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 ^{10}B isotope is irradiated with slow (thermal) neutrons, an [n,α] reaction ensues, giving ^{7}Li and ^{4}He 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 compounds[2] 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, nontoxic, 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] porphyrins[5] and DNA binders[6] 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 retinoids[12] and the availability of three-dimensional (3D) structure information[13] 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

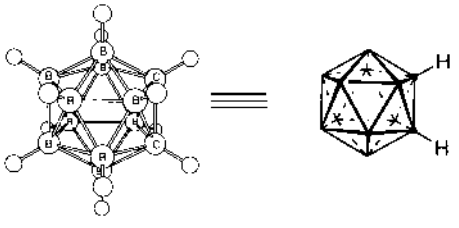

Fig. 1

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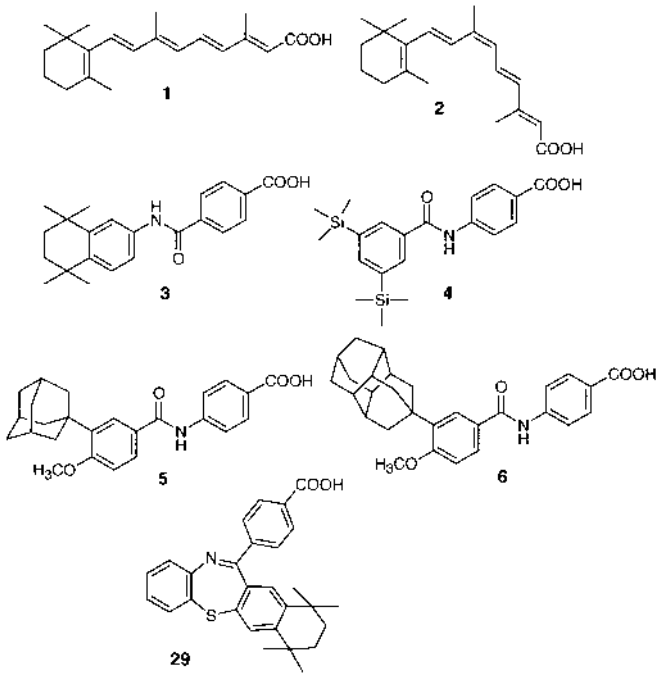


Fig. 2

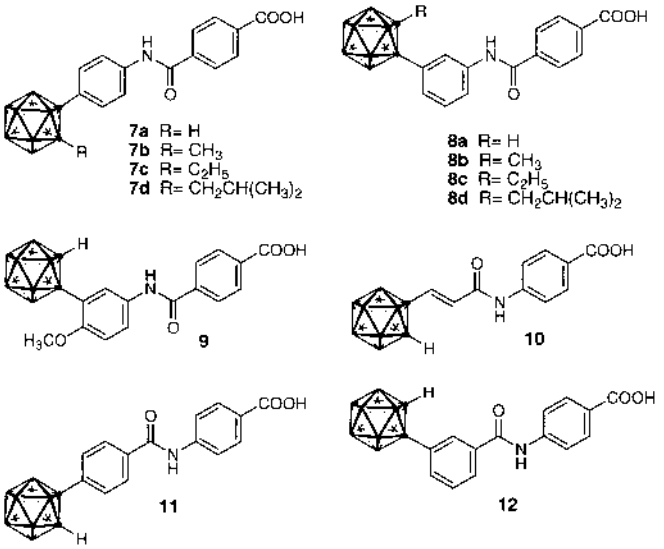


Fig. 3

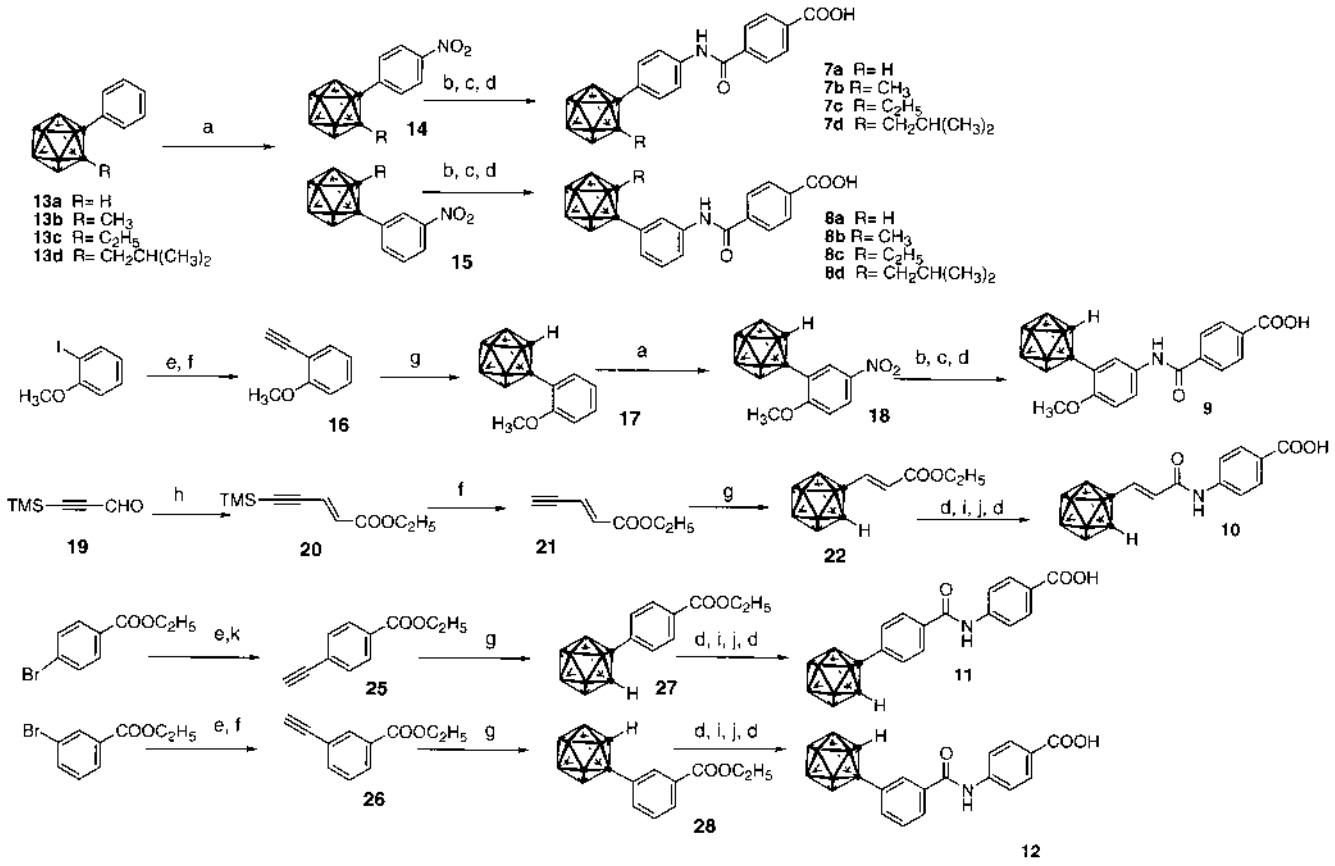
differentiation activity of **5** toward human promyelocytic leukemia cells (HL-60) is only moderate and the maximum response obtained with **5** was smaller than that with **3**. It appears that **5** may be a partial agonist–antagonist. Introduction of a bulkier hydrophobic group, such as the pentacyclotetradecane (diamantyl) group (TD550, **6**), afforded clear antagonistic activity.[15] 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*-dodecaborane (**13a**), which is easily prepared from ethynylbenzene and decaborane(14) ($B_{10}H_{14}$).[16] Compound **13a** was converted to 1-phenyl-2-alkyl-1,2-dicarba-*closo*-dodecaboranes (**13b**—**d**) by lithiation followed by reaction with alkyl halide, in high yields. Nitration of **13a** with a mixed acid system has been reported to afford a mixture of 3- and 4-nitro isomers,[16] or a mixture of 2- and 4-nitro isomers[17] under similar conditions. We found that nitration of **13a** with mixed acid/CH_2Cl_2 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 nitration of 1-phenyl-2-alkyl-1,2-carboranes (**13b**—**d**).[18] 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**) (89%). Reaction of **16** with decaborane(14) in the presence of acetonitrile afforded 1-(2′-methoxyphenyl)-1,2-dicarba-*closo*-dodecaborane (**17**) (49%). Nitration 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-al (**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%). Decaboranylation 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.[19] 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.[20] 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^{-6} M. However, examination of their ability to inhibit the differentiation-inducing ability of Am80 (**3**) indicated that these carborane-containing compounds are retinoidal antagonists (Fig. 4); they inhibited the activity of Am80 at the concentration of 1×10^{-6} M. For example, the response to Am80 at 3.3×10^{-10} M (55% NBT positive cells) was reduced in the presence of 1×10^{-6} M **7a** to 23%. The compounds bearing an alkyl group at the 2-position of the 1,2-carborane cage (**7b**—



a) HNO_3, H_2SO_4/ CH_2Cl_2; b) H_2, Pd-C/ EtOH; c) terephthalic acid monomethyl ester chloride/ pyridine; d) KOH/ H_2O-THF; e) ethynyltrimethylsilane, $(PPh_3)_2PdCl_2$, CuI, iso-Pr_2NH, THF; f) K_2CO_3/ EtOH; g) decaborane(14)/ CH_3CN-C_6H_6; h) $(EtO)_2POCH_2COOEt$, NaH/ THF; i) $(COCl)_2$, DMF (cat)/ CH_2Cl_2; j) methyl 4-aminobenzoate/ pyridine; k) $(n\text{-}C_4H_9)_4N^+F^-$/ THF.

Chart 1

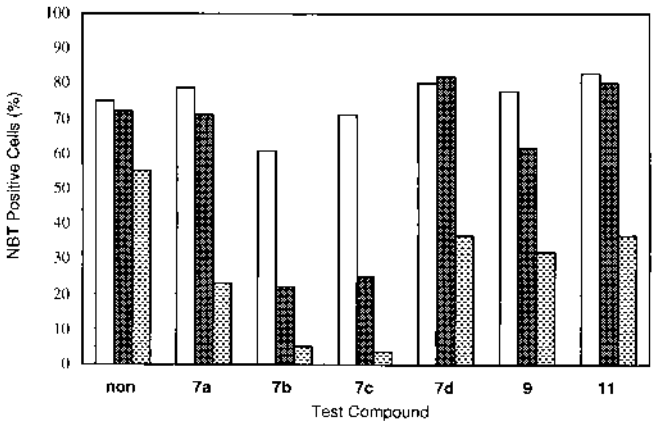


Fig. 4. Effect of Carborane-Containing Compounds at 1.0×10^{-6} M Concentration on HL-60 Cell Differentiation Induced by Am80

□ 3.3×10^{-9} M Am80, ■ 1.0×10^{-9} M Am80, ⊡ 3.3×10^{-10} M Am80.

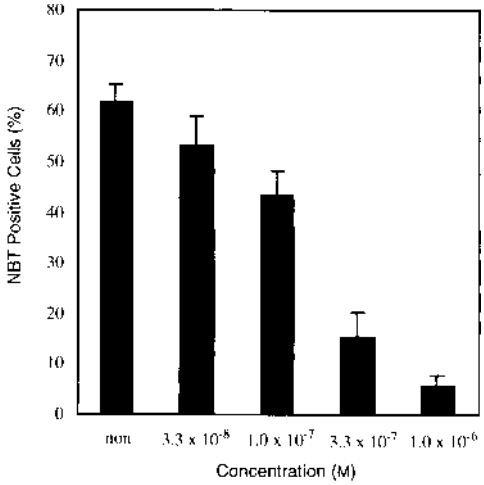


Fig. 5. Effect of Compound **7b** at 3.3×10^{-8}—1.0×10^{-6} M Concentration on HL-60 Cell Differentiation Induced by 3.3×10^{-3} M Am80

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^{-10} M Am80, 0, 3.3×10^{-8}, 1×10^{-7}, 3.3×10^{-7} and 1×10^{-6} 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-

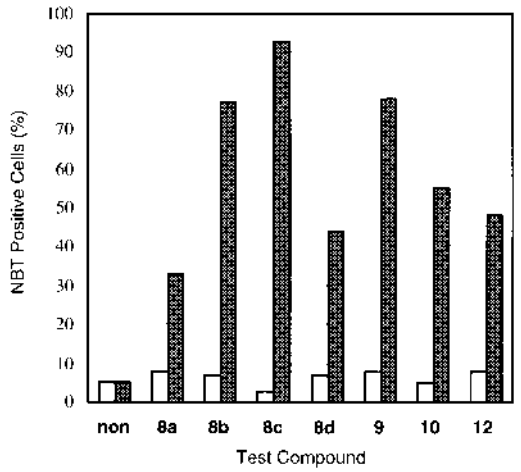


Fig. 6. HL-60 Cell Differentiation-Inducing Activity of Carborane-Containing Compounds at 1.0×10^{-6} M Concentration in the Presence of HX630 (1.0×10^{-7} M)

□ non, ■ 1.0×10^{-7} M HX630.

carboranyl derivatives **7** and **11**. Compounds **8** and **12** were almost inactive as differentiation inducers at concentrations below 10^{-6} M (less than 10% cellular response). However, the extent of differentiation (less than 10%) induced by 1×10^{-6} M **8** or **12** was significantly increased by the addition of 1×10^{-7} M HX630, (Fig. 2, **29**) which is a potent retinoidal synergist[21] (Fig. 6). For example, the response to **8c** at 1×10^{-6} M (less than 10%) was enhanced to 93% in the presence of 1×10^{-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 1×10^{-6} M.

The carborane-containing compounds show clear substituent effects, as follows. 1) The 4-carboranyl-substituted compounds showed antagonistic activity but no agonistic activity even in the presence of the potent synergist HX630. 2) The 3-carboranyl-substituted compounds showed potential agonistic activity, but no antagonistic activity. Compound **9**, which was designed as a 1,2-carborane 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 carborane cage has similar effects to the diamantyl group. The substituent effects of carboranes 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 carboranes are applicable as the hydrophobic moiety of biologically active molecules. In addition, there is a possibility that the carborane-containing retinoids synthesized here for the first time may be of value for BNCT 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 BNCT, 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-dicarba-*closo*-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 ($CDCl_3$) δ 1.50—3.50 (10H, br m), 3.97 (1H, br s), 7.33 (2H, m), 7.39 (1H, m), 7.49 (2H, m).

1-Methyl-2-phenyl-1,2-dicarba-*closo*-dodecaborane (13b) To a solution of **13a** (950 mg, 4.31 mmol) in dry Et_2O (15 ml) was added dropwise a 1.54 M solution of *n*-BuLi in hexanes (2.8 ml, 4.31 mmol) 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 was quenched with 2 N HCl, and the whole was extracted with Et_2O. The organic layer was washed with water and brine, dried over Na_2SO_4 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 ($CDCl_3$) δ 1.50—3.50 (10H, br m), 1.69 (3H, s), 7.39 (2H, m), 7.45 (1H, m), 7.65 (2H, m). HR-MS: Calcd for $C_9H_{18}B_{10}$: 234.2412. Found: 234.2422.

1-Ethyl-2-phenyl-1,2-dicarba-*closo*-dodecaborane (13c) **13c** was prepared from **13a** (1.00 g, 4.54 mmol), *n*-BuLi (1. 6 M 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 ($CDCl_3$) δ 0.97 (3 H, t, J=7.5 Hz), 1.50—3.50 (10H, br m), 1.85 (2H, q, J=7.5 Hz), 7.38 (2H, m), 7.45 (1H, m), 7.64 (2H, m). HR-MS: Calcd for $C_{10}H_{20}B_{10}$: 248.2568. Found: 248.2559.

1-Isobutyl-2-phenyl-1,2-dicarba-*closo*-dodecaborane (13d) **13d** was prepared from **13a** (1.00 g, 4.54 mmol), *n*-BuLi (1.6 M 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 ($CDCl_3$) δ 0.80 (6H, d, J=6.6 Hz), 1.50—3.50 (10H, br m), 1.65 (2H, d, J=5.5 Hz), 1.71 (1H, m), 7.39 (2H, m), 7.46 (1H, m), 7.62 (2H, m). HR-MS: Calcd for $C_{12}H_{24}B_{10}$: 276.2881. Found: 276.2894.

General Procedure for Nitration of 13a—d: 4-(2-Methyl-1,2-dicarba-*closo*-dodecaboran-1-yl)nitrobenzene (14b) and 3-(2-Methyl-1,2-dicarba-*closo*-dodecaboran-1-yl)nitrobenzene (15b) A solution of **13b** (900 mg, 3.84 mmol) in CH_2Cl_2 (17.5 ml) was added dropwise to a solution of concentrated HNO_3 and concentrated H_2SO_4 (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 CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, 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 ($CDCl_3$) δ 1.50—3.50 (10H, br m), 1.73 (3H, s), 7.87 (2H, d, J=9.0 Hz), 8.26 (2H, d, J=9.0 Hz). HR-MS: Calcd for $C_9H_{17}B_{10}NO_2$: 279.2262. Found: 279.2264. **15b**: Colorless prisms (AcOEt–hexane); mp 126—127 °C; ^{1}H-NMR ($CDCl_3$) δ 1.50—3.50 (10H, br m), 1.74 (3H, s), 7.64 (1H, t, J=8.1 Hz), 8.01 (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 $C_9H_{17}B_{10}NO_2$: 279.2262. Found: 279.2243.

14a and **15a**: Purification by silica gel flash column chromatography (eluent: hexane/AcOEt, 8 : 1) gave **14a** (65%) and **15a** (19%). **14a**: colorless prisms (AcOEt–hexane); mp 170—172 °C; ^{1}H-NMR ($CDCl_3$) δ 1.50—3.50 (10H, br m), 4.02 (1H, br s), 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 ($CDCl_3$) δ 1.50—3.50 (10H, br m), 4.03 (1H, br s), 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, t, J=2.0 Hz).

14c and **15c**: Purification by silica gel flash column chromatography (eluent: hexane/AcOEt, 30 : 1) gave **14c** (35%) and **15c** (51%). **14c**: colorless prisms (AcOEt–hexane); mp 136—137 °C; ^{1}H-NMR ($CDCl_3$) δ 1.00 (3H, t, J=7.5 Hz), 1.50—3.50 (10H, br m), 1.86 (2H, q, J=7.5 Hz), 7.85 (2H, d, J=

9.0 Hz), 8.25 (2H, d, J=9.0 Hz). HR-MS: Calcd for $C_{10}H_{19}B_{10}NO_2$: 293.2419. Found: 293.2440. **15c**: Colorless prisms (AcOEt–hexane); mp 108—109 °C; ^{1}H-NMR ($CDCl_3$) δ 1.01 (3 H, t, J=7.5 Hz), 1.50—3.50 (10H, br m), 1.87 (2H, q, J=7.5 Hz), 7.63 (1H, t, J=8.1 Hz), 7.99 (1H, ddd, J=0.7, 2.0, 8.1 Hz), 8.33 (1H, ddd, J=0.7, 2.0, 8.1 Hz), 8.51 (1H, t, J=2.0 Hz). HR-MS: Calcd for $C_{10}H_{19}B_{10}NO_2$: 293.2419. 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; ^{1}H-NMR ($CDCl_3$) δ 0.83 (6H, d, J=6.6 Hz), 1.50—3.50 (10H, br m), 1.65 (2H, d, J=5.5 Hz), 1.74 (1H, m), 7.84 (2H, d, J=9.2 Hz), 8.26 (2H, d, J=9.2 Hz). *Anal*. Calcd for $C_{12}H_{23}B_{10}NO_2$: 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 112—113 °C; ^{1}H-NMR ($CDCl_3$) δ 0.83 (6H, d, J=6.6 Hz), 1.50—3.50 (10H, br m), 1.66 (2H, d, J=5.5 Hz), 1.74 (1H, m), 7.63 (1H, t, J=8.1 Hz), 7.98 (1H, ddd, J=0.7, 2.0, 8.1 Hz), 8.35 (1H, ddd, J=0.7, 2.0, 8.1 Hz), 8.50 (1H, t, J=2.0 Hz). *Anal*. Calcd for $C_{12}H_{23}B_{10}NO_2$: C, 44.84; H, 7.21, N, 4.36. Found: C, 44.60; H, 7.04; N, 4.36.

General Procedure for Preparing 7a—7d from 14a—14d, and 8a—8d from 15a—15d: 4-[4-(2-Methyl-1,2-dicarba-*closo*-dodecaboran-1-yl)-phenylcarbamoyl]benzoic Acid (7b) A solution of **14b** (349 mg, 1.25 mmol) in EtOH (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-dicarba-*closo*-dodecaboran-1-yl)aniline (95%). ^{1}H-NMR ($CDCl_3$) δ 1.40—3.50 (10H, br m), 1.68 (3H, s), 4.01 (2H, br), 6.62 (2H, d, J=8.6 Hz), 7.39 (2H, d, J=8.6 Hz). To a solution of the amine (100 mg, 0.401 mmol) in pyridine (2.5 ml) was added terephthalic acid monomethyl ester chloride (119 mg, 0.599 mmol) at 0 °C. The mixture was stirred at room temperature for 3 h. The reaction was quenched with 2 N HCl and the whole was extracted with AcOEt. The organic layer was washed with water, saturated aqueous $NaHCO_3$, water and brine, dried over Na_2SO_4 and concentrated. Purification by silica gel flash column chromatography (eluent: CH_2Cl_2/hexane, 3 : 2 to 2 : 1) gave methyl 4-[4-(2-methyl-1,2-dicarba-*closo*-dodecaboran-1-yl)phenylcarbamoyl]benzoate (96%). ^{1}H-NMR ($CDCl_3$) δ 1.50—3.50 (10H, br m), 1.71 (3H, s), 3.97 (3H, s), 7.66 (2H, d, J=9.2 Hz), 7.70 (2H, d, J=9.2 Hz), 7.91 (1H, br s), 7.93 (2H, d, J=8.6 Hz), 8.18 (2H, d, J=8.6 Hz). To a solution of the methyl benzoate (140 mg, 0.34 mmol) in THF (2 ml) was added 1 N KOH (0.68 ml), and the mixture was stirred at room temperature for 14 h. The reaction was quenched with 2 N HCl, and the whole was extracted with AcOEt. The organic layer was washed with water and brine, dried over Na_2SO_4 and concentrated. Purification by silica gel flash column chromatography (eluent: $CHCl_3$/MeOH, 5 : 1) gave **7b** (98%). **7b**: Colorless needles (AcOEt–hexane); mp >300 °C; ^{1}H-NMR (DMSO-d_6) δ 1.40—3.20 (10H, br m), 1.74 (3H, s), 7.71 (2H, d, J=8.8 Hz), 7.91 (2H, d, J=8.8 Hz), 8.04 (2H, d, J=8.6 Hz), 8.08 (2H, d, J=8.6 Hz), 10.66 (1H, s), 13.32 (1H, br). *Anal*. Calcd for $C_{17}H_{23}B_{10}NO_3$: C, 51.37; H, 5.83; N, 3.52. Found: C, 51.13; H, 5.68; N, 3.37.

7a: Colorless needles (AcOEt–hexane); mp >300 °C; ^{1}H-NMR (DMSO-d_6) δ 1.40—3.20 (10H, br m), 5.74 (1H, br s), 7.58 (2H, d, J=8.8 Hz), 7.81 (2H, d, J=8.8 Hz), 8.03 (2H, d, J=8.0 Hz), 8.07 (2H, d, J=8.0 Hz), 10.59 (1H, s), 13.30 (1H, br). *Anal*. Calcd for $C_{16}H_{21}B_{10}NO_3$: C, 50.12; H, 5.52; N, 3.65. Found: C, 49.95; H, 5.35; N, 3.92.

7c: Colorless needles (AcOEt–hexane); mp >300 °C; ^{1}H-NMR (DMSO-d_6) δ 0.93 (3H, t, J=7.5 Hz), 1.40—3.20 (10H, br m), 1.90 (2H, q, J=7.5 Hz), 7.69 (2H, d, J=8.8 Hz), 7.90 (2H, d, J=8.8 Hz), 8.04 (2H, d, J=8.8 Hz), 8.08 (2H, d, J=8.6 Hz), 10.65 (1H, s), 13.30 (1H, br). *Anal*. Calcd for $C_{18}H_{25}B_{10}NO_3$: C, 52.54; H, 6.12; N, 3.40. Found: C, 52.32; H, 6.22; N, 3.27.

7d: Colorless needles (AcOEt–hexane); mp 291—293 °C; ^{1}H-NMR (DMSO-d_6) δ 0.79 (6H, d, J=6.6 Hz), 1.40—3.20 (10H, br m), 1.65 (1H, m), 1.75 (2H, d, J=5.5 Hz), 7.69 (2H, d, J=8.8 Hz), 7.91 (2H, d, J=8.8 Hz), 8.03 (2H, d, J=8.8 Hz), 8.07 (2H, d, J=8.8 Hz), 10.64 (1H, s), 13.40 (1H, br). *Anal*. Calcd for $C_{20}H_{29}B_{10}NO_3$: C, 54.65; H, 6.65; N, 3.19. Found: C, 54.44; H, 6.63; N, 2.89.

8a: Colorless needles (AcOEt–hexane); mp 284—286 °C; ^{1}H-NMR (DMSO-d_6) δ 1.40—3.20 (10H, br m), 5.76 (1H, br s), 7.33 (1H, m), 7.39 (1H, t, J=8.1 Hz), 7.91 (1H, m), 8.05 (2H, d, J=8.3 Hz), 8.08 (2H, d, J=8.3 Hz), 8.11 (1H, m), 10.57 (1H, s), 13.30 (1H, br). *Anal*. Calcd for $C_{16}H_{21}B_{10}NO_3$: C, 50.12; H, 5.52; N, 3.65. Found: C, 50.03; H, 5.25; N, 3.77.

8b: Colorless needles (AcOEt–hexane); mp 284—286 °C; ^{1}H-NMR (DMSO-d_6) δ 1.40—3.20 (10H, br m), 1.77 (3H, s), 7.45 (1H, br d, J=8.2 Hz), 7.49 (1H, t, J=8.2 Hz), 8.05 (1H, br d, J=8.2 Hz), 8.06 (2H, d, J=8.6 Hz), 8.09 (2H, d, J=8.6 Hz), 8.25 (1H, br s), 10.61 (1H, s), 13.30 (1H, br). HR-MS: Calcd for $C_{17}H_{23}B_{10}NO_3$: 397.2681. Found: 397.2683.

8c: Colorless needles (AcOEt–hexane); mp 272—274 °C; ^{1}H-NMR (DMSO-d_6) δ 0.94 (3H, t, J=7.5 Hz), 1.40—3.20 (10H, br m), 1.93 (2H, q, J=7.5 Hz), 7.43 (1H, br d, J=8.3 Hz), 7.48 (1H, t, J=8.3 Hz), 8.06 (1H, br d, J=8.3 Hz), 8.06 (2H, d, J=8.8 Hz), 8.09 (2H, d, J=8.8 Hz), 8.23 (1H, br s), 10.59 (1H, s), 13.25 (1H, br). *Anal*. Calcd for $C_{18}H_{25}B_{10}NO_3$: C, 52.54; H, 6.12; N, 3.40. Found: C, 52.61; H, 6.41; N, 3.34.

8d: Colorless needles (AcOEt–hexane); mp 297—299 °C; ^{1}H-NMR (DMSO-d_6) δ 0.79 (6H, d, J=6.6 Hz), 1.40—3.20 (10H, br m), 1.64 (1H, m), 1.78 (2H, d, J=6.1 Hz), 7.43 (1H, br d, J=8.0 Hz), 7.49 (1H, t, J=8.0 Hz), 8.05 (1H, br d, J=8.0 Hz), 8.07 (2H, d, J=8.8 Hz), 8.09 (2H, d, J=8.8 Hz), 8.22 (1H, br s), 10.59 (1H, s), 13.24 (1H, br). *Anal*. Calcd for $C_{20}H_{29}B_{10}NO_3$: C, 54.65; H, 6.65; N, 3.19. Found: C, 54.47; H, 6.63; N, 2.96.

2-Ethynylanisole (16) A mixture of 2-iodoanisole (4.0 g, 17.1 mmol), ethynyltrimethylsilane (2.52 g, 25.6 mmol), diisopropylamine (3.63 g, 35.9 mmol), copper(I) iodide (65.1 mg, 0.341 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 the whole was extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4, then concentrated. Purification by silica gel flash column chromatography (eluent: hexane to hexane/AcOEt, 30 : 1) gave 2-[(trimethylsilyl)ethynyl]anisole as an orange oil (quantitative yield). ^{1}H-NMR ($CDCl_3$) δ 0.27 (9H, s), 3.88 (3H, s), 6.86 (1H, d, J=8.1 Hz), 6.89 (1H, dt, J=1.1, 7.7 Hz), 7.28 (1H, m), 7.44 (1H, dd, J=1.8, 7.7 Hz). K_2CO_3 (2.36 g, 17.1 mmol) was added to a solution of 2-[(trimethylsilyl)ethynyl]-anisole (3.49 g, 17.1 mmol) in EtOH (35 ml), and 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 Na_2SO_4 and concentrated. Purification by silica gel flash column chromatography (eluent: hexane/CH_2Cl_2, 20 : 1 to 10 : 1) gave **16** (89%). **16**: pale yellow oil; ^{1}H-NMR ($CDCl_3$) δ 3.31 (1H, s), 3.91 (3H, s), 6.90 (1H, d, J=8.4 Hz), 6.92 (1H, dt, J=0.9, 7.3 Hz), 7.33 (1H, ddd, J=1.8, 7.3, 8.4 Hz), 7.47 (1H, dd, J=1.8, 7.3 Hz).

1-(2-Methoxyphenyl)-1,2,-dicarba-*closo*-dodecaborane (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** (49%). **17**: Colorless needles (AcOEt–hexane); mp 132—133 °C; ^{1}H-NMR ($CDCl_3$) δ 1.50—3.50 (10H, br m), 3.85 (3H, s), 5.36 (1H, br s), 6.89 (1H, dd, J=1.1, 8.4 Hz), 6.96 (1H, ddd, J=1.1, 7.3, 8.1 Hz), 7.32 (1H, ddd, J=1.5, 7.3, 8.4 Hz), 7.61 (1H, dd, J=1.5, 8.1 Hz). HR-MS: Calcd for $C_9H_{18}B_{10}O$: 250.2361. Found: 250.2387.

1-(2-Methoxy-5-nitrophenyl)-1,2,-dicarba-*closo*-dodecaborane (18) Compound **18** was prepared from **17** by the same method as that used for preparation of **14** and **15**. Purification by silica gel flash column chromatography (eluent: hexane/AcOEt, 3 : 1) gave **18** (70%). **18**: Colorless needles (AcOEt–hexane); mp 224—225 °C; ^{1}H-NMR ($CDCl_3$) δ 1.50—3.50 (10H, br m), 4.00 (3H, s), 5.18 (1H, br s), 7.02 (1H, d, J=9.2 Hz), 8.24 (1H, dd, J=2.6, 9.2 Hz), 8.58 (1H, d, J=2.6 Hz). *Anal*. Calcd for $C_9H_{17}B_{10}NO_3$: C, 36.60; H, 5.80; N, 4.74. Found: C, 36.40; H, 6.05; N, 4.76.

4-[3-(1,2-Dicarba-*closo*-dodecaboran-1-yl)-4-methoxyphenylcarbamoyl]-benzoic Acid (9) Compound **9** was synthesized from **18** by the same method as that used for preparation of **7b**. **9**: Colorless needles (AcOEt–hexane); mp 280—282°C; ^{1}H-NMR (DMSO-d_6) δ 1.40—3.20 (10H, br m), 3.84 (3H, s), 5.96 (1H, br s), 7.13 (1H, d, J=8.8 Hz), 7.90 (1H, dd, J=2.2, 8.8 Hz), 8.04 (2H, d, J=8.8 Hz), 8.07 (2H, d, J=8.8 Hz), 8.11 (1H, d, J=2.2 Hz), 10.41 (1H, s), 13.24 (1H, br). *Anal*. Calcd for $C_{17}H_{23}B_{10}NO_4$: C, 49.38; H, 5.61; N, 3.39. Found: C, 49.13; H, 5.73; N, 3.41.

3-(Trimethylsilyl)-2-propyn-1-al (19) To a solution of ethynyltrimethylsilane (5.0 g, 50.9 mmol) in dry Et_2O (50 ml) was added dropwise 1.6 M *n*-BuLi in hexanes (35.0 ml, 56.0 mmol) at 0 °C under an Ar atmosphere. The mixture was stirred at 0 °C for 1 h. *N*,*N*-dimethylformamide (DMF) (3.72 g, 50.9 mmol) in Et_2O (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 2 N HCl and extracted with Et_2O. The organic layer was washed with water, saturated aqueous $NaHCO_3$ and brine, and dried over Na_2SO_4. Purification by distillation (40—45 °C/15 mmHg) gave **19** (28%). **19**: Colorless oil; ^{1}H-NMR ($CDCl_3$) δ 0.27 (9H, s), 9.17 (1H, s).

Ethyl 5-Trimethylsilyl-(*E*)-2-penten-4-ynoate (20) To a suspension of NaH (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 at-

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 extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4, then concentrated. The residue was purified by silica gel flash column chromatography (eluent: hexane to hexane/AcOEt, 50 : 1) to give **20** (65%). **20**: Colorless oil; ^{1}H-NMR ($CDCl_3$) 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) K_2CO_3 (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 1 h. The reaction was quenched with 2 N HCl, and extracted with AcOEt. The organic layer was washed with water and brine, dried over Na_2SO_4, then concentrated. Purification by silica gel flash column chromatography gave **21** (79%). **21**: Colorless oil; ^{1}H-NMR ($CDCl_3$) δ 1.30 (3H, t, 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, 2.90 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 concentrated. Purification by silica gel flash column chromatography (eluent: hexane/AcOEt, 10 : 1) gave **22** (64%). **22**: Colorless prisms (hexane); mp 68—69 °C; ^{1}H-NMR ($CDCl_3$) δ 1.30 (3H, t, J=7.1 Hz), 1.50—3.40 (10H, br m), 3.69 (1H, br s), 4.22 (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 $C_7H_{18}B_{10}O_2$: C, 34.70; H, 7.49. Found: C, 34.41; H, 7.66.

4-[2-(1,2-Dicarba-*closo*-dodecaboran-1-yl)-(*E*)-ethenylcarboxamido]-benzoic Acid (10) To a solution of **22** (220 mg, 0.908 mmol) in THF (5 ml) was added 1 N KOH (1.82 ml), and the mixture was stirred at room temperature for 7 h. The reaction was quenched with 2 N HCl, and the whole was extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4, then concentrated. Purification by silica gel flash column chromatography (eluent: $CHCl_3$/MeOH, 10 : 1) gave 3-(1,2-dicarba-*closo*-dodecaboran-1-yl)-(*E*)-propenoic acid (74%). ^{1}H-NMR (DMSO-d_6) δ 1.40—3.20 (10 H, br m), 5.47 (1H, br s), 6.22 (1H, d, J=15.4 Hz), 6.92 (1H, d, 15.4 Hz), 13.00 (1H, br). To a solution of the acid (60 mg, 0.28 mmol) in CH_2Cl_2 (1 ml) was added oxalyl chloride (53.3 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 (46.6 mg, 0.308 mmol) was added. The mixture was stirred for 18 h at room temperature, then the reaction was quenched with 2 N HCl, and the whole was extracted with AcOEt. The organic layer was washed with water, saturated aqueous $NaHCO_3$, water and brine, dried over Na_2SO_4, and concentrated. Purification by silica gel flash column chromatography (eluent: hexane/AcOEt, 5 : 1) gave methyl 4-[2-(1,2-dicarba-*closo*-dodecaboran-1-yl)-(*E*)-ethenylcarboxamido]benzoate (44%). ^{1}H-NMR ($CDCl_3$) δ 1.50—3.50 (10H, m), 3.72 (1H, br s), 3.91 (3H, s), 6.37 (1H, d, J=15.0 Hz), 6.96 (1H, d, J=15.0 Hz), 7.40 (1H, br s), 7.64 (2H, d, J=8.8 Hz), 8.04 (2H, d, J=8.8 Hz). HR-MS: Calcd for $C_{13}H_{21}B_{10}NO_3$: 347.2524. Found: 347.2534. To a solution of the methyl benzoate (36 mg, 0.104 mmol) in THF (1 ml) was added 1 N KOH (0.468 ml), and the mixture was stirred at room temperature for 36 h. The reaction was quenched with 2 N HCl, and the whole was extracted with AcOEt. The organic layer was washed with water and brine, dried over Na_2SO_4, then concentrated. Purification by silica gel flash column chromatography (eluent: $CHCl_3$/MeOH, 50 : 1 to 5 : 1) gave **10** (39%). **10**: Colorless needles (AcOEt–hexane); mp >300 °C; ^{1}H-NMR ($CDCl_3$) δ 1.40—3.20 (10H, br m), 5.50 (1H, br s), 6.67 (1H, d, J=15.1 Hz), 6.98 (1H, d, J=15.1 Hz), 7.73 (2H, d, J=8.8 Hz), 7.92 (2H, d, J=8.8 Hz), 10.62 (1H, s), 12.75 (1H, br). HR-MS: Calcd for $C_{12}H_{19}B_{10}NO_3$: 333.2368. Found: 333.2367.

Ethyl 4-Ethynylbenzoate (25) A mixture of ethyl 4-bromobenzoate (1.5 g, 6.55 mmol), ethynylbenzene (965 mg, 9.82 mmol), diisopropylamine (1.39 g, 13.7 mmol), copper(I) iodide (25 mg, 0.131 mmol), and bis(triphenylphosphine)palladium(II) chloride (184 mg, 0.262 mmol) in dry THF (10 ml) was heated at 45 °C for 4 h under an Ar atmosphere. The reaction was quenched with water and the whole was extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4, then concentrated. Purification by silica gel flash column chromatography (eluent: hexane/AcOEt, 100 : 1) gave ethyl 4-[(trimethylsilyl)ethynyl]benzoate (73%). ^{1}H-NMR ($CDCl_3$) δ 0.26 (9H, s), 1.39 (3H, t, J=7.2 Hz), 4.37 (2H, q, J=7.2 Hz), 7.51 (2H, d, J=8.6 Hz), 7.97 (2H, d, J=8.6 Hz). To a solution of ethyl 4-[(trimethylsilyl)ethynyl]benzoate (1.15 g, 4.67 mmol) in THF (10 ml) was added dropwise 1 M tetrabutylammonium fluoride in THF (5.14 ml) at 0 °C. The mixture was stirred for 30 min at room temperature, then the reaction was quenched with water and extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. Purification by silica gel flash column chromatography (eluent: hexane/AcOEt, 20 : 1) gave **25** (40%). **25**: Colorless oil; ^{1}H-NMR ($CDCl_3$) δ 1.40 (3H, t, J=7.1 Hz), 3.23 (1H, s), 4.38 (2H, q, J=7.1 Hz), 7.55 (2H, d, J=8.2 Hz), 8.00 (2H, d, J=8.2 Hz).

Ethyl 4-(1,2-Dicarba-*closo*-dodecaboran-1-yl)benzoate (27) A mixture of **25** (320 mg, 1.84 mmol) and decaborane(14) (337 mg, 2.76 mmol) in acetonitrile (1 ml) and benzene (15 ml) was refluxed for 3 d under an Ar atmosphere, then the reaction mixture was concentrated. Purification by silica gel flash column chromatography (eluent: hexane/AcOEt, 15 : 1) gave **27** (71%). **27**: Colorless flakes (ethanol); mp 111—112 °C; ^{1}H-NMR ($CDCl_3$) δ 1.39 (3H, t, J=7.1 Hz), 1.50—3.50 (10H, br m), 4.01 (1H, br s), 4.39 (2H, q, J=7.1 Hz), 7.54 (2H, d, J=8.8 Hz), 8.00 (2H, d, J=8.8 Hz). HR-MS: Calcd for $C_{11}H_{20}B_{10}O_2$: 292.2466. Found: 292.2487.

4-{[4-(1,2-Dicarba-*closo*-dodecaboran-1-yl)phenyl]carboxamido}benzoic Acid (11) To a solution of **27** (374 mg, 1.28 mmol) in THF (5 ml) was added 1 N KOH (3.84 ml), and the mixture was stirred at room temperature for 15 h. The reaction was quenched with 2 N HCl, and the whole was extracted with AcOEt. The organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated. The residual crystals were washed with hexane to give 4-(1,2-dicarba-*closo*-dodecaboran-1-yl)benzoic acid. ^{1}H-NMR (DMSO-d_6) δ 1.40—3.20 (10H, br m), 5.88 (1H, br s), 7.72 (2H, d, J=8.5 Hz), 7.94 (2H, d, J=8.5 Hz), 13.29 (1H, br). To a suspension of the acid (140 mg, 0.53 mmol) in CH_2Cl_2 (1.5 ml) was added oxalyl chloride (202 mg, 1.59 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 (1.5 ml) and methyl 4-aminobenzoate (84.0 mg, 0.556 mmol) was added. The mixture was stirred for 15 h at room temperature, then the reaction was quenched with 2 N HCl, and the whole was extracted with AcOEt. The organic layer was washed with water, saturated aqueous $NaHCO_3$, water and brine, dried over Na_2SO_4, and concentrated. Purification by silica gel flash column chromatography (eluent: hexane/AcOEt, 3 : 1) gave methyl 4-{[4-(1,2-dicarba-*closo*-dodecaboran-1-yl)phenyl]carboxamido}benzoate (48% from **27**). ^{1}H-NMR ($CDCl_3$) 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). To a solution of the methyl benzoate (94 mg, 0.236 mmol) in THF (3 ml) was added 1 N KOH (1.18 ml), and the mixture was stirred at 40 °C for 16 h. The reaction was quenched with 2 N HCl, and the whole was extracted with AcOEt. The organic layer was washed with water and brine, dried over Na_2SO_4, then concentrated. Purification by silica gel flash column chromatography (eluent: $CHCl_3$/MeOH, 5 : 1) gave **11** (41%). **11**: Colorless needles (AcOEt); mp >300 °C; ^{1}H-NMR (DMSO-d_6) 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=8.8 Hz), 7.95 (2H, d, J=8.8 Hz), 10.61 (1H, s), 12.80 (1H, br). *Anal*. Calcd for $C_{16}H_{21}B_{10}NO_3$: C, 50.12; 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), ethynylbenzene (644 mg, 6.56 mmol), diisopropylamine (929 mg, 9.20 mmol), copper(I) iodide (16.6 mg, 0.0872 mmol), and bis-(triphenylphosphine)palladium(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 Na_2SO_4, then concentrated. Purification by silica gel flash column chromatography (eluent: hexane/AcOEt, 50 : 1) gave ethyl 3-[(trimethylsilyl)ethynyl]benzoate (90%). ^{1}H-NMR ($CDCl_3$) δ 0.26 (9H, s), 1.40 (3H, t, J=7.1 Hz), 4.38 (2H, q, J=7.1 Hz), 7.38 (1H, dd, J=7.3, 8.3 Hz), 7.63 (1H, d, J=7.3 Hz), 7.98 (1H, d, J=8.3 Hz), 8.13 (1H, s). K_2CO_3 (583 mg, 4.22 mmol) was added to a solution of ethyl 3-[(trimethylsilyl)ethynyl]benzoate (1.04 g, 4.22 mmol) in EtOH (10 ml), and the mixture was stirred at room temperature for 2 h, then concentrated. The residue was taken up in AcOEt. The organic layer was washed with water and brine, and dried over Na_2SO_4, then concentrated. Purification by silica gel flash column chromatography (eluent: hexane/AcOEt, 30 : 1) gave **26** (96%). **26**: Colorless needles; mp 36—37 °C; ^{1}H-NMR ($CDCl_3$) δ 1.40 (3H, t, J=7.1 Hz), 3.12 (1H, s), 4.34 (2H, q, J=7.1 Hz), 7.41 (1H, t, J=7.8 Hz), 7.66 (1H, dt, 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; ^{1}H-NMR ($CDCl_3$) 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, q. J=1.7 Hz). HR-MS: Calcd for $C_{11}H_{20}B_{10}O_2$: 292.2466. Found: 292.2474.

4-{[3-(1,2-Dicarba-*closo*-dodecaboran-1-yl)phenyl]carboxamido}benzoic Acid (12) **12** was prepared from **28** by the same procedure as that used for **11**. **12**: Colorless needles (AcOEt–hexane); mp 236—239 °C; ^{1}H-NMR (DMSO-d_6) 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 (2 H, d, J=8.8 Hz), 8.04 (1H, br d, J=8.0 Hz), 8.05 (1H, br s), 10.61 (1 H, s), 12.89 (1H, br). HR-MS: Calcd for $C_{16}H_{21}B_{10}NO_3$: 383.2524. Found: 383.2542. *Anal*. Calcd for $C_{16}H_{21}B_{10}NO_3 \cdot 0.5\,H_2O$: C, 48.97; H, 5.65; N, 3.57. Found: C, 48.99; H, 5.83; N, 3.49.

References and Notes

1) Hawthorne M. F., *Angew. Chem., Int. Ed. Engl*., **32**, 950—984 (1993); Slatkin D. N., *Brain*, **114**, 1609—1629 (1991).
2) For a recent review see: Soloway A. H., Tjarks W., Barnum B. A., Rong F.-G., Barth R. F., Codogni I. M., Wilson J. G., *Chem. Rev*., **98**, 1515—1562 (1998).
3) Yamamoto Y., Seko T., Nakamura H., Nemoto H., Hojo H., Nukai N., Hashimoto Y., *J. Chem. Soc. Chem. Commun*., **1992**, 157—158; Tjarks W., Anisuzzaman A. K. M., Liu L., Soloway A. H., Barth R. F., Perkins D. J., Adams D. M., *J. Med. Chem*., **35**, 1628—1631 (1992).
4) Leukart O., Caviezel M., Eberle A., Escher E., Tun-Kyi A., Schwyzer R., *Helv. Chim. Acta*, **59**, 2184—2187 (1976); Wyzlic I. M., Soloway A. H., *Tetrahedron Lett*., **33**, 7489—7492 (1992); Radel P. A., Kahl A. B., *J. Org. Chem*., **61**, 4582—4588 (1996).
5) Miura M., Gabel D., Oenbrink G., Fairchild R. G., *Tetrahedron Lett*., **31**, 2247—2250 (1990).
6) Davis M. A., Soloway A. H., *J. Med. Chem*., **10**, 730—732 (1967); Kelly D. P., Bateman S. A., Martin R. F., Reum M. E., Rose M., Whittaker A. D., *Aust. J. Chem*., **47**, 247—262 (1994); Yamamoto Y., Cai J., Nakanura H., Sadayori N., Nemoto H., *J. Org. Chem*., **60**, 3352—3357 (1995).
7) Sweet F., *Steroids*, **37**, 223—238 (1981); Sweet F., Samant B. R., "Synthesis and Application of Isotope Labeled Compounds" ed. by Ducan W. P., Susa A. B., Elsevier: Amsterdam, 1982, p. 175.
8) Bregradze V. I., *Chem. Rev*., **92**, 209—223 (1992).
9) Cunliffe W. J., Miller,A. J., Eds., "Retinoid Therapy", MTP Press Ltd., Lancaster, 1984; Bollag W., Holdener E. E., *Ann. Oncol*., **3**, 513—526 (1992).
10) Sporn M. B., Roberts A. B., Goodman D. S., Eds., "The Retinoids," 2nd ed., Raven Press, New York, 1994.
11) Evans R. M., *Science*, **240**, 889—895 (1988).
12) Shudo K., Kagechika H., *Adv. Drug Res*., **24**, 81—119 (1993).
13) Bourguet W., Ruff M., Chambon P., Gronemeyer H., Moras D., *Nature* (London), **375**, 377—382 (1995); Renaud J.-P., Rochel N., Ruff M., Vivat V., Chambon P., Gronemeyer H., Moras D., *ibid.* **378**, 681—689 (1995).
14) Darmon M., Rocher M., Cavey M. T., Nartin B., Rabilloud T., Delescluse C., Shroot B., *Skin Pharmacol*., **1**, 161—175 (1988).
15) Kaneko S., Kagechika H., Kawachi E., Hashimoto Y., Shudo K., *Med. Chem. Res*., **1**, 220—225 (1991).
16) Hawthorne M. F., Berry T. E., Wegner P. A., *J. Am. Chem. Soc*., **87**, 4746—4750 (1965).
17) Scobie M., Threadgill M. D., *J. Chem. Soc. Perkin Trans. 1*, **1994**, 2059—2063.
18) The icosahedral cage carbon atoms are generally found in an electron-deficient system. The electronic bonding structure of the two cage carbons in the carboranes still remains ambiguous. Wu S.-H., Jones M., *Inorg. Chem*., **27**, 2005—2008 (1988). The substituents at the 2-position of the carborane influence the orientation of the plane of the phenyl ring relative to the C-C in the cage. Crystallographic analysis of 1-phenyl-2-alkyl-1,2-carboranes has been reported. Brain P. T., Cowie, J., Donohoe D. J., Hnyk D., Rankin D. W. H., Reed D., Reid B. D., Robertson H. E., Welch A. J., *ibid.*, **35**, 1701—1708 (1996).
19) Austin W. B., Bilow N., Kelleghan J., Lau K. S., *J. Org. Chem*., **46**, 2280—2286 (1981).
20) Collins S. J., Ruscetti F. W., Gallagher R. E., Gallo R. C., *J. Exp. Med*., **149**, 964—974 (1979).
21) Umemiya H., Fukasawa H., Ebisawa M., Eyrolles L., Kawachi E., Eisenmann G., Gronemeyer H., Hashimoto Y., Shudo K., Kagechika H., *J. Med. Chem*., **40**, 4222—4234 (1997).