2H), 4.84 (d, J = 1.1 Hz, 1H), 4.75 (d, J = 1.1 Hz, 1H), 4.35–4.43 (m, 1H), 4.29–4.15 (m, 4H), 2.45 (s, 3H), 2.21–2.16 (m, 1H) 1.88–1.82 (m, 1H), 1.35 (s, 3H), 1.30 (s, 3H).

4.2.5. *trans*-4-(2-Hydroxyethyl)-2,2,5-trimethyl-1,3-dioxane (12) and *cis*-4-(2-hydroxyethyl)-2,2,5-trimethyl-1,3-dioxane (13)

Pd on C (105 mg) was added to a solution of compound **10** (260 mg, 0.88 mmol) in methanol (8 mL), and the solution was stirred under atmospheric hydrogen at room temperature for 1 h. Insoluble materials were filtered off through Celite, then the filtrate was concentrated. Purification by silica gel column chromatography (eluent; *n*-hexane/ethyl acetate = 40:1) gave a diastereo mixture of intermediates (4.76 g, 65%). Then the product (265 mg, 0.92 mmol) was dissolved in THF (10 mL), and a solution of tetra-*n*-butylammonium fluoride (1.0 M in THF, 1.20 mL, 1.20 mmol) was added at 0 °C, and then the mixture was stirred for 2.5 h at room temperature. The reaction was quenched with saturated aqueous ammonium chloride, extracted with ethyl acetate, washed with brine, dried with Na_2SO_4 and then concentrated. Purification by silica gel column chromatography (eluent; *n*-hexane/ethyl acetate; 5:1) gave compound **12** (38.4 mg, 31% as isolated yield) and compound **13** (45.4 mg, 37% as isolated yield). Large vicinal coupling constant (11.7 Hz) for 6-position proton of **12** (3.53 ppm) is account for by antiperiplanar conformation of C(5)-H and C(6)-H of the *trans* compound. Small vicinal coupling constant (1.6 Hz) for 6-position proton of **13** (3.58 ppm) is account for by synclinal conformation of C(5)-H and C(6)-H of the *cis* compound. **12**: ^1H NMR (600 MHz, $CDCl_3$) δ 3.83–3.73 (m, 3H), 3.70 (dd, J = 11.7 Hz, 5.1 Hz, 1H), 3.53 (dd, J = 11.7 Hz, 11.7 Hz, 1H), 2.67 (dd, J = 7.2 Hz, 3.8 Hz, 1H), 1.93–1.88 (m, 1H), 1.81–1.73 (m, 1H), 1.71–1.65 (m, 1H), 1.47 (s, 3H), 1.39 (s, 3H), 0.75 (d, J = 6.7 Hz, 3H); **13**: ^1H NMR (600 MHz, $CDCl_3$) δ 4.21 (ddd, J = 10.0 Hz, 2.8 Hz, 2.8 Hz, 1H), 4.13 (dd, J = 11.6 Hz, 2.9 Hz, 1H),

3.88–3.73 (m, 2H), 3.58 (dd, J = 11.5 Hz, 1.6 Hz, 1H), 2.36 (m, 1H), 1.89–1.83 (m, 1H), 1.52–1.43 (m, 5H), 1.39 (s, 3H), 1.10 (d, J = 7.0 Hz, 3H).

4.2.6. *trans*-4-(2-*p*-Toluenesulfonyloxyethyl)-2,2,5-trimethyl-1,3-dioxane (14)

Pyridine (50 μL, 0.61 mmol) and *p*-toluenesulfonyl chloride (48.0 mg, 0.23 mmol) were added to a solution of compound **12** (20.0 mg, 0.11 mmol) in dichloromethane (2.0 mL) at 0 °C. The mixture was stirred for 1 h at room temperature, the reaction was quenched with saturated aqueous ammonium chloride, extracted with ethyl acetate, washed with brine, dried with Na_2SO_4 and then concentrated. Purification by silica gel column chromatography (eluent; *n*-hexane/ethyl acetate; 4:1) gave compound **14** (14.9 mg, 41%) as colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.79 (d, J = 8.2 Hz, 2H), 7.34 (d, J = 8.2 Hz, 2H), 4.18 (dd, J = 9.6 Hz, 5.0 Hz, 1H), 4.11 (m, 1H), 3.65 (dd, J = 11.7 Hz, 5.1 Hz, 1H), 3.54 (dd, J = 10.0 Hz, 2.2 Hz, 1H), 3.46 (dd, J = 11.7 Hz, 11.7 Hz, 1H), 2.45 (s, 3H), 2.06–2.00 (m, 1H) 1.62–1.55 (m, 2H), 1.32 (s, 3H), 1.27 (s, 3H), 0.71 (d, J = 6.7 Hz, 3H).

4.2.7. 4-(2-*t*-Butyldimethylsilyloxyethyl)-6,6-dimethyl-5,7-dioxaspiro[2.5]octane (15)

To a solution of compound **10** (116 mg, 0.385 mmol) in diethyl ether (5.0 mL) were added diazomethane (0.5 M solution in diethyl ether, 4.25 mL, 2.13 mmol) and $Pd(acac)_2$ (8.7 mg, 0.035 mmol) at −20 °C, then the mixture was stirred for 15 min at −20 °C. Insoluble materials were filtered off through Celite. This process was repeated four times, and the crude product was purified by silica gel column chromatography (eluent; *n*-hexane/ethyl acetate; 30:1) to give compound **15** (73.8 mg, 60%) as colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.43 (dd, J = 9.8 Hz, 2.1 Hz, 1H), 4.25 (dd, J = 11.7 Hz, 2.1 Hz, 1H), 3.71–3.63 (m, 2H), 2.98 (d, J = 11.7 Hz, 1H), 1.51 (s, 3H), 1.41 (s, 3H), 1.31–1.17 (m, 2H), 0.89 (s, 9H), 0.80–0.73 (m, 1H), 0.45–0.38 (m, 2H), 0.18–0.05 (m, 1H), 0.04 (s, 6H).

4.2.8. 6,6-Dimethyl-4-(2-*p*-toluenesulfonyloxyethyl)-5,7-dioxaspiro[2.5]octane (16)

A solution of tetra-*n*-butylammonium fluoride (1.0 M in THF, 0.60 mL, 0.60 mmol) was added to a solution of compound **15** (155 mg, 0.50 mmol) in THF (5.0 mL) at 0 °C, and then the mixture was stirred for 3.5 h at room temperature. The reaction was quenched with saturated aqueous ammonium chloride, extracted with ethyl acetate, washed with brine, dried with Na_2SO_4 and then concentrated. Purification by silica gel column chromatography (eluent; *n*-hexane/ethyl acetate; 1:1) gave intermediate alcohol (66.9 mg, 70%). Intermediate alcohol: ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.46 (dd, J = 10.4 Hz, 2.0 Hz, 1H), 4.25 (dd, J = 11.8 Hz, 2.0 Hz, 1H), 3.77–3.72 (m, 2H), 2.99 (d, J = 11.8 Hz, 1H), 2.45 (dd, J = 7.1 Hz, 3.7 Hz, 1H), 1.55 (s, 3H), 1.48–1.43 (m, 4H), 1.27–1.22 (m, 1H), 0.85–0.82 (m, 1H), 0.50–0.45 (m, 1H), 0.41–0.36 (m, 1H), 0.22–0.17 (m, 1H). The obtained alcohol (66.9 mg, 0.359 mmol) was dissolved in dichloromethane (4.0 mL), and pyridine (1.2 mL) and *p*-toluenesulfonyl chloride (141 mg, 0.718 mmol) were added to the solution at 0 °C. The mixture was stirred for 22 h at room temperature, the reaction was quenched with saturated aqueous sodium bicarbonate, extracted with ethyl acetate, washed with brine, dried with Na_2SO_4 and then concentrated. Purification by silica gel column chromatography (eluent; *n*-hexane/ethyl acetate; 4:1) gave compound **16** (26.6 mg, 22%) as colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.79 (d, J = 8.0 Hz, 2H), 7.35 (d, J = 8.0 Hz, 2H), 4.29 (dd, J = 8.7 Hz, 3.8 Hz, 1H), 4.19 (dd, J = 11.8 Hz, 2.0 Hz, 1H), 4.17–4.05 (m, 2H), 2.95 (d, J = 11.8 Hz, 1H), 2.45 (s 3H), 1.40–1.33 (m, 8H) 0.71–0.66 (m, 1H), 0.46–0.41 (m, 1H), 0.36–0.31 (m, 1H), 0.20–0.15 (m, 1H).

4.2.9. *trans*-4-(2-*t*-Butyldimethylsilyloxyethyl)-5-hydroxy-2,2-dimethyl-1,3-dioxane (17) and *cis*-4-(2-*t*-butyldimethylsilyl oxyethyl)-5-hydroxy-2,2-dimethyl-1,3-dioxane (18)

$NaBH_4$ (1.09 g, 28.7 mmol) was added to a solution of compound **9** (4.14 g, 14.4 mmol) in methanol (100 mL) at 0 °C and stirred for 10 min at room temperature. Then the reaction mixture was diluted with ethyl acetate. The organic layer was washed with water and brine, dried with Na_2SO_4 and evaporated, then purified by silica gel column chromatography (eluent: *n*-hexane/ethyl acetate; 2:1) to give **17** (2.17 g, 7.45 mmol, 52%) and **18** (1.23 g,4.24 mmol, 30%). Compound **17**: colorless oil, ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.48 (d, J = 2.4 Hz, 1H), 3.94 (dd, J = 11.3 Hz, 5.5 Hz, 1H), 3.85 (ddd, J = 10.8 Hz, 4.1 Hz, 4.1 Hz, 1H), 3.75 (m, 1H), 3.64 (ddd, J = 10.1 Hz, 5.7 Hz, 5.7 Hz, 1H), 3.63 (dd, J = 11.3 Hz, 9.6 Hz 1H), 3.46 (dddd, J = 9.6 Hz, 9.6 Hz, 5.5 Hz, 2.4 Hz, 1H), 1.83 (m, 2H), 1.47 (s, 3H), 1.39 (s, 3H), 0.91 (s, 9H), 0.10 (s, 6H). **18**: colorless oil, ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.11 (ddd, J = 6.9 Hz, 5.7 Hz, 1.2 Hz, 1 H,), 4.06 (dd, J = 12.2 Hz, 1.7 Hz, 1H), 3.83 (dd, J = 12.2 Hz, 2.2 Hz, 1H), 3.70 (m, 2H), 3.34 (ddd, J = 10.4 Hz, 2.2 Hz, 1.7 Hz, 1H), 2.70 (d, J = 10.5 Hz, 1H), 1.79 (m, 2H), 1.46 (s, 3H), 1.41 (s, 3H), 0.90 (s, 9H), 0.54 (s, 6H).

4.2.10. *trans*-5-Benzyloxy-4-(2-*t*-butyldimethylsilyloxyethyl)-2,2-dimethyl-1,3-dioxane (19)

NaH (248 mg, 7.75 mmol) was added to a solution of compound **17** (1.50 g, 5.16 mmol) in DMF (50 mL) at 0 °C and stirred for 10 min at 0 °C. Then to the reaction mixture was added benzyl bromide (1.47 g, 8.61 mmol) at 0 °C, and stirred for 30 min at 0 °C. Then the reaction was quenched with water at 0 °C, and then diluted with ethyl acetate. The organic layer was washed with water and brine, dried with Na_2SO_4 and evaporated, then purified by silica gel column chromatography (eluent: *n*-hexane/ethyl acetate; 10:1) to give 2.00 g (5.16 mmol, 100%) of **19** as colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36–7.27 (m, 5H), 4.57 (d, J = 11.6 Hz, 1H), 4.52 (d, J = 11.6 Hz, 1H), 3.91 (dd, J = 11.3 Hz, 5.1 Hz, 1H), 3.85 (ddd, J = 9.1 Hz, 9.1 Hz, 2.7 Hz, 1H), 3.70 (m, 2H), 3.67 (dd, J = 11.3 Hz, 7.4 Hz, 1H), 3.28 (ddd, J = 9.1 Hz, 9.1 Hz, 5.1 Hz, 1H), 2.08 (m, 1H), 1.57 (m, 1H), 1.44 (s, 3H), 1.35 (s, 3H), 0.90 (s, 9H), 0.45 (s, 6H).

4.2.11. *cis*-5-Benzyloxy-4-(2-*t*-butyldimethylsilyloxyethyl)-2,2-dimethyl-1,3-dioxane (20)

Compound **20** was prepared from **18** by a similar manner used for synthesis of **19**. Compound **20**: 87%, colorless oil, ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36–7.25 (m, 5H), 4.76 (d, J = 12.4 Hz, 1H), 4.48 (d, J = 12.4 Hz, 1H), 4.12 (ddd, J = 8.8 Hz, 3.5 Hz, 2.0 Hz, 1H), 4.03 (dd, J = 12.8 Hz, 2.2 Hz, 1H), 3.90 (dd, J = 12.8 Hz, 2.2 Hz, 1H), 3.67 (m, 1H), 3.55 (m, 1H), 3.11 (ddd, J = 2.1 Hz, 2.1 Hz, 2.1 Hz, 1H), 1.93 (m, 1H), 1.65 (s, 3H), 1.43 (s, 6H), 0.87 (s, 9H), 0.01 (s, 6H).

4.2.12. *trans*-5-Benzyloxy-4-(2-hydroxyethyl)-2,2-dimethyl-1,3-dioxane (21)

A solution of tetra-*n*-butylammonium fluoride (1.00 M in THF, 6.20 mL, 6.20 mmol) was added to a solution of compound **19** (1.99 g, 5.16 mmol) in THF (50 mL) at 0 °C and stirred for 18 h at room temperature. Then the reaction mixture was diluted with ethyl acetate. The organic layer was washed with water and brine, dried with Na_2SO_4 and evaporated, then purified by silica gel column chromatography (eluent: *n*-hexane/ethyl acetate; 2:1 to 1:1) to give 1.19 g (4.47 mmol, 86%) of **21** as colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37–7.29 (m, 5H), 4.58 (d, J = 11.5 Hz, 1H), 4.49 (d, J = 11.5 Hz, 1H), 3.95 (dd, J = 11.4 Hz, 5.2 Hz, 1H), 3.91 (ddd, J = 9.0 Hz, 9.0 Hz, 3.4 Hz, 1H), 3.74 (m, 2H), 3.69 (dd, J = 11.4 Hz, 9.0 Hz, 1H), 3.37 (ddd, J = 9.0 Hz, 9.0 Hz, 5.2 Hz, 1H), 2.40 (t, J = 5.5 Hz, 1H), 2.05 (m, 1H), 1.74 (m, 1H), 1.84 (s, 3H), 1.37 (s, 3H).

4.2.13. *cis*-5-Benzyloxy-4-(2-hydroxyethyl)-2,2-dimethyl-1,3-dioxane (22)

Compound **22** was prepared from **20** by a similar manner used for synthesis of **21**. Compound **22**: 94%, colorless oil, ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37–7.26 (m, 5H), 4.77 (d, J = 12.3 Hz, 1H), 4.48 (d, J = 12.3 Hz, 1H), 4.12 (m, 1H), 4.03 (dd, J = 12.8 Hz, 2.2 Hz, 1H), 3.92 (dd, J = 12.8 Hz, 2.2 Hz, 1H), 3.70 (m, 2H), 3.15 (ddd, J = 2.2 Hz, 2.2 Hz, 2.2 Hz, 1H), 2.11 (m, 1H), 2.05 (m, 1H), 1.63 (m, 1H), 1.46 (s, 3H), 1.44 (s, 3H).

4.2.14. *trans*-5-Benzyloxy-4-(2-*p*-toluenesulfonyloxyethyl)-2,2,-dimethyl-1,3-dioxane (23)

4-*N*,*N*-Dimethylaminopyridine (1.12 g, 9.15 mmol) and *p*-toluenesulfonyl chloride (1.16 g, 6.10 mmol) were added to a solution of **21** (800 mg, 3.05 mmol) in CH_2Cl_2 (30 mL) at 0 °C and then the mixture was stirred for 1 h at room temperature. The reaction mixture was diluted with ethyl acetate. The organic layer was washed with water and brine, dried with Na_2SO_4 and evaporated, then purified by silica gel column chromatography (eluent: *n*-hexane/ethyl acetate; 5:1) to give 1.28 mg (3.05 mmol, 100%) of **23** as colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (m, 2H), 7.36–7.26 (m, 7H), 4.52 (d, J = 11.6 Hz, 1H), 4.45 (d, J = 11.6 Hz, 1H), 4.13 (m, 2H), 3.89 (dd, J = 11.4 Hz, 5.2 Hz, 1H), 3.73 (ddd, J = 9.1 Hz, 9.1 Hz, 2.9 Hz, 1H), 3.61 (dd, J = 11.4 Hz, 9.1 Hz, 1H), 3.22 (ddd, J = 9.1 Hz, 9.1 Hz, 5.1 Hz, 1H), 2.43 (s, 3H), 2.18 (m, 1H), 1.67 (m, 1H), 1.34 (s, 3H), 1.28 (s, 3H).

4.2.15. *cis*-5-Benzyloxy-4-(2-*p*-toluenesulfonyloxyethyl)-2,2,-dimethyl-1,3-dioxane (24)

Compound **24** was prepared from **22** by a similar manner used for synthesis of **23**. Compound **24**: 73%, colorless oil, ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (m, 2H), 7.36–7.25 (m, 7H), 4.71 (d, J = 12.2 Hz, 1H), 4.41 (d, J = 12.2 Hz, 1H), 4.12 (m, 1H), 4.01 (m, 2H), 4.00 (dd, J = 12.8 Hz, 2.2 Hz, 1H), 3.86 (dd, J = 12.8 Hz, 2.2 Hz, 1H), 3.06 (ddd, J = 2.2 Hz, 2.2 Hz, 2.2 Hz, 1H), 2.44 (s, 3H), 2.07 (m, 1H), 1.77 (m, 1H), 1.36 (s, 3H), 1.34 (s, 3H).

4.2.16. 1-Hydroxymethyl-1,12-dicarba-*closo*-dodecaborane (26)

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 **26** (66%) as a colorless solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.5–1.5 (br m, 10H), 3.47 (d, J = 7.3 Hz, 2H), 2.7 (br s, 1H), 1.55 (t, J = 7.3 Hz, 1H).

4.2.17. 1-Benzyloxymethyl-1,12-dicarba-*closo*-dodecaborane (27)

NaH (206 mg, 8.61 mmol) was added to a solution of **26** (1.00 g, 5.74 mmol) in DMF (30 mL) at 0 °C, and the mixture stirred for 10 min at 0 °C. Then benzyl bromide (1.47 g, 8.61 mmol) was further added at 0 °C and then stirred for 30 min 0 °C. Then the reaction was quenched with water at 0 °C and the reaction mixture was diluted with ethyl acetate. The organic layer was washed with water and brine, dried with Na_2SO_4 and evaporated, then purified by silica gel column chromatography (eluent: *n*-hexane/ethyl acetate; 10:1) to give 1.52 g (5.74 mmol, 100%) of **27** as colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20–7.33 (m, 5H), 4.39 (s, 2H), 3.5–1.5 (br m, 10H), 3.29 (s, 2H), 2.67 (br s, 1H).

4.2.18. 1-Benzyloxymethyl-12-(5-ethyl-5-triethylsilyloxyheptyl) -1,12-dicarba-*closo*-dodecaborane (28)

A solution of *n*-BuLi (1.58 M in *n*-hexane, 5.50 mL, 8.61 mmol) was added to a solution of **27** (1.50 g, 5.74 mmol) in THF (50 mL) at 0 °C and then the mixture was stirred for 1 h at room temperature. A solution of 7-bromo-3-ethylhept-3-yloxytriethylsilane (2.91 g, 8.61 mmol) in THF (8.0 mL) was added to the mixture at 0 °C, and then stirred for 1 h at room temperature. Then the reaction was quenched with water, and the reaction mixture was diluted with ethyl acetate. The organic layer was washed with water and brine, dried with Na_2SO_4 and evaporated, then purified by silica gel column chromatography (eluent: *n*-hexane/ethyl acetate; 1:0 to 10:1) to give 2.45 g (4.70 mmol, 82%) of **28** as yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20–7.32 (m, 5H), 4.38 (s, 2H), 3.30 (s, 2H), 2.80–1.50 (br m, 10H), 1.58 (t, J = 7.0 Hz, 2H), 1.37 (q, J = 7.2 Hz, 4H), 1.25 (t, J = 6.8 Hz, 2H), 1.07 (m, 4H), 0.90 (t, J = 7.5 Hz, 9H), 0.76 (t, J = 7.2 Hz, 6H), 0.52 (q, J = 7.5 Hz, 6H).

4.2.19. 1-(5-Ethyl-5-triethylsilyloxyheptyl)-12-hydroxymethyl-1,12-dicarba-*closo*-dodecaborane (29)

Under H_2 atomosphere, 20% $Pd(OH)_2$/C (230 mg) was added to a solution of **28** (100 mg, 0.192 mmol) in THF (5.0 mL) and stirred for 10 min at room temperature. Then the reaction mixture was filtrated and concentrated, the crude product was purified by silica gel column chromatography (eluent: *n*-hexane/ethyl acetate; 20:1) to give 87.2 mg (0.192 mmol, 100%) of **29** as white solid. ^{1}H NMR^{1}H NMR (500 MHz, $CDCl_3$) δ 3.48 (d, J = 7.4 Hz, 2H), 2.80–1.50 (br m, 10H), 1.59 (t, J = 8.1 Hz, 2H), 1.47 (t, J = 7.4 Hz 1H), 1.34 (q, J = 7.4 Hz, 4H), 1.25 (t, J = 6.2 Hz, 2H), 1.11 (m, 4H), 0.90 (t, J = 8.0 Hz, 9H), 0.75 (t, J = 7.4 Hz 6H), 0.52 (q, J = 8.0 Hz 6H).

4.2.20. 1-(5-Ethyl-5-triethylsilyloxyheptyl)-12-(2-(5-methylene-2,2-dimethyl-1,3-dioxan-4-yl)ethoxymethyl)-1,12-dicarba-*closo*-dodecaborane (30)

To a suspension of NaH (38.1 mg, 0.954 mmol) in DMF (2.0 mL) was added a solution of **29** (165 mg, 0.382 mmol) in DMF (2.0 mL) and **11** (130 mg, 0.398 mmol) in DMF (2.0 mL), and the mixture was stirred at room temperature for 2 h. NaH (30.6 mg, 0.766 mmol) was further added, and stirring was continued for 17 h. The reaction was quenched with water, and the reaction mixture was diluted with ethyl acetate. The organic layer was washed with water and brine, dried with Na_2SO_4 and evaporated, then purified by silica gel column chromatography (eluent: *n*-hexane/ethyl acetate; 30:1) to give 99.3 mg (44%) of **30** as colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.83 (s, 1H), 4.80 (s, 1H), 4.45–4.43 (m, 1H), 4.29 (d, J = 13.5 Hz, 1H) 4.21 (d, J = 13.5 Hz, 1H), 3.47–3.43 (m, 1H), 3.41–3.37 (m, 1H), 3.32 (d, J = 10.7 Hz, 1H), 3.27 (d, J = 10.7 Hz, 1H), 2.80–1.50 (br m, 10H), 2.07–1.97 (m, 1H), 1.69–1.64 (m, 1H), 1.61–1.58 (m, 2H), 1.48 (s, 3H), 1.41–1.35 (m, 7H), 1.28–1.20 (m, 2H), 1.12–1.02 (m, 4H), 0.92 (t, J = 8.0 Hz, 9H), 0.77 (t, J = 7.5 Hz, 6H), 0.53 (q, J = 8.0 Hz, 6H).

4.2.21. 1-(5-Ethyl-5-hydroxyheptyl)-12-(3,5-dihydroxy-4-meth ylene)pentyloxymethyl-1,12-dicarba-*closo*-dodecaborane (31)

1 M HCl (1.0 mL) was added to a solution of **30** (37.2 mg, 0.0636 mmol) in MeOH/THF 1:1 (2.0 mL) at 0 °C, and then the mixture stirred for 1 h at room temperature. The reaction mixture was diluted with ethyl acetate, then the organic layer was washed with water and brine, dried with Na_2SO_4 and concentrated, then purified by silica gel column chromatography (eluent: *n*-hexane/ethyl acetate) to give **31** (21.2 mg, 0.0492 mmol, 77%) as colorless solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.13 (s, 1H), 5.11 (s, 1H), 4.42 (m, 1H), 4.25 (dd, J = 13.1 Hz, 4.6 Hz, 1H), 4.16 (dd, J = 13.1 Hz, 6.4 Hz, 1H), 3.50 (m, 2H), 3.30 (s, 2H), 2.98 (d, J = 3.4 Hz, 1H), 2.80–1.50 (br m, 10H), 2.11 (t, J = 5.3 Hz, 1H), 1.89 (m, 1H), 1.80 (m, 1H), 1.60 (m, 2H), 1.39 (q, J = 7.4 Hz, 4H), 1.28 (m, 2H), 1.11 (m, 4H), 0.98

(s, 1H), 0.81 (t, J = 7.4 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.5, 112.2, 80.9, 74.4, 73.6, 73.3, 70.1, 64.2, 37.9. 37.7, 35.2, 30.9, 30.0, 22.9, 7.7; LRMS (ESI+) 453 [(M+Na)+]; HRMS (ESI+) m/z 455.3922 [(M+Na)+: calcd for $C_{18}H_{42}B_{10}NaO_4$, 455.3910].

4.2.22. 1-(5-Ethyl-5-triethylsilyloxyheptyl)-12-{2-(*trans*-2,2,5-trimethyl-1,3-dioxan-4-yl)ethoxymethyl}-1,12-dicarba-*closo*-dodecaborane (32)

To a suspension of NaH (20.1 mg, 0.500 mmol) in DMF (0.3 mL) was added a solution of **29** (29.5 mg, 0.068 mmol) in DMF (0.5 mL) and **14** (14.9 mg, 0.045 mmol) in DMF (1.0 mL), and the mixture was stirred at room temperature for 2 h. The reaction was quenched with water, and the reaction mixture was diluted with ethyl acetate. The organic layer was washed with water and brine, dried with Na_2SO_4 and evaporated, then purified by silica gel column chromatography (eluent: *n*-hexane/ethyl acetate; 20:1) to give 13.8 mg (52%) of **32** as colorless solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.67 (dd, J = 11.6, 5.1 Hz, 1H), 3.54 (ddd, J = 9.7 Hz, 9.7 Hz, 2.1 Hz, 1H), 3.50 (dd, J = 11.7 Hz, 11.7 Hz, 1H), 3.38–3.35 (m, 2H), 3.31 (d, J = 11.6 Hz, 1H), 3.24 (d, J = 10.7 Hz, 1H), 2.80–1.50 (br m, 10H), 1.85–1.82 (m, 1H), 1.61–1.59 (m, 2H), 1.46–1.35 (m, 1H), 1.41 (s, 3H), 1.35 (s, 3H), 1.28–1.26 (m, 3H), 1.11–1.06 (m, 4H), 0.92 (t, J = 7.9 Hz, 9H), 0.77 (t, J = 7.4 Hz, 6H), 0.74 (d, J = 6.7 Hz, 3H) 0.53 (q, J = 7.9 Hz, 6H).

4.2.23. 1-(5-Ethyl-5-hydroxyheptyl)-12-(3,5-dihydroxy-4-methyl)pentyloxymethyl-1,12-dicarba-*closo*-dodecaborane (33)

2 M HCl (0.25 mL) was added to a solution of **32** (13.8 mg, 0.023 mmol) in MeOH/THF 1:3 (1.0 mL) at 0 °C, and then the mixture stirred for 1 h at room temperature. The reaction was quenched by addition of aqueous sodium bicarbonate, diluted with ethyl acetate. The organic layer was washed with water and brine, dried with Na_2SO_4 and concentrated, then purified by silica gel column chromatography (eluent: *n*-hexane/ethyl acetate; 1:1) to give **33** (9.1 mg, 91%) as colorless solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.71–3.62 (m, 3H), 3.58–3.55 (m, 1H), 3.51–3.48 (m, 1H), 3.41 (br s, 1H), 3.31 (s, 2H), 3.18 (s, 1H), 2.80–1.50 (br m, 10H), 1.74–1.68 (m, 3H), 1.63 (m, 2H), 1.39 (q, J = 7.5 Hz, 4H), 1.30–1.28 (m, 2H), 1.25 (s, 1H), 1.14–1.09 (m, 4H), 0.81 (d, J = 7.0 Hz, 3H), 0.81 (t, J = 7.5 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 80.98, 77.64, 74.40, 73.73, 71.05, 67.69, 40.07, 37.96, 37.74, 34.11, 30.89, 30.01, 22.87, 13.93, 7.74; LRMS (ESI+) 455 [(M+Na)+]; HRMS (ESI+) m/z 457.4076 [(M+Na)+: calcd for $C_{18}H_{44}B_{10}NaO_4$, 457.4066].

4.2.24. 1-(5-Ethyl-5-hydroxyheptyl)-12-(3,5-dihydroxy-4-methyl)pentyloxymethyl-1,12-dicarba-*closo*-dodecaborane (34)

10% Pd/C (18.2 mg) was added to a solution of **30** (35.2 mg, 0.060 mmol) in methanol (1.5 mL) and stirred for 10 min at room temperature under H_2 atomosphere. Then the reaction mixture was filtrated and concentrated, the crude product was purified by silica gel column chromatography (eluent: *n*-hexane/ethyl acetate; 1:1) to give 15.6 mg (60%) of **34** as 75:25 mixture with **33** (50% de). ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.96–3.94 (m, 0.7H), 3.71–3.62 (m, 2.3H), 3.58–3.55 (m, 1H), 3.51–3.48 (m, 1H), 3.31 (s, 2H), 3.04 (br s, 1H), 2.80–1.50 (br m, 10H), 2.61 (br s, 1H), 1.74–1.68 (m, 3H), 1.63 (m, 2H), 1.39 (q, J = 7.5 Hz, 4H), 1.30–1.28 (m, 2H), 1.14–1.09 (m, 4H), 0.90 (d, J = 7.0 Hz, 2.3H), 0.81 (d, J = 7.0 Hz, 0.7H), 0.81 (t, J = 7.5 Hz, 6H); LRMS (ESI+) 455 [(M+Na)+]; HRMS (ESI+) m/z 457.4070 [(M+Na)+: calcd for $C_{18}H_{44}B_{10}NaO_4$, 457.4066].

4.2.25. 1-(5-Ethyl-5-triethylsilyloxyheptyl)-12-{2-(6,6-dimethyl-5,7-dioxaspiro[2.5]octan-4-yl)ethoxymethyl)-1,12-dicarba-*closo*-dodecaborane (35)

To a suspension of NaH (60% in oil, 14.2 mg, 0.357 mmol) in DMF (0.5 mL) was added a solution of **29** (46.3 mg, 0.107 mmol) in DMF (0.5 mL) and **16** (26.6 mg, 0.078 mmol) in DMF (1.0 mL), and the mixture was stirred at room temperature for 2 h. The reaction was quenched with water, and the reaction mixture was diluted with ethyl acetate. The organic layer was washed with water and brine, dried with Na_2SO_4 and evaporated, then purified by silica gel column chromatography (eluent: *n*-hexane/ethyl acetate; 20:1) to give 17.9 mg (38%) of **35** as colorless solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.30–4.27 (m, 1H), 4.23 (dd, J = 11.7, 2.0 Hz, 1H), 3.40–3.22 (m, 3H), 2.80–1.50 (br m, 10H), 2.96 (d, J = 11.7 Hz, 1H), 1.67–1.56 (m, 2H), 1.50 (s 3H), 1.41–1.36 (m, 7H), 1.29–1.26 (m, 2H) 1.22–1.15 (m, 2H), 1.15–1.04 (m, 4H), 0.92 (t, J = 8.0 Hz, 9H), 0.77 (t, J = 7.4 Hz, 6H), 0.74–0.72 (m, 1H), 0.53 (q, J = 8.0 Hz, 6H), 0.44–0.35 (m, 2H), 0.19–0.13 (m, 1H).

4.2.26. 1-(5-Ethyl-5-hydroxyheptyl)-12-{3-hydroxy-3-(1-hydroxymethyl)cyclopropyl}propoxymethyl-1,12-dicarba-*closo*-dodecaborane (36)

2 M HCl (0.5 mL) was added to a solution of **35** (17.9 mg, 0.030 mmol) in MeOH/THF 1:3 (1.0 mL) at 0 °C, and then the mixture stirred for 1 h at room temperature. The reaction was quenched by addition of aqueous sodium bicarbonate, diluted with ethyl acetate. The organic layer was washed with water and brine, dried with Na_2SO_4 and concentrated, then purified by silica gel column chromatography (eluent: *n*-hexane/ethyl acetate; 1:1) to give **36** (7.1 mg, 53%) as colorless solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.06 (dd, J = 11.5 Hz, 1.3 Hz, 1H), 3.54 (m, 1H), 3.46 (ddd, J = 9.0 Hz, 9.0 Hz, 3.9 Hz, 1H), 3.30 (s, 2H), 3.23 (dd, J = 9.9 Hz, 2.1 Hz, 1H), 3.17 (br s, 1H), 3.07 (d, J = 11.5 Hz, 1H), 2.80–1.50 (br m, 10H), 2.04–1.97 (m, 1H), 1.74–1.68 (m, 1H), 1.65–1.57 (m, 2H), 1.39 (q, J = 7.4 Hz, 4H), 1.31–1.26 (m, 3H), 1.15–1.09 (m, 4H), 0.82 (t, J = 7.4, Hz, 6H), 0.69–0.63 (m, 2H), 0.38–0.35 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 78.5, 74.4, 74.0, 70.8, 67.6, 38.0, 37.7, 33.8, 31.2, 30.0, 26.0, 22.9, 11.0, 7.6, 7.5; LRMS (ESI+) 467 [(M+Na)+]; HRMS (ESI+) m/z 469.4076 [(M+Na)+: calcd for $C_{19}H_{44}B_{10}NaO_4$, 469.4066].

4.2.27. 1-(5-Ethyl-5-triethylsilyloxyheptyl)-12-{2-(*trans*-5-benzyloxy-2,2-dimethyl-1,3-dioxan-4-yl)ethoxymethyl}-1,12-dicarba-*closo*-dodecaborane (37)

Compound **37** was prepared from **29** by the similar procedure that in case of compound **35** but using compound **23** as a reaction substrate (98%). Compound **37**: colorless oil, ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25–7.34 (m, 5H), 4.54 (d, J = 11.6 Hz, 1H), 4.47 (d, J = 11.6 Hz, 1H), 3.89 (dd, J = 11.4 Hz, 5.2 Hz, 1H), 3.73 (ddd, J = 9.1 Hz, 9.1 Hz, 2.9 Hz, 1H), 3.63 (dd, J = 11.4 Hz, 9.1 Hz, 1H), 3.34 (m, 2H), 3.28 (d, J = 10.8 Hz, 1H), 3.21 (d, J = 10.8 Hz, 1H), 3.20 (ddd, J = 9.1 Hz, 9.1 Hz, 5.1 Hz, 1H), 2.80–1.50 (br m, 10H), 2.00 (m, 2H), 1.58 (t, J = 8.2 Hz, 2H), 1.41 (s, 3H), 1.36 (q, J = 7.4 Hz, 4H), 1.32 (s, 3H), 1.25 (t, J = 7.8 Hz, 2H), 1.06 (m, 4H), 0.90 (t, J = 8.0 Hz, 9H), 0.75 (t, J = 7.4 Hz, 6H), 0.51 (q, J = 8.0 Hz, 6H).

4.2.28. 1-(5-Ethyl-5-triethylsilyloxyheptyl)-12-{2-(*cis*-5-benzyloxy-2,2-dimethyl-1,3-dioxan-4-yl)ethoxymethyl}-1,12-dicarba-*closo*-dodecaborane (38)

Compound **38** was prepared from **29** by the similar procedure that in case of compound **35** but using compound **24** as a reaction substrate (90%). Compound **38**: colorless oil, ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34–7.26 (m, 5H), 4.74 (d, J = 12,3 Hz, 1H), 4.46 (d, J = 12.3 Hz, 1H), 4.03 (dd, J = 12.8 Hz, 2.2 Hz, 1H), 4.01(m, 1H), 3.90 (dd, J = 12.8 Hz, 2.2 Hz, 1H), 3.33 (m, 1H), 3.19 (s, 2H), 3.18 (m, 1H), 3.08 (ddd, J = 2.2 Hz, 2.2 Hz, 2.2 Hz, 1H), 2.80–1.50 (br m, 10H), 1.90 (m, 1H), 1.65–1.57 (m, 3H), 1.42 (s, 3H), 1.38 (s, 3H), 1.37 (q, J = 7.4 Hz, 4H), 1.27 (m, 2H), 1.08 (m, 4H), 0.90 (t, J = 7.8 Hz, 9H), 0.77 (t, J = 7.4 Hz, 6H), 0.51 (q, J = 7.8 Hz, 6H).

4.2.29. 1-(5-Ethyl-5-triethylsilyloxyheptyl)-12-{2-(*trans*-5-hydroxy-2,2-dimethyl-1,3-dioxan-4-yl)ethoxymethyl}-1,12-dicarba-*closo*-dodecaborane (39)

Under H_2 atomosphere, 20% $Pd(OH)_2/C$ (88.0 mg) was added to **37** (882 mg, 0.130 mmol) in THF (30 mL) and stirred for 30 min at room temperature. Insoluble materials were filtrated off and the filtrate was concentrated, then the crude product was purified by silica gel column chromatography (eluent: *n*-hexane/ethyl acetate; 10:1) to give **39** (685 mg, 90%) as colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.90 (dd, J = 11.3 Hz, 5.4 Hz, 1H), 3.62 (m, 1H), 3.60 (dd, J = 11.3 Hz, 9.4 Hz, 1H), 3.44 (m, 3H), 3.34 (d, J = 10.7 Hz, 1H), 3.30 (d, J = 10.7 Hz, 1H), 2.80–1.50 (br m, 10H), 2.70 (d, J = 4.4 Hz, 1H), 1.90 (m, 1H), 1.75 (m, 1H), 1.60 (t, J = 8.0 Hz, 2H), 1.44 (s, 3H), 1.40 (q, J = 7.9 Hz, 4H), 1.36 (s, 3H), 1.25 (m, 2H), 1.09 (m, 4H), 0.91 (t, J = 7.9 Hz, 9H), 0.77 (t, J = 7.5 Hz, 6H), 0.53 (q, J = 7.9 Hz, 6H).

4.2.30. 1-(5-Ethyl-5-triethylsilyloxyheptyl)-12-{2-(*cis*-5-hydroxy-2,2-dimethyl-1,3-dioxan-4-yl)ethoxymethyl}-1,12-dicarba-*closo*-dodecaborane (40)

Compound **40** was prepared by the similar procedure that in case of compound **39** but using compound **38** as a reaction substrate (89%). **40**: colorless oil, ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.06 (dd, J = 12.2 Hz, 2.2 Hz, 1H), 4.03 (m, 1H), 3.82 (dd, J = 12.2 Hz, 2.0 Hz, 1H), 3.36 (m, 2H), 3.33–3.26 (m, 3H), 2.80–1.50 (br m, 10H), 2.52 (d, J = 11.2 Hz, 1H), 1.76 (m, 2H), 1.60 (m, 2H), 1.46 (s, 3H), 1.37 (s, 3H), 1.36 (q, J = 7.8 Hz, 4H), 1.27 (m, 2H), 1.10 (m, 4H), 0.92 (t, J = 7.4 Hz, 9H), 0.77 (t, J = 7.8 Hz, 6H), 0.54 (q, J = 7.4 Hz, 6H).

4.2.31. 1-(5-Ethyl-5-triethylsilyloxyheptyl)-12-{2-(*trans*-2,2-dimethyl-5-methoxy-1,3-dioxan-4-yl)ethoxymethyl}-1,12-dicarba-*closo*-dodecaborane (41)

NaH (4.0 mg, 0.102 mmol) was added to **39** (40.0 mg, 0.0679 mmol) in DMF (2.0 mL) and stirred for 10 min at 0 °C. Then MeI (19.3 mg, 0.136 mmol) was added to the reaction mixture at 0 °C, and stirred at 0 °C for 30 min and at room temperature for 1 h. Then the reaction was quenched with water, and diluted with ethyl acetate. The organic layer was washed with water and brine, dried with Na_2SO_4 and concentrated. Purification by silica gel column chromatography (eluent: *n*-hexane/ethyl acetate; 10:1 to 5:1) gave 36.2 mg (0.0600 mmol, 89%) of **41** as colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.95 (dd, J = 11.5 Hz, 5.1 Hz, 1H), 3.66 (ddd, J = 9.1 Hz, 9.1 Hz, 2.9 Hz, 1H), 3.60 (dd, J = 11.4 Hz, 9.1 Hz, 1H), 3.38 (m, 2H), 3.35 (s, 3H), 3.31 (d, J = 10.8 Hz, 1H), 3.25 (d, J = 10.8 Hz, 1H), 3.01 (ddd, J = 9.1 Hz, 9.1 Hz, 5.1 Hz, 1H), 2.80–1.50 (br m, 10H), 1.99 (m, 1H), 1.60 (m, 2H), 1.51 (m, 1H), 1.42 (s, 3H), 1.37 (q, J = 7.8 Hz, 4H), 1.34 (s, 3H), 1.26 (m, 2H), 1.07 (m, 4H), 0.90 (t, J = 7.4 Hz, 9H), 0.77 (t, J = 7.8 Hz, 6H), 0.51 (q, J = 7.4 Hz, 6H).

4.2.32. 1-(5-Ethyl-5-triethylsilyloxyheptyl)-12-{2-(*cis*-2,2-dimethyl-5-methoxy-1,3-dioxan-4-yl)ethoxymethyl}-1,12-dicarba-*closo*-dodecaborane (42)

Compound **42** was prepared by the similar procedure that in case of compound **41** but using compound **40** as a reaction substrate (97%). Compound **42**: colorless oil, ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.04 (d, J = 12.9 Hz, 2.0 Hz, 1H), 4.03 (m, 1H), 3.91 (dd, J = 12.9 Hz, 2.0 Hz, 1H), 3.41 (m, 1H), 3.38 (s, 3H), 3.33 (m, 1H), 3.29 (d, J = 10.7 Hz, 1H), 3.25 (d, J = 10.7 Hz, 1H), 2.88 (ddd, J = 2.0 Hz, 2.0 Hz, 2.0 Hz, 1H), 2.80–1.50 (br m, 10H), 1.86 (m, 1H), 1.68 (m, 1H), 1.60 (m, 2H), 1.45 (s, 3H), 1.38 (s, 3H), 1.36 (q, J = 7.8 Hz, 4H), 1.27 (m, 2H), 1.08 (m, 4H), 0.91 (t, J = 7.4 Hz, 9H), 0.77 (t, J = 7.8 Hz, 6H), 0.52 (q, J = 7.4 Hz, 6H).

4.2.33. 1-(5-Ethyl-5-hydroxyheptyl)-12-(3,4,5-trihydroxypentyloxy)methyl-1,12-dicarba-*closo*-dodecaborane (43)

1 M HCl (1.0 mL) was added to a solution of **39** (23.0 mg, 0.039 mmol) in MeOH/THF 1:1 (2.0 mL) at 0 °C, and then the mixture stirred for 1.5 h at room temperature. The mixture was diluted with ethyl acetate, then the organic layer was washed with water and brine, dried with Na_2SO_4 and concentrated. Purification by silica gel column chromatography (eluent: *n*-hexane/ethyl acetate; 1:1) to give **43** (15.0 mg, 88%) as colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.81 (m, 1H), 3.77 (m, 2H), 3.54 (m, 3H), 3.33 (d, J = 10.7 Hz, 1H), 3.30 (d, J = 10.7 Hz, 1H), 3.04 (d, J = 3.0 Hz, 1H), 2.80–1.50 (br m, 10H), 2.57 (d, J = 6.0 Hz, 1H), 2.14 (t, J = 5.8 Hz, 1H), 1.77 (m, 2H), 1.61 (t, J = 7.6 Hz, 2H), 1.40 (q, J = 7.5 Hz, 4H), 1.28 (t, J = 7.8 Hz, 2H), 1.11 (m, 4H), 1.00 (s, 1H), 0.81 (t, J = 7.5 Hz, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 7.71, 22.8, 30.0, 30.1, 32.2, 37.7, 37.9, 63.6, 70.4. 73.0, 73.6, 73.7, 74.4, 76.4, 81.0; LRMS (ESI+) 457 [(M+Na)+]; HRMS (ESI+) m/z 459.3866 [(M+Na)+: calcd for $C_{17}H_{42}B_{10}NaO_5$, 459.3859].

4.2.34. 1-(5-Ethyl-5-hydroxyheptyl)-12-(3,4,5-trihydroxypentyloxy)methyl-1,12-dicarba-*closo*-dodecaborane (44)

Compound **44** was prepared by the similar procedure that in case of compound **43** but using compound **40** as a reaction substrate (88%). Compound **44**: colorless oil, ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.83 (m, 1H), 3.73 (m, 2H), 3.53 (m, 2H), 3.50 (m, 1H), 3.31 (s, 2H), 3.08 (d, J = 3.2 Hz, 1H), 2.80–1.50 (br m, 10H), 2.75 (d, J = 3.6 Hz, 1H), 2.22 (dd J = 6.9 Hz, 5.1 Hz, 1H), 1.86 (m, 1H), 1.69 (m, 1H), 1.65 (m, 2H), 1.38 (q, J = 7.5 Hz, 4H), 1.27 (m, 2H), 1.10 (m, 4H), 0.99 (s, 1H), 0.80 (t, J = 7.5 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 80.9, 74.4, 73.6, 73,5, 72.0, 70.0, 64.7, 37.9, 37.7, 32.8, 30.9, 30.0, 22.9, 7.7; LRMS (ESI+) 457 [(M+Na)+]; HRMS (ESI+) m/z 459.3865 [(M+Na)+: calcd for $C_{17}H_{42}B_{10}NaO_5$, 459.3859].

4.2.35. 1-(5-Ethyl-5-hydroxyheptyl)-12-(3,5-dihydroxy-4-methoxypentyloxy)methyl-1,12-dicarba-*closo*-dodecaborane (45)

Compound **45** was prepared by the similar procedure that in case of compound **43** but using compound **41** as a reaction substrate (93%). **45**: colorless oil, ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.88 (m, 1H), 3.79 (dd, J = 6.1 Hz, 4.4 Hz, 1H), 3.56 (m, 1H), 3.49 (ddd, J = 9.0 Hz, 9.0 Hz, 4.0 Hz, 1H), 3.44 (s, 3H), 3.32 (d, J = 10.8 Hz, 1H), 3.29 (d, J = 10.8 Hz. 1H), 3.08 (m, 1H), 2.99 (d, J = 2.6 Hz, 1H), 2.80–1.50 (br m, 10H), 2.33 (t, J = 6.2 Hz, 1H), 2.05 (m, 1H), 1.74 (m, 1H), 1.63 (m, 2H), 1.39 (q, J = 7.4 Hz, 4H), 1.27 (m, 2H), 1.11 (m, 4H), 0.98 (s, 1H), 0.81 (t, J = 7.4 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 83.2, 80.9, 74.4, 73.6, 71.6, 70.6, 61.0, 57.8, 53,4, 37.9, 37.7, 32.6, 30.9, 30.0, 22.9, 7.71; LRMS (ESI+) 471 [(M+Na)+]; HRMS (ESI+) m/z 473.4027 [(M+Na)+: calcd for $C_{18}H_{44}B_{10}NaO_5$, 473.4015].

4.2.36. 1-(5-Ethyl-5-hydroxyheptyl)-12-(3,5-dihydroxy-4-methoxypentyloxy)methyl-1,12-dicarba-*closo*-dodecaborane (46)

Compound **46** was prepared by the similar procedure that in case of compound **43** but using compound **42** as a reaction substrate (95%). **46**: colorless oil, ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.91(m, 1H), 3.85 (m, 1H), 3.68 (m, 1H), 3.50 (m, 2H), 3.48 (s, 3H), 3.30 (s, 2H), 3.20 (ddd, J = 4.5 Hz, 4.5 Hz, 4.5 Hz, 1H), 2.80–1.50 (br m, 10H), 2.78 (d, J = 3.6 Hz, 1H), 2.17 (t, J = 6.0 Hz, 1H), 1.73 (m, 2H), 1.61 (m, 2H), 1.37 (q, J = 7.5 Hz, 4H), 1.27 (m, 2H), 1.10 (m, 4H), 0.98 (s, 1H), 0.80 (t, J = 7.5 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 82.2, 80.8, 74.3, 73.5, 70.7, 69.6, 61.2, 58.4, 37.9, 37.7, 32.3, 30.9, 30.0, 22.9, 7.71; LRMS (ESI+) 471 [(M + Na)+]; HRMS (ESI+) m/z 473.4029 [(M+Na)+: calcd for $C_{18}H_{44}B_{10}NaO_5$, 473.4015].

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$(OH)_2D_3$ 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.

Acknowledgments

This work was partly supported by JSPS KAKENHI Grant Nos. 23790128 and 25360146 (to F.S.), No. 24590137 (to A.T.), No. 22136013 (to H.K.), JSPS Core-to-Core Program, A. Advanced Research Networks, and MEXT Platform for Drug Discovery, Informatics, and Structural Life Science, Japan. A.T. thanks The Naito Foundation for financial support.

References and notes

1. Evans, R. M. *Science* **1988**, *240*, 889.
2. 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.
3. *Vitamin D*; Feldman, D., Pike, J. W., Glorieux, F. H., Eds., 2nd ed.; Elsevier Academic Press: New York, 2005.
4. 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.
5. Hosoda, S.; Tanatani, A.; Wakabayashi, K.; Nakano, Y.; Miyachi, H.; Nagasawa, K.; Hashimoto, Y. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4327.
6. 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.
7. Wongmayura, A.; Fujii, S.; Ito, S.; Kano, A.; Taoda, Y.; Kawachi, E.; Kagechika, H.; Tanatani, A. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 1756.
8. Fujii, S.; Kano, A.; Songkram, C.; Masuno, H.; Taoda, Y.; Kawachi, E.; Hirano, T.; Tanatani, A.; Kagechika, H. *Bioorg. Med. Chem.* **2014**, *22*, 1227.
9. *Carboranes*; Grimes, R. N., Ed., 2nd ed.; Elsevier Academic Press: New York, 2011.
10. *The Borane, Carborane, Carbocation Continuum*; Casanova, J., Ed.; Wiley Interscience: New York, 1998.
11. 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; (d) Issa, F.; Kassiou, M.; Rendina, L. M. *Chem. Rev.* **2011**, *111*, 5701.
12. Fujii, S.; Kano, A.; Masuno, H.; Songkram, C.; Kawachi, E.; Hirano, T.; Tanatani, A.; Kagechika, H. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 4515.
13. Sicinski, R. R.; Prahl, J. M.; Smith, C. M.; DeLuca, H. F. *J. Med. Chem.* **1998**, *41*, 4662.
14. Konno, K.; Maki, S.; Fujishima, T.; Liu, Z.; Miura, D.; Chokki, M.; Takayama, H. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 151.
15. Konno, K.; Fujishima, T.; Maki, S.; Liu, Z.; Miura, D.; Chokki, M.; Ishizuka, S.; Yamaguchi, K.; Kan, Y.; Kurihara, M.; Miyata, N.; Smith, C.; DeLuca, H. F.; Takayama, H. *J. Med. Chem.* **2000**, *43*, 4247.
16. Fujishima, T.; Konno, K.; Nakagawa, K.; Tanaka, M.; Okano, T.; Kurihara, M.; Miyata, N.; Takayama, H. *Chem. Biol.* **2001**, *1011*, 8.
17. Aungst, R. A., Jr.; Funk, R. L. *J. Am. Chem. Soc.* **2001**, *123*, 9455.
18. Soboleva, S. G.; Gren', A. I.; Samitov, Y. Y.; Bogatskii, A. V. *Chem. Heterocycl. Compds.* **1972**, *8*, 1321.
19. Review of reactions of carboranes Kaszynski, P. *Collect. Czech. Chem. Commun.* **1999**, *64*, 895.
20. Mangelsdorf, D. J.; Koeffler, H. P.; Donaldson, C. A.; Pike, J. W.; Haussler, M. R. *J. Cell Biol.* **1984**, *98*, 391.
21. Perlman, K. L.; Sicinski, R. R.; Schnoes, H. K.; DeLuca, H. F. *Tetrahedron Lett.* **1990**, *31*, 1823.
22. Vanhooke, J. L.; Benning, M. M.; Bauer, C. B.; Pike, J. W.; DeLuca, H. F. *Biochemistry* **2004**, *43*, 4101.