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 indicate 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. When the $^{10}$B isotope is irradiated with slow (thermal) neutrons, an $[n,\alpha]$ reaction ensues, giving $^7$Li and $^4$He nuclei with high kinetic energy (2.4 MeV). The $\alpha$-particle and lithium ion dissipate their kinetic energy before traveling one cell diameter (ca. 10 $\mu$m) 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 which have the capacity for selectively targeting malignant cells and which can be accumulated intracellulary 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, amino acids, porphyrins and DNA binders have been synthesized in attempts to target boron to tumors. From the viewpoint of potential for the rapid targeting of tumor cells, receptor nucleic acid 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.

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. 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.

Fig. 1

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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.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) (B10H14).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 isomers17 under similar conditions. We found that nitration of 13a with mixed acid/CH3Cl2 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–Giemsas 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 1×10−5 M 7a to 23%. The compounds bearing an alkyl group at the 2-position of the 1,2-carborane cage (7b—
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 $3.3 \times 10^{-8}$ M Am80, 0, $3.3 \times 10^{-8}$, $1 \times 10^{-7}$, $3.3 \times 10^{-7}$ and $1 \times 10^{-6}$ 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-
agonistic activity, but no antagonistic activity. Compound 3 even in the presence of the potent synergist HX630. 2) constituent effects, as follows. 1) The 4-carboranyl-substituted synergist 21) (Fig. 6). For example, the response to 10 extent of differentiation (less than 10%) induced by 1 of 10 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 23) (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 is similar to that used for the preparation of 13b. Purification by silica gel column chromatography (elu- ent: hexane) gave 13c (88%). 13c: Colorless prisms (hexane); mp 68—69 °C; 1H-NMR (CDCl3) δ 0.97 (3H, t, J = 5.5 Hz), 1.71 (1H, m), 1.79 (2H, m), 1.96 (1H, m), 7.15 (2H, m). HR-MS: Calcd for C10H17B10O: 275.2549. Found: 275.2549.

1-Isobutyl-2-phenyl-1,2-dicarba-dodecaborane (13d) 13d was prepared from 13a (1.00 g, 4.54 mmol) and 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 13d. Purification by silica gel column chromatography (elu- ent: hexane) gave 13d (19%). 13d: Colorless prisms (hexane); mp 65—66 °C; 1H-NMR (CDCl3) δ 0.80 (6H, d, J = 6.6 Hz), 1.50—3.50 (10H, br m), 3.97 (1H, br s), 7.52 (2H, m), 7.70 (2H, d, J = 8.2 Hz) ppm. HR-MS: Calcd for C10H19B9NO: 271.2526. Found: 271.2524.

General Procedure for Nitration of 13a—d: 4-(2-Methyl-1,2-dicarba- close-dodecaboran-1-yl)nitrobenzene (14b) and 3-(2-Methyl-1,2-di- carba-dodecaboran-1-yl)nitrobenzene (15b) A solution of 13b (900 mg, 3.84 mmol) in CHCl3 (17.5 ml) was added dropwise to a solution of concentrated HNO3 and concentrated H2SO4 (15 : 85, v/v) (17.5 ml) 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 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 (elu- ent: hexane) gave 13b (94%). 13b: Colorless prisms (hexane); mp 102—103 °C; 1H-NMR (CDCl3) δ 1.50—3.50 (10H, br m), 1.69 (3H, s), 3.79 (2H, m), 7.45 (1H, m), 7.65 (2H, m). HR-MS: Calcd for C11H17B10N: 248.2568. Found: 248.2569.

Experimental General Remarks Melting points were obtained on a Yanagimoto micro hot stage without correction. 1H-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 ethylbenzene (5.5 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 atmosp- here, then concentrated. Purification by silica gel column chromatography (elu- ent: hexane) gave 13a (74%). 13a: Colorless prisms (hexane); mp 66—67 °C; 1H-NMR (CDCl3) δ 1.50—3.50 (10H, br m), 3.97 (1H, br s), 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 Et2O (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 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 (elu- ent: hexane) gave 13b (94%). 13b: Colorless prisms (hexane); mp 102—103 °C; 1H-NMR (CDCl3) δ 1.50—3.50 (10H, br m), 1.69 (3H, s), 3.79 (2H, m), 7.45 (1H, m), 7.65 (2H, m). HR-MS: Calcd for C11H17B10N: 248.2568. Found: 248.2569.

Fig. 6. HL-60 Cell Differentiation-Inducing Activity of Carborane-Con- taining Compounds at 1.0×10−6 M Concentration in the Presence of HX630 (1.0×10−6 M)
Purification by silica gel flash column chromatography (elucent: hexane/AcOEt; 30:1) gave 14d (73%) and 15d (47%). 14d: Colorless prisms (AcOEt-hexane); mp 108—109 °C; 1H-NMR (CDCl 3) δ 1.01 (3 H, t, J = 7.5 Hz), 1.50—3.50 (10H, brm), 1.87 (2H, q, J = 7.5 Hz), 7.63 (1H, t, J = 8.9 Hz), 7.99 (1H, dd, 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: Caled for C17H26B10NO3: 525.54. Found: 527.65.

8d: Colorless needles (AcOEt-hexane); mp 272—274 °C; 1H-NMR (DMSO-d 6) δ 0.94 (3H, t, J = 7.5 Hz), 1.40—3.20 (10H, brm), 1.93 (2H, q, J = 7.5 Hz), 7.43 (1H, br d, J = 8.3 Hz), 7.48 (1H, t, J = 8.8 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 (3H, br s), 10.59 (1H, s), 13.25 (1H, br). Anal. Caled for C17H23B10NO3: C, 52.54; H, 6.31; N, 3.14. Found: C, 52.61; H, 6.41; N, 3.34.

2-Ethynylanisole (16) A mixture of 2-iodoanisole (4.0 g, 17.1 mmol), ethynyltrimethylsilane (252.0 mg, 3.56 mmol), disopropylamine (3.6 g, 35.9 mmol), copper(I) iodide (65.1 mg, 0.341 mmol), and bis(triphenylphosphine) palladium(II) chloride (0.52 mg, 0.012 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 Na2SO4, then concentrated. Purification by silica gel flash column chromatography (elucent: hexane to hexane/AcOEt; 30:1) gave 16 (86%). 16: Pale yellow oil; 1H-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 = 1.2, 7.3, 8.4 Hz), 7.47 (1H, dd, J = 1.8, 7.3 Hz).

1-(2-Methoxyphenyl)-1,2-dicarboxylic acid (17) A mixture of 16 (1.30 g, 9.84 mmol) and decaborene (14) (1.80 g, 14.7 mmol) in acetonitrile (5 ml) and benzene (50 ml) was refluxed for 23 h under an Arg atmosphere, then concentrated. Purification by silica gel flash column chromatography (elucent: hexane to hexane/AcOEt; 40:1) gave 17 (49%). 17: Colorless needles (AcOEt-hexane); mp 132—133 °C; 1H-NMR (CDCl 3) δ 1.50—3.50 (10H, brm), 3.85 (3H, s), 5.43 (1H, brs), 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: Caled for C22H16B10O4: 350.2361. Found: 250.2387.

1-(2-Methoxy-5-nitrophenyl)-1,2-dicarboxylic acid (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 (elucent: hexane/AcOEt, 3:1) gave 18 (70%). 18: Colorless needles (AcOEt-hexane); mp 224—225 °C; 1H-NMR (CDCl 3) δ 1.50—3.50 (10H, brm), 4.00 (3H, s), 5.18 (1H, brs), 7.02 (1H, ddd, J = 1.2, 8.8 Hz), 8.04 (2H, d, J = 8.8 Hz), 8.07 (2H, d, J = 8.8 Hz), 8.11 (1H, dt, J = 1.1, 7.3 Hz), 10.18 (1H, br). Anal. Caled for C22H16B10NO4: C, 50.12; H, 5.52; N, 3.65. Found: C, 49.95; H, 5.35; N, 3.92.

1-(2-Methoxy-5-nitrophenyl)-1,2-dicarboxylic acid (18) Compound 18 was synthesized from 17 by the same method as that used for preparation of 7b. 9: Colorless needles (AcOEt-hexane); mp 280—282 °C; 1H-NMR (DMSO-d 6) δ 1.40—3.20 (10H, brm), 3.84 (3H, s), 5.96 (1H, brs), 7.13 (1H, ddd, J = 1.2, 8.8 Hz), 7.90 (1H, dd, J = 1.2, 8.8 Hz), 8.04 (2H, d, J = 8.8 Hz), 8.07 (2H, d, J = 8.8 Hz), 8.11 (1H, dt, J = 1.1, 7.3 Hz), 10.18 (1H, br). Anal. Caled for C22H16B10NO4: C, 50.12; H, 5.52; N, 3.65. Found: C, 50.03; H, 5.25; N, 3.77.

8a: Colorless needles (AcOEt-hexane); mp 284—286 °C; 1H-NMR (DMSO-d 6) δ 1.40—3.20 (10H, brm), 3.75 (1H, brs), 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). 8b: Colorless needles (AcOEt-hexane); mp 284—286 °C; 1H-NMR (DMSO-d 6) δ 1.40—3.20 (10H, brm), 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, brs), 10.61 (1H, s), 13.10 (1H, br). HR-MS: Caled for C17H22B10NO3: 397.2681. Found: 397.2683.

2-Alkylcloso-1,2-dicarboxylic acid (21) A solution of ethynyltrimethylsilane (5.0 g, 50.9 mmol) in dry Et2O (50 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 3M HCl and extracted with Et2O. The organic layer was washed with water, saturated aqueous NaHCO3 and brine, and dried over Na2SO4. Purification by distillation (40—60 °C/15 mmHg) gave 21 (20%). 19: Colorless oil; 1H-NMR (CDCl 3) δ 0.27 (9H, s), 9.17 (1H, s).

Ethyl 5-Trimethylsilyl-(E)-2-pent-4-enoate (20) A suspension of NaN (556 mg, 13.9 mmol) in THF (7 ml) was added dropwise ethyl diethylphosphonooctane (3.12 g, 13.9 mmol) in THF (7 ml) 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 Et2O (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 2M HCl and extracted with Et2O. The organic layer was washed with water, saturated aqueous NaHCO3 and brine, and dried over Na2SO4. Purification by distillation (40—60 °C/15 mmHg) gave 20 (28%). 18: Colorless oil; 1H-NMR (CDCl 3) δ 0.27 (9H, s), 9.17 (1H, s).
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 Na2SO4, then concentrated. The residue was purified by silica gel flash column chromatography (eluent: hexane/hexane/AcOEt, 50:1) to give 28 (40%).

25. Colorless oil; 1H-NMR (CDCl3) δ 1.40—3.20 (10H, br m), 8.84 (2H, d, J = 8.8 Hz) and 8.79 (2H, d, J = 8.8 Hz). HR-MS: Calculated for C36H20B10O2: 292.2450. Found: 292.2460.

**Ethy 4-(1,2-Dicarba-closo-dodecaboran-1-yl)-phenyl[carboxamido]benzoic Acid (27)**  A solution of 27 (374 mg, 1.28 mmol) in THF (5 ml) was added 1 N KOH (1.82 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 Na2SO4, and concentrated. Purification by silica gel flash column chromatography (eluent: hexane/hexane/AcOEt, 50:1) gave ethyl 3-[(trimethylsilyl)ethynyl]benzoate (90%).

26. **Ethy 3-[(1,2-Dicarba-closo-dodecaboran-1-yl)-aryl][carboxamido]benzoic Acid (28)**  To a solution of 28 (374 mg, 1.28 mmol) in THF (5 ml) was added 1 N KOH (1.82 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 Na2SO4, and concentrated. Purification by silica gel flash column chromatography (eluent: hexane/hexane/AcOEt, 50:1) gave ethyl 3-[(trimethylsilyl)ethynyl]benzoate (90%).
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—3.20 (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 C₁₅H₂₁B₁₀NO₃·0.5 H₂O: C, 48.97; H, 5.65; N, 3.57. Found: C, 48.99; H, 5.83; N, 3.57.

References and Notes