Dicarba-closo-dodecaboranes as a Pharmacophore. Retinoidal Antagonists and Potential Agonists

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Synthesis and biological evaluation of the first dicarba-closo-dodecaborane (carborane) derivatives of retinoids are described. Their retinoidal activity were examined in terms of the differentiation-inducing ability toward human promyelocytic leukemia HL-60 cells. High retinoidal activity (agonist or antagonist for retinoic acid receptor (RAR)) requires a carboxylic acid moiety and an appropriate hydrophobic group located at a suitable position on the molecule. The 4-carboranyl-substituted compounds (7, 11) showed antagonistic activity but no agonistic activity even in the presence of the potent synergist HX630. On the other hand, the 3-carboranyl-substituted compounds (8, 12) showed potential agonistic activity, but no antagonistic activity. The results indicates that carboranes are applicable as the hydrophobic moiety of biologically active molecules.

Key words carborane; dicarba-closo-dodecaborane; retinoid; differentiation; boron neutron capture therapy

Boron neutron capture therapy (BNCT) is of increasing interest for the treatment of cancers such as gliomas and melanomas.1) When the 10B isotope is irradiated with slow (thermal) neutrons, an [n,α] reaction ensues, giving Li and 4He nuclei with high kinetic energy (2.4 MeV). The α-particle and lithium ion dissipate their kinetic energy before traveling one cell diameter (ca.10 μm) in biological tissue and damage is limited to the cell containing the boron. One of the major challenges in the development of BNCT has been the design and synthesis of boron compounds2) which have the capacity for selectively targeting malignant cells and which can be accumulated intracellularly at a sufficient concentration to deliver an effective radiation dosage. One stable, non-toxic, and synthetically amenable functionality that allows significant amounts of boron incorporation for BNCT is the 1,2-dicarba-closo-dodecaborane (o-carborane) cage. Carborane-containing nucleic acid precursors,3) amino acids,4) porphyrins5) and DNA binders6) have been synthesized in attempts to target boron to tumors. From the viewpoint of potential for the rapid targeting of tumor cells, nuclear receptor ligands which bind to estrogen, thyroid, progesterone and retinoic acid receptors are promising synthetic targets, although it is not clear whether a concentration sufficient to deliver an effective dosage can be achieved. Several estrogen-related compounds bearing carboranes have been reported.7)

In contrast to the interest in carboranes for BNCT, little attention has been paid to carboranes as building blocks of biologically active compounds. Most carborane-containing compounds which have been synthesized are composed of cellular building blocks (nucleic acid, amino acid, etc.), to which carborane units are added. Carboranes are a class of carbon-containing polyhedral boron-cluster compounds.8) One of their most striking features is the ability of the 2 carbon atoms and 10 boron atoms to adopt icosahedral geometry in which the carbon and boron atoms are hexacoordinated. This feature of the icosahedral structure gives rise to the unusual properties of such molecules and their carbon and boron derivatives. For example, the stability of the carborane cage has been demonstrated under many reaction conditions and the hydrophobic character is comparable to that of hydrocarbons. In this article, we describe the synthesis and biological evaluation of carborane-containing retinoids in order to test the applicability of carboranes as a hydrophobic moiety. Figure 1 illustrates the structure of 1,2-dicarba-closo-dodecaborane (carborane). In icosahedral cage structures throughout this paper, closed circles (•••) represent carbon atom and other vertices represent BH units.

Design and Synthesis of Carborane-Containing Retinoids Retinoids, i.e., all-trans-retinoic acid (Fig. 2, 1) and its analogs, are of particular interest as chemopreventive and therapeutic agents in the fields of dermatology and oncology.9) Retinoids are able to induce differentiation of a wide spectrum of cell types, such as embryonal carcinoma cells, promyelocytic leukemia cells, and normal and malignant keratinocytes.10) The mechanism of these effects on cell differentiation and morphogenesis involves modulation of specific gene transcription through the retinoic acid receptors (RAR-α, β, γ).11) A number of retinoids are known to be agonists of retinoic acid, and they bind to RARs. The retinoidal actions are also modulated by retinoid X receptors (RXR-α, β, γ)), which bind 9-cis-retinoic acid (2).10) Recent work on the design of synthetic retinoids12) and the availability of three-dimensional (3D) structure information13) have revealed the structural requirements for the appearance of retinoidal activity, including subtype-selectivity. For example, the retinobenzoic acids Am80 (3) and Am555S (4), which activate RAR-α and -β, exhibit potent retinoidal activities. High binding affinity for RAR requires a carboxylic acid moiety and an appropriate hydrophobic group located at a suitable position on the molecule, such as in 3 and 4.12) A retinobenzoic acid with a bulky hydrophobic group, CD-394 (5), has been reported to be a strong differentiation inducer of F9 mouse embryonal carcinoma cells.14) However, the

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differentiation activity of 5 toward human promyelocytic leukemia cells (HL-60) is only moderate and the maximum response obtained with 5 was smaller than that with 3. It appears that 5 may be a partial agonist-antagonist. Introduction of a bulkier hydrophobic group, such as the pentacyclooctadecane (diamantyl) group (TD550, 6), afforded clear antagonistic activity. These results led us to synthesize and investigate compounds having carboranes as a hydrophobic moiety, as shown in Fig. 3.

The syntheses of the designed molecules are summarized in Chart 1. Compounds 7 and 8 were prepared from 1-phenyl-1,2-dicarba-closo-dodecarbaborane (13a), which is easily prepared from ethynylbenzene and decaborane(14) (B_{10}H_{14}). Compound 13a was converted to 1-phenyl-2-alkyl-1,2-dicarba-closo-dodecarbanes (13b—d) by lithiation followed by reaction with alkyl halide, in high yields. Nitrification of 13a with a mixed acid system has been reported to afford a mixture of 3- and 4-nitro isomers, or a mixture of 2- and 4-nitro isomers under similar conditions. We found that nitrification of 13a with mixed acid/CH₂Cl₂ afforded the 4-nitro (14a) and 3-nitro (15a) isomers in 65% and 19% yields, respectively. The 3-nitro isomers were the major isomers in the case of nitrification of 1-phenyl-2-alkyl-1,2-carboranes (13b—d). Isolated yields of the 4-nitro (14b—d) and 3-nitro (15b—d) isomers were 35—37% and 47—57%. Catalytic hydrogenation of the nitro group of 14 or 15 followed by reaction with terephthalic acid monomethyl ester chloride gave esters in yields of 58—97%. Hydrolysis of the ester group gave 7 and 8 in yields of 71—98%. Compound 9 was prepared from 2-iodoanisole. Palladium-catalyzed coupling of 2-iodoanisole with ethynyltrimethylsilane followed by deprotection of the trimethylsilyl group gave 2-ethynylanisole (16) (99%). Reaction of 16 with decaborane(14) in the presence of acetonitrile afforded 1-(2′-methoxyphenyl)-1,2-dicarba-closo-dodecarbaborane (17) (49%). Nitrification of 17 gave the 5′-nitro isomer as the sole product in 70% yield. Catalytic hydrogenation, followed by coupling with terephthalic acid monomethyl ester chloride and hydrolysis afforded 9 (68%). Compound 10, in which the distance between the hydrophobic carborane group and the carboxylic acid moiety is shortened, was prepared from 3-trimethylsilyl-2-propyn-1-ol (19). Reaction of 19 with triethylphosphonoacetate in the presence of sodium hydride gave 20 (65%). Deprotection of the trimethylsilyl group gave ethyl pent-2-en-4-ynoic acid (21) (79%). Decarborylation with decaborane(14) gave the unsaturated ester 22 (64%), which was converted to the acyl chloride by alkaline hydrolysis and treatment with oxalyl chloride. Condensation of the acyl chloride with methyl 4-aminobenzoate followed by hydrolysis gave 10 (13%). Compounds 11 and 12 were prepared from ethyl 4- (25) and 3-ethynylbenzoate (26), respectively. The ethynyl benzoates were obtained from ethyl 4- and 3-bromobenzoates using the reported method. The ethyl ethynylbenzoates 25 and 26 were converted to acyl chlorides by alkaline hydrolysis and treatment with oxalyl chloride. Condensation of the acyl chlorides with methyl 4-aminobenzoate followed by hydrolysis gave 11 and 12 (20—37%).

**Biological Activity of Carborane-Containing Retinoids**

The biological activity of compounds 7—12 was examined by use of the assay of differentiation induction of HL-60 cells to granulocytes. The morphological changes were examined by microscopy after Wright–Giemsa staining, and the percentages of differentiated cells were determined with nitro blue tetrazolium (NBT) reduction assay as a functional marker of differentiation. Compounds bearing 1,2-carborane at the 4-position of the benzene nucleus (7, 11) were completely inactive as differentiation inducers at concentrations below 10⁻⁸ M. However, examination of their ability to inhibit the differentiation-inducing ability of Am80 (3) indicated that these carborane-containing compounds are retinoid antagonists (Fig. 4); they inhibited the activity of Am80 at the concentration of 1×10⁻⁴ M. For example, the response to Am80 at 3.3×10⁻⁴ M (55% NBT positive cells) was reduced in the presence of 1×10⁻⁴ M 7a to 23%. The compounds bearing an alkyl group at the 2-position of the 1,2-carborane cage (7b—
(PPh₃)₂PdCl₂, CuI, iso-Pr₂NH, THF; f) K₂CO₃/ EtOH; g) decaborane(14)/ CH₂Cl₂-C₆H₆, h) (Er(OTf)₃)PO(OEt)₂, NaH/ THF; i) (COC)₃POH, DMF (cat)/ CH₂Cl₂; j) methyl 4-aminobenzoate/ pyridine; k) (n-C₆H₄)₃N⁺TF⁻/ THF.

Chart 1

Fig. 4. Effect of Carborane-Containing Compounds at 1.0×10⁻⁶ M Concentration on HL-60 Cell Differentiation Induced by Am80

Fig. 5. Effect of Compound 7b at 3.3×10⁻⁵–1.0×10⁻⁶ M Concentration on HL-60 Cell Differentiation Induced by 3.3×10⁻⁵ M Am80

The percentage of differentiation were averages of four repetition for each experiment. Each point represents the mean±S.E. (n=4).

d) also exhibited potent activity. The most potent of them (7b) dose-dependently decreased the percentage of differentiated cells induced by Am80 (in the presence of 3.3×10⁻⁵ M Am80, 0, 3.3×10⁻⁶, 1×10⁻⁷, 3.3×10⁻⁸ and 1×10⁻⁹ M 7b, afforded 62, 53, 43, 15 and 6% differentiated cells, respectively, in a separate experiment (Fig. 5)). Compound 11, in which the -NHCO- group of 7a is replaced with -CONH- and compound 9, which is the 1,2-carborane analog of CD-394 (5) or TD550 (6), exhibited a similar antagonistic activity to that of 7a.

On the other hand, the biological activities of the compounds with 1,2-carborane at the 3-position of the benzene nucleus (8, 12) were different in nature from that of the 4-
carbonyl derivatives 7 and 11. Compounds 8 and 12 were almost inactive as differentiation inducers at concentrations below $10^{-7}$M (less than 10% cellular response). However, the extent of differentiation (less than 10%) induced by $1 \times 10^{-6}$M 8 or 12 was significantly increased by the addition of $1 \times 10^{-7}$M HX630. (Fig. 2, 29) which is a potent retinoidal synergist[11] (Fig. 6). For example, the response to 8 at $1 \times 10^{-6}$M (less than 10%) was enhanced to 93% in the presence of $1 \times 10^{-7}$M HX630. The synergistic activities of HX630 result from binding to the RXR site of RXR–RAR heterodimers, and the binding enhances the activities of RAR-specific ligands such as Am80. The smaller molecule 10 exhibited a similar activity to that of 8 and 12. These compounds show no antagonistic activity (such as those of 7, 9 and 11) at $1 \times 10^{-6}$M.

The carbonyl-containing compounds show clear sub- stantial effects, as follows. 1) The 4-carbonyl-stabilized substituted compounds showed antagonistic activity but no agonistic activity even in the presence of the potent synergist HX630. 2) The 3-carbonyl-stabilized substituted compounds showed potential agonistic activity, but no antagonistic activity. Compound 9, which was designed as a 1,2-carbonyl analog of the retinoid partial agonist CD-394 (5) or antagonist TD550 (6), expectedly exhibited antagonistic activity almost equal to that of TD550 (6) and weak agonistic activity. These results indicate that the carbonyl cage has similar effects to the diamantyl group. The resultant side effects of carbonyl compounds also suggest that the presence of methoxy groups in which the methyl group is directed to the outer side by a bulky substituent in 9 and 6 is important for the appearance of the characteristic activities.

The results of this study demonstrate that carboxylenes are applicable as the hydrophobic moiety of biologically active molecules. In addition, there is a possibility that the carbonyl-containing retinoids synthesized here for the first time may be of value for BNC of cancers with retinoid receptors. Receptor site density is generally believed to be too low to afford a ligand concentration sufficient to deliver an effective radiation dose in BNC, however, the compounds with mild affinity for RAR and non-toxicity for cells will be possibly effective by concentrating boron in the cell nucleus.

### Experimental

**General Remarks** Melting points were obtained on a Yanagimoto micro hot stage without correction. $^1$H-NMR spectra were recorded with a JEOL JNM-FX-400 spectrometer (400 MHz), with tetramethylsilane (TMS) as an internal standard and chemical shifts are given in ppm as δ values from TMS. Mass spectra were recorded on a JEOL JMS-D-300 for EI (electron ionization)-Mass. Column chromatography was performed on silica gel (Merck 7734 or 9385 (flash chromatography)).

**1-Phenyl-1,2-dicarboxy-cyclo-dodecaborane (13a)** A mixture of ethynylbenzene (5.51 g, 53.9 mmol) and decaborane(14) (2.64 g, 21.6 mmol) in acetonitrile (5.5 ml) and benzene (55 ml) was refluxed for 4 d under an Ar atmosphere, then concentrated. Purification by silica gel column chromatography (eluent: hexane) gave 13a (74%). 13a: Colorless prisms (hexane); mp 66–67°C; $^1$H-NMR (CDCl₃) δ 1.50 – 3.10 (1H, brm), 3.97 (1H, brs), 7.33 (2H, m), 7.39 (1H, m), 7.49 (2H, m).

**1-Methyl-1-phenyl-1,2-dicarboxy-cyclo-dodecaborane (13b)** To a solution of 13a (950 mg, 4.31 mmol) in dry Et₂O (15 ml) was added dropwise a 1.54 M solution of n-BuLi in hexanes (2.8 ml, 4.31 mol) at 0°C under an Ar atmosphere. The mixture was stirred at room temperature for 3 h. The solution was cooled to –78°C and methyl iodide (673 mg, 4.74 mmol) in tetrahydrofuran (THF) (3 ml) was added dropwise, then the mixture was stirred at –78°C–room temperature for 16 h. The reaction mixture was quenched with 2N HCl, and the whole was extracted with Et₂O. The organic layer was washed with water and brine, dried over Na₂SO₄, and concentrated. Purification of the residue by silica gel column chromatography (eluent: hexane) gave 13b (94%). 13b: Colorless prisms (hexane); mp 102–103°C; $^1$H-NMR (CDCl₃) δ 0.97 (3H, t, J = 7.5 Hz), 1.71 (7H, m), 7.39 (2H, m), 7.46 (1H, m), 7.62 (2H, m). HR-MS: Calcd for C₂₁H₂₅B₂O₇: 324.2421. Found: 324.2422.

**1-Ethyl-2-phenyl-1,2-dicarboxy-cyclo-dodecaborane (13c)** 13c was prepared from 13a (1.00 g, 4.54 mmol), n-BuLi (1.6 mol solution in hexane 2.55 ml, 4.08 mmol) and ethyl iodide (835 mg, 4.54 mmol) in a manner similar to that used for the preparation of 13b. Purification by silica gel column chromatography (eluent: hexane) gave 13c (88%). 13c: Colorless prisms (hexane); mp 68–69°C; $^1$H-NMR (CDCl₃) δ 0.97 (3H, t, J = 7.5 Hz), 2.18 (3H, s), 3.89 (2H, brm), 7.28 (2H, m), 7.46 (1H, m), 7.64 (2H, m). HR-MS: Calcd for C₂₁H₂₅B₂O₇: 324.2426. Found: 324.2458.

**1-Isobutyl-2-phenyl-1,2-dicarboxy-cyclo-dodecaborane (13d)** 13d was prepared from 13a (1.00 g, 4.54 mmol), n-BuLi (1.6 mol solution in hexane 2.55 ml, 4.08 mmol) and isobutyl iodide (708 mg, 4.54 mmol) in a manner similar to that used for the preparation of 13b. Purification by silica gel column chromatography (eluent: hexane) gave 13d (50%) and recovered 13a (39%). 13d: Colorless prisms (hexane); mp 65–66°C; $^1$H-NMR (CDCl₃) δ 0.80 (6H, d, J = 6.6 Hz), 1.50–3.50 (10H, brm), 2.28 (2H, m), 7.28 (2H, m), 7.46 (1H, m), 7.62 (2H, m). HR-MS: Calcd for C₂₁H₂₇B₂O₇: 327.2884. Found: 327.2894.

**General Procedure for Nitration of 13a–d:** 12-(2-Methyl-1,2-dicarboxy-cyclo-dodecaboran-1-yl)nitrobenzene (14b) and 3-(2-Methyl-1,2-dicarboxy-cyclo-dodecaboran-1-yl)nitrobenzene (15b) A solution of 13b (16 mg, 3.84 mmol) in CH₂Cl₂ (17.5 ml) was added dropwise to a solution of concentrated HNO₃, and concentrated HSO₃ (15.85 v/v) (17.5 ml) at 0°C. The mixture was stirred at room temperature for 4 h, then poured onto ice and extracted with CH₂Cl₂. The organic layer was washed with brine, dried over Na₂SO₄, and concentrated. Purification by silica gel flash column chromatography (eluent: hexane/AcOEt, 30:1) gave 14b (34%) and 15b (57%). 14b: Colorless prisms (AcOEt–hexane); mp 105–106°C; $^1$H-NMR (CDCl₃) δ 1.50–3.50 (10H, brm), 1.73 (3H, s), 7.87 (2H, d, J = 9.0 Hz), 8.01 (1H, ddd, J = 9.0, 8.1 Hz), 8.13 (1H, ddd, J = 1.1, 2.0, 8.1 Hz), 8.34 (1H, ddd, J = 1.1, 2.0, 8.1 Hz), 8.53 (1H, t, J = 2.0 Hz). HR-MS: Calcd for C₂₁H₂₅B₂O₇NO: 329.2262. Found: 329.2264.

14a and 15a: Purification by silica gel flash column chromatography (eluent: hexane/AcOEt, 8:1) gave 14a (65%) and 15a (15%). 14a: Colorless prisms (AcOEt–hexane); mp 170–172°C; $^1$H-NMR (CDCl₃) δ 1.50–3.50 (10H, brm), 4.02 (1H, brs), 7.67 (2H, d, J = 9.2 Hz), 8.21 (2H, d, J = 9.2 Hz).

15a: Colorless prisms; mp 142–143°C ($^1$H-NMR (CDCl₃) δ 1.50–3.50 (10H, brm), 4.03 (1H, brs), 7.58 (1H, t, J = 8.1 Hz), 7.86 (1H, ddd, J = 0.9, 2.0, 8.1 Hz), 8.28 (1H, ddd, J = 0.9, 2.0, 8.1 Hz), 8.34 (1H, J = 1.1, 2.0, 8.1 Hz), 8.53 (1H, t, J = 2.0 Hz). HR-MS: Calcd for C₂₁H₂₇B₂O₇N: 329.2262. Found: 329.2263.
9.0 Hz), 8.25 (2H, d, J = 9.0 Hz). HR-Ms: Calculated for C_{19}H_{18}B_{2}N_{2}O; 293.2419. Found: 293.2400. 15c: Colorless prisms (AcOEt-hexane); mp 108–109°C; 1H-NMR (CDCl3) δ 1.01 (3H, t, J = 7.5 Hz), 1.50–3.50 (10H, brm), 1.87 (2H, q, J = 7.5 Hz), 7.63 (1H, t, J = 8.1 Hz), 7.99 (1H, dd, J = 0.7, 2.0, 6.3 Hz), 8.23 (1H, dd, J = 0.7, 2.0, 8.1 Hz), 8.51 (1H, t, J = 2.0 Hz). HR-MS: Calculated for C_{19}H_{18}B_{2}N_{2}O; 293.2409. Found: 293.2437.

14d and 15d: Purification by silica gel flash column chromatography (eluent: hexane/AcOEt, 30:1) gave 14d (37%) and 15d (47%); 14d: Colorless prisms (AcOEt-hexane); mp 84–85°C; 1H-NMR (CDCl3) δ 0.83 (6H, d, J = 6.6 Hz), 1.50–3.50 (10H, brm), 1.65 (2H, dJ = 5.5 Hz), 1.74 (1H, m), 7.84 (2H, dJ = 9.2 Hz), 8.26 (2H, dJ = 9.2 Hz). Anal. Calculated for C_{19}H_{18}B_{2}N_{2}O; C: 44.84; H: 7.21; N: 4.36. Found: C: 44.75; H: 7.34; N: 4.32. 15d: Colorless prisms (AcOEt-hexane); mp 118–120°C (dec); 1H-NMR (CDCl3) δ 0.83 (6H, d, J = 6.4 Hz), 1.50–3.50 (10H, brm), 1.66 (2H, dJ = 5.5 Hz), 1.74 (1H, m), 7.63 (1H, t, J = 8.1 Hz), 7.98 (1H, dd, J = 0.7, 2.0, 8.1 Hz), 8.35 (1H, dd, J = 0.7, 2.0, 8.1 Hz), 8.50 (1H, t, J = 2.0 Hz). Anal. Calculated for C_{19}H_{18}B_{2}N_{2}O; C: 44.84; H: 7.21; N: 4.36. Found: C: 44.46; H: 7.04, N: 4.36.

General Procedure for Preparing 7a—7d from 14a—14d, and 8a—8d from 15a—15d: 4-[2-(Methyl-1,2-dicarbos-closodicoborad-1-yl)-phenylcarbamoyl]benzoic Acid (7b) A solution of 14d (349 mg, 1.25 mmol) in EtOAc (25 ml) was hydrogenated over 10% Pd/C (87 mg) at room temperature for 1 h under atmospheric pressure of hydrogen. After removal of the catalyst by filtration, the filtrate was concentrated to give 4-2-(methyl-1,2-dicarbos-closodicoborad-1-yl)-phenylcarbamoyl]benzoic acid (7b) (167 mg, 2.44 mmol, 59% yield). 1H-NMR (CDCl3) δ 1.00–3.50 (10H, brm), 1.65 (2H, dJ = 5.5 Hz), 7.65 (1H, t, J = 8.1 Hz), 7.99 (1H, dd, J = 0.7, 2.0, 8.1 Hz), 8.23 (1H, dd, J = 0.7, 2.0, 8.1 Hz), 8.50 (1H, t, J = 2.0 Hz). Anal. Calculated for C_{19}H_{18}B_{2}N_{2}O; C: 44.84; H: 7.21; N: 4.36. Found: C: 44.60; H: 7.04, N: 4.36.

2-Ethynylanisole (16) A mixture of 2-iodoanisole (4.0 g, 17.1 mmol), ethynyltrимethylsилane (2.52 g, 25.6 mmol), diisopropylamine (3.63 g, 35.9 mmol), copper(I) iodide (65.1 mg, 0.34 mmol), and bis(triphenylphosphine) palladium(II) chloride (360 mg, 0.512 mmol) in dry THF was stirred at room temperature for 3 h. The reaction was quenched with water and AcOH was extracted with AcOEt. The organic layer was washed with brine, dried over NaSO4, then concentrated. Purification by silica gel flash column chromatography (eluent: hexane to hexane/AcOEt, 30:1) gave 2-[trimethylisilyl]ethynylanisole as an orange oil (quantitative yield). 1H-NMR (CDCl3) δ 0.27 (9H, s), 3.88 (3H, s), 6.86 (1H, d, J = 8.1 Hz), 6.89 (1H, dJ = 1.1, 1.7 Hz), 7.28 (1H, m), 7.44 (1H, dd, J = 1.8, 7.7 Hz), KCO3 (2.36 g, 17.1 mmol) was added to a solution of 2-[trimethylisilyl]ethynylanisole (16, 1.14 g, 3.49 mmol) in dry THF for 1 h. The mixture was stirred at room temperature for 1 h, then concentrated. The residue was taken up in AcOEt. The organic layer was washed with water and brine, dried over NaSO4 and concentrated. Purification by silica gel flash column chromatography (eluent: hexane/CH2Cl2, 20:1 to 10:1) gave 16 (86%). 16: pale yellow oil; 1H-NMR (CDCl3) δ 3.31 (1H, s), 3.91 (3H, s), 6.90 (1H, dJ = 8.4 Hz), 6.92 (1H, dd, J = 0.9, 7.3 Hz), 7.33 (1H, dd, J = 1.8, 7.3 Hz), 7.47 (1H, dJ = 8.4 Hz). 1H-NMR (CDCl3) δ 8.1, 7.3. 1-(2-Methoxyphenyl)-1,2-dicarbos-closodicoboradene (17) A mixture of 16 (1.30 g, 9.84 mmol) and decaborane (14) (1.80 g, 14.7 mmol) in acetonitrile (5 ml) and benzene (50 ml) was refluxed for 23 h under an Ar atmosphere, then concentrated. Purification by silica gel flash column chromatography (eluent: hexane to hexane/AcOEt, 40:1) gave 17 (99%). 17: Colorless needles (AcOEt-hexane); mp 132–133°C; 1H-NMR (CDCl3) δ 1.50–3.50 (10H, brm), 3.85 (3H, s), 5.56 (2H, dJ = 8.6 Hz), 7.16 (1H, dJ = 8.1 Hz), 8.46 (1H, dJ = 8.4 Hz), 9.66 (1H, dJ = 1.1, 7.3, 8.1 Hz), 7.32 (1H, dd, J = 1.5, 7.3, 8.4 Hz), 7.61 (1H, dd, J = 1.5, 8.1 Hz). HR-Ms: Calculated for C_{19}H_{18}B_{2}O_{5}: 250.2361. Found: 250.2387.

1-(2-Methoxy-5-nitrophenyl)-1,2-dicarbos-closodicoboradene (18) Compound 18 was prepared from 17 by the same method as that used for preparation of 17. 9: Colorless needles (AcOEt-hexane); mp 230–282°C; 1H-NMR (CDCl3) δ 1.40–3.20 (10H, brm), 3.84 (3H, s), 5.96 (1H, brs), 7.13 (1H, dJ = 8.8 Hz), 7.90 (1H, dd, J = 2.2, 8.8 Hz), 8.04 (2H, dJ = 8.8 Hz), 8.07 (2H, dJ = 8.8 Hz), 8.11 (1H, dJ = 2.2 Hz), 10.41 (1H, s), 13.24 (1H, br. Anal. Calculated for C_{19}H_{18}B_{2}NO; C: 34.98; H: 5.61; N: 3.39. Found: C: 40.13; H: 5.3; 7.3. 3-Trimethylisilyl-2-propyn-1-ol (19) To a solution of ethynyltrimethylsilane (5.0 g, 50.9 mmol) in dry EtO (20 ml) was added dropwise at below 5°C over 30 min, then the mixture was stirred at room temperature for 2 h. The reaction was quenched with 2N HCl and extracted with EtO. The organic layer was washed with water, saturated aqueous NaHCO3, and brine, and dried over NaSO4. Purification by distillation gave 19 (28%); 3-Trimethylisilyl-2-propyn-1-ol (19). 19: Colorless oil; 1H-NMR (CDCl3) δ 0.27 (9H, s), 9.17 (1H, s). Ethyl 5-Trimethylisilyl-2-penten-4-ynoate (20) To a suspension of NaN (556 mg, 13.9 mmol) in THF (7 ml) was added dropwise ethyl diethylphosphonoacetate (3.12 g, 13.9 mmol) in THF (7 ml) under an Ar atmosphere.
mosphere. The mixture was stirred at room temperature for 30 min, then 19 in THF (7 mL) was added dropwise at 0°C. After having been stirred for 1.5 h at room temperature, the reaction mixture was poured into ice water, and the mixture was extracted with AcOEt. The organic layer was washed with brine, dried over Na₂SO₄, and filtered. The residue was purified by silica gel column chromatography (eluent: hexane/hexane/acetone, 50:10 to 20:1 give 65%). 20: Colorless oil; [H-NMR (CDCl₃)] δ 0.21 (9H, s), 1.29 (3H, t, J=7.2 Hz), 4.21 (2H, q, J=7.2 Hz), 6.24 (1H, d, J=15.9 Hz), 6.74 (1H, d, J=15.9 Hz).

Ethyl (E)-2-Penten-4-ynoate (21) K₂CO₃ (563 mg, 4.07 mmol) was added to a solution of 20 (800 mg, 4.07 mmol) in EtOH (10 mL), and the mixture was stirred at room temperature for 30 min, then the reaction mixture was washed with 2x HCl, and extracted with AcOEt. The organic layer was washed with water and brine, dried over Na₂SO₄, and then purified. Purification by silica gel column chromatography (eluent: hexane/hexane/acetone, 80:10) gave 21 (79%). 21: Colorless oil; [H-NMR (CDCl₃)] δ 1.30 (3H, J=7.1 Hz), 3.34 (1H, dd, J=0.7, 2.4 Hz), 4.23 (2H, q, J=7.1 Hz), 6.32 (1H, dd, J=0.7, 15.9 Hz), 6.72 (1H, dd, J=2.4, 15.9 Hz).

Ethyl 3-(1,2-dicarba-closo-dodecaboran-1-yl)-(E)-acrylate (22) A mixture of 21 (360 mg, 2.99 mmol) and decaborane(14) (532 mg, 4.35 mmol) in acetonitrile (1.5 mL) and benzene (15 mL) was refluxed for 17 h under an Ar atmosphere. The reaction mixture was collected. Purification by silica gel flash column chromatography (eluent: hexane/acetone, 10:1) gave 22 (64%). 22: Colorless prisms (hexane); mp 68–69°C; [H-NMR (CDCl₃)] δ 1.30 (3H, J=7.1 Hz), 1.50–3.40 (10H, br m), 3.69 (1H, br s), 4.42 (2H, q, J=7.1 Hz), 6.20 (1H, d, J=15.4 Hz), 6.84 (1H, d, J=15.4 Hz). Anal: Calcd for C₁₁H₁₁B₆O₢: C, 74.7; H, 7.49. Found: C, 74.4; H, 7.66.

4-(1,2-Dicarba-closo-dodecaboran-1-yl)-(E)-ethenylcarboxamido)benzoic Acid (24) A solution of 22 (220 mg, 0.908 mmol) in THF (5 mL) was added 1x KOH (3.84 mL, 3.94 mmol) and the mixture was stirred at room temperature for 7 h. After 1 h, the reaction was quenched with 2x HCl, and the whole was extracted with AcOEt. The organic layer was washed with brine, dried over Na₂SO₄, and then purified. Purification by silica gel flash column chromatography (eluent: CHCl₃/MeOH, 9:1) gave 4-(1,2-dicarba-closo-dodecaboran-1-yl)-(E)-propenoic acid (74%). [H-NMR (DMSO-d₆)] δ 1.40–3.20 (10H, br m), 3.57 (1H, br s), 6.22 (1H, d, J=15.4 Hz), 6.92 (1H, d, J=15.4 Hz), 13.00 (1H, br). To a solution of the acid (60 mg, 0.28 mmol) in CHCl₃ (1 mL) was added oxalyl chloride (53.2 mg, 0.42 mmol) and a catalytic amount of DMF (1 drop). The mixture was stirred for 1 h at room temperature, then concentrated. The residue was dissolved in pyridine (1 mL) and methyl 4-aminobenzoate (66.4 mg, 0.308 mmol) was added. The mixture was stirred for 18 h at room temperature, then the reaction was cooled and quenched with 2x HCl, and the whole was extracted with AcOEt. The organic layer was washed with water, saturated aqueous NaHCO₃, water and brine, dried over Na₂SO₄, and then filtered. Purification by silica gel flash column chromatography (eluent: hexane/acetone, 5:1) gave methyl 4-(1,2-dicarba-closo-dodecaboran-1-yl)-[E]-ethenylcarboxamido)benzoate (48% from 27). [H-NMR (CDCl₃)] δ 1.50–3.50 (10H, m), 3.92 (3H, s), 4.02 (1H, br s), 7.62 (2H, d, J=8.4 Hz), 7.72 (2H, d, J=8.8 Hz), 7.84 (2H, d, J=8.4 Hz), 7.89 (1H, br s), 8.07 (2H, d, J=8.8 Hz). A solution of the methyl benzoate (94 mg, 0.236 mmol) in THF (3 mL) was added 1x KOH (1.18 mL), and the mixture was stirred at 40°C for 16 h. The reaction was quenched with 2x HCl, and the whole was extracted with AcOEt. The organic layer was washed with water and brine, dried over Na₂SO₄, and then filtered. Purification by silica gel flash column chromatography (eluent: CHCl₃/MeOH, 5:1) gave 11 (41%). 11: Colorless needles (AcOEt); mp >300°C; [H-NMR (DMSO-d₆)] δ 1.40–3.20 (10H, br m), 5.92 (1H, br s), 7.76 (2H, d, J=8.8 Hz), 7.88 (2H, d, J=8.8 Hz), 7.94 (2H, d, J=8.4 Hz), 8.08 (2H, d, J=8.4 Hz), 8.12 (1H, S, br), 8.34 (1H, brs), 9.33 (1H, brs) ppm. Anal: Calcd for C₁₅H₁₂B₆NO₃: C, 50.18; H, 5.52; N, 3.65. Found: C, 50.18; H, 5.80; N, 3.41.

Ethyl 3-Ethynylbenzoate (26) A mixture of ethyl 3-bromobenzoate (1.0 g, 4.37 mmol), ethylbenzene (644 mg, 6.56 mmol), disopropylamine (929 mg, 9.20 mmol), copper(I) iodide (16.6 mg, 0.872 mmol), and bis(triphenylphosphine)palладium(II) chloride (123 mg, 0.175 mmol) in dry THF (8 mL) was heated at 45°C for 5 h under an Ar atmosphere. After cooling, the reaction mixture was diluted with water and extracted with AcOEt. The organic layer was washed with brine, dried over Na₂SO₄, and then filtered. Purification by silica gel flash column chromatography (eluent: hexane/AcOEt, 50:1) gave 26 (96%). 26: Colorless needles; mp 36–37°C; [H-NMR (CDCl₃)] δ 0.40 (3H, t, J=7.1 Hz), 1.32 (1H, t, J=7.1 Hz), 4.38 (2H, q, J=7.1 Hz), 7.41 (1H, J=7.8 Hz), 7.66 (1H, d, J=7.8, 1.5 Hz), 8.03 (1H, dt, J=7.8, 1.5 Hz), 8.17 (1H, t, J=1.5 Hz).

Ethyl 3-(1,2-Dicarba-closo-dodecaboran-1-yl)benzoate (28) Compound 28 was prepared from 26 (635 mg, 3.65 mmol) and decaborane(14) (446 mg, 3.65 mmol) in a manner similar to that described for 27. Purifica-
tion by silica gel flash column chromatography (eluent: hexane/AcOEt, 20:1) gave 28 (68%). 28: Colorless flakes (ethanol); mp 168–169°C, 1H-NMR (CDCl3) δ 1.41 (3H, t, J=7.7 Hz), 1.50–3.50 (10H, m), 4.04 (1H, br s), 4.40 (2H, q, J=7.1 Hz), 7.43 (1H, t, J=7.7 Hz), 7.70 (1H, ddd, J=1.1, 2.2, 7.7 Hz), 8.07 (1H, dt, J=7.7, 1.1 Hz), 8.10 (1H, t, J=1.7 Hz). HR-MS: Cacl for C21H20B2O3: 392.2466. Found: 392.2474.

4-[[3-(1,2-Dicarboxyloxydocosan-1-yl)phenyl]carboxamido]benzoic Acid (12) was prepared from 28 by the same procedure as that used for 11. 12: Colorless needles (AcOEt–hexane); mp 236–239°C, 1H-NMR (DMSO-d6) δ 1.40–3.20 (10H, br m), 5.89 (1H, br s), 7.60 (1H, t, J=8.0 Hz), 7.82 (1H, br d, J=8.0 Hz), 7.86 (2H, d, J=–8.8 Hz), 7.95 (2H, d, J=8.8 Hz), 8.04 (1H, br d, J=–8.8 Hz), 8.05 (1H, br s), 10.61 (1H, s), 12.89 (1H, br). HR-MS: Cacl for C31H24B2O7: 383.2523. Found: 383.2542. Anal. Calcd for C31H24B2O7: C, 48.97%; H, 5.65%; N, 3.57. Found: C, 48.99; H, 5.83; N, 3.49.

References and Notes