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Structure Determination of a 1:2 Threitol-Boronic Acid Complex: Comments on the Structural Controversy between 5,5- and 6,6-Membered Rings

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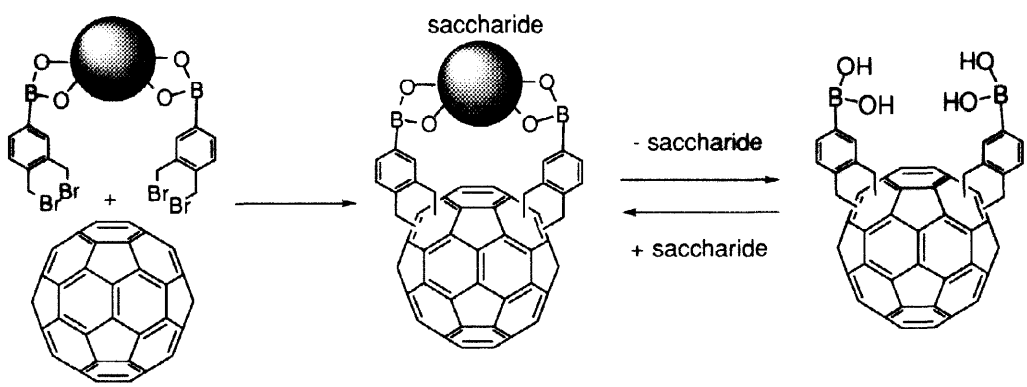
Abstract: The complexation between D-threitol (**1**) and 2,4,6-[3,4-bis(bromomethyl)phenyl]boroxin (**2**) selectively afforded D-threitol-1,3:2,4-bis[-3,4-(bisbromomethyl)phenylboronate] (**4**) including two six-membered rings, whose structure was identified by means of NMR and IR spectroscopy and X-ray crystallographic analysis. The superior stability of **4** over **3** including two five-membered rings was discussed.

INTRODUCTION

The molecular imprinting technique has been studied to synthesize a matrix having an affinity with target molecules used as a template.[1-3] Recently, we have proposed a new concept in the molecular imprinting technique, in which saccharides as template as well as target molecule, boronic acids as functional groups, and [60]fullerene as a base of matrix are selected.[4]



Scheme 1

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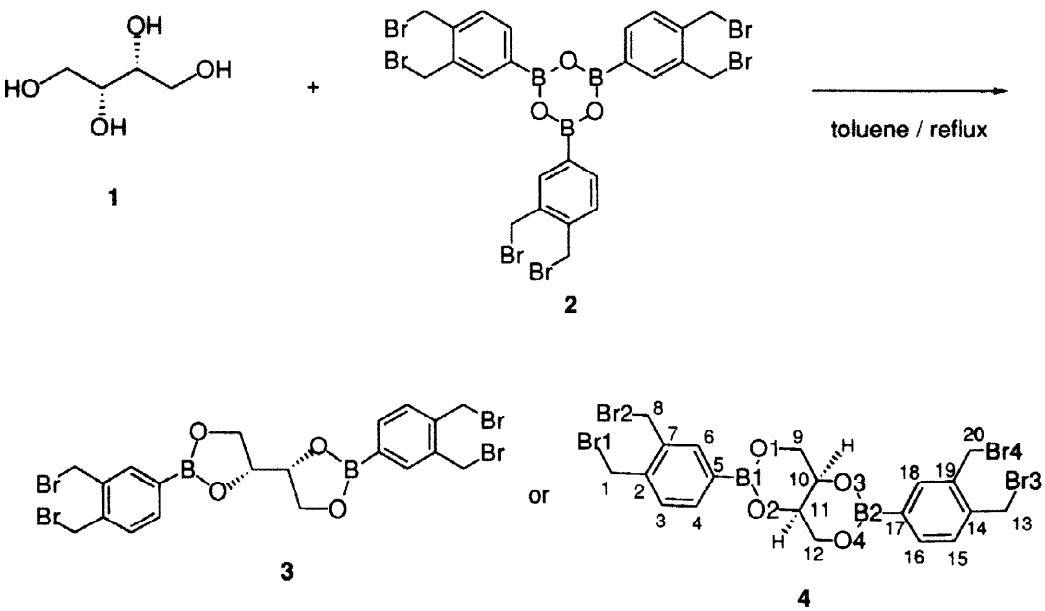
The principle idea in the study is the regioselective double [4+2]cycloaddition[5] between [60]fullerene and saccharide-bis[-3,4-bis(bromomethyl)phenylboronate] and the subsequent reversible removal and re-binding of a saccharide template based on saccharide-boronic acid interaction[6] (Scheme 1). In this study, D-threitol (**1**) was used as one of the saccharide templates and its bisboronate regioselectively reacted with [60]fullerene. Although threitol with four hydroxy groups is one of the simplest saccharides, the structure determination of the 1:2 threitol-boronic acid complex has never been studied except for a few reports without detailed discussions.[7] One can propose the two possible structures, D-threitol-1,2:3,4-bis(arylboronate) **3** and D-threitol-1,3:2,4-bis(arylboronate) **4**, for the complexation between D-threitol (**1**) and 2,4,6-[3,4-bis(bromomethyl)phenyl]boroxin (**2**) (Scheme 2), because arylboronic acid can react either with a 1,2-diol moiety or with a 1,3-diol moiety of the saccharide to form a five- or a six-membered boronate ring, respectively.[6,8,9] In order to precisely estimate the orientation between two bis(bromomethyl)phenyl groups, one must clarify which structure is adopted by the 1:2 complex. In this paper, we would like to report the first structure determination of this interesting complex by spectroscopic methods and X-ray crystallography.



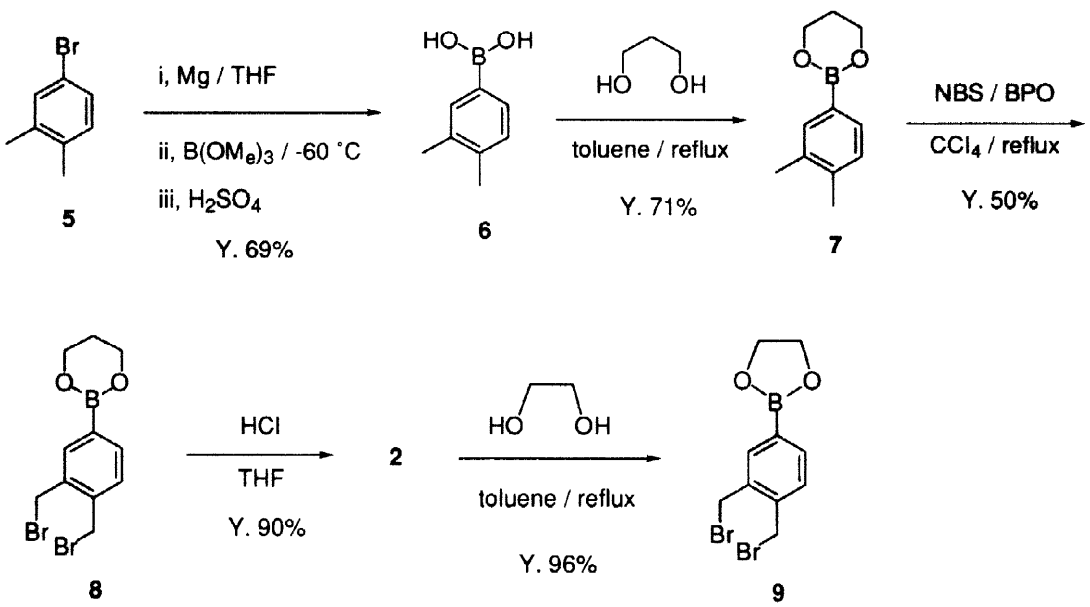
Scheme 2

RESULTS AND DISCUSSION

According to Scheme 3, **2** was prepared from 4-bromo-*o*-xylene (**5**). The cyclic trimer structure[6,10] of **2** in the solid state was proposed on the basis of IR spectroscopy and elemental analysis: the IR spectrum (KBr) of **2** did not show the absorption band due to the hydroxy stretching vibration and the result of elemental analysis for **2** was close to the values calculated on the basis of the cyclic trimer structure. Six- and five- membered boronates **8** and **9** were also prepared and used as reference compounds.

The complexation between **1** and **2** was carried out in refluxing toluene with azeotropic removal of water. This treatment afforded the corresponding bisboronate complex in 82% yield as shown in Scheme 2. The ^1H NMR spectrum of the threitol-boronate complex in $CDCl_3$ shows the formation of the single isomer but not that

of the isomeric mixture. The three aromatic proton peaks (at 7.31 and 7.72 ppm as doublets with J = 7.6 Hz and at 7.77 ppm as a singlet) and the two bromomethyl proton peaks (at 4.63 and 4.65 ppm as singlets) indicate that this complex has the highly symmetrical structure. The protons of the threitol moiety in the complex are characterized by the large geminal coupling constant and the two vicinal coupling constants of almost zero values, as indicated by two sets of doublets at 4.32 and 4.43 ppm with J = 12.4 Hz and one singlet at 4.51 ppm. The splitting pattern is commensurate with those of threitol-bisboronate complexes reported previously.[7] The ^{13}C NMR spectroscopy is also supportive of the 1:2 threitol-boronate complex structure (see experimental section). However, the ^{1}H and ^{13}C NMR spectral data are not sufficient to assign the complex to either **3** or **4**.



Scheme 3

^{11}B NMR spectroscopy has been a useful determination method for the ring-size of saccharide-boronate complexes.[11] The ^{11}B signal of five-membered boronate **9** (at 31.12 ppm) in $CDCl_3$ was observed at lower magnetic field compared to that of six-membered boronate **8** (at 26.53 ppm), indicating the similar trend with the previous proposal.[11] The ^{11}B signal of threitol-bisboronate complex at 27.71 ppm was close to that of **8**, suggesting the possibility of **4** rather than that of **3**.

The structure of **4** is also estimated by means of IR spectroscopy. In general, IR spectra of arylboronates are characterized by strong absorptions at 1360-1310 cm^{-1} attributed to the B-O stretching vibrations.[12] The IR spectrum (KBr) of **4** showed the absorption band due to the B-O stretching vibration at 1320 cm^{-1}, which was very similar to that (at 1318 cm^{-1}) of **8**. In contrast, the B-O stretching vibration of **9** was shifted to high frequency region (at 1339 cm^{-1}) compared to those of **4** and **8**.

Finally, the structure of **4** was determined by means of X-ray crystallographic analysis (Fig. 1). The two six-membered boronate rings of **4** take a sofa form, in which the C(10) and C(11) atoms are deviated from the planes B (composed of C(9), O(1), B(1), O(2), and C(11)) and B' (composed of C(10), O(3), B(2), O(4), and C(12)) with the angles of 51.4° and 46.6°, respectively. In each arylboronate moiety of **4**, the benzene ring

(A/A') and the boronate ring are approximately parallel with dihedral angle of 13.5° (6.2°) between A (A') and B (B') rings, indicating that the compound is stabilized by the overlap between the empty *p*-orbital of boron atom and the π-electrons of benzene ring.

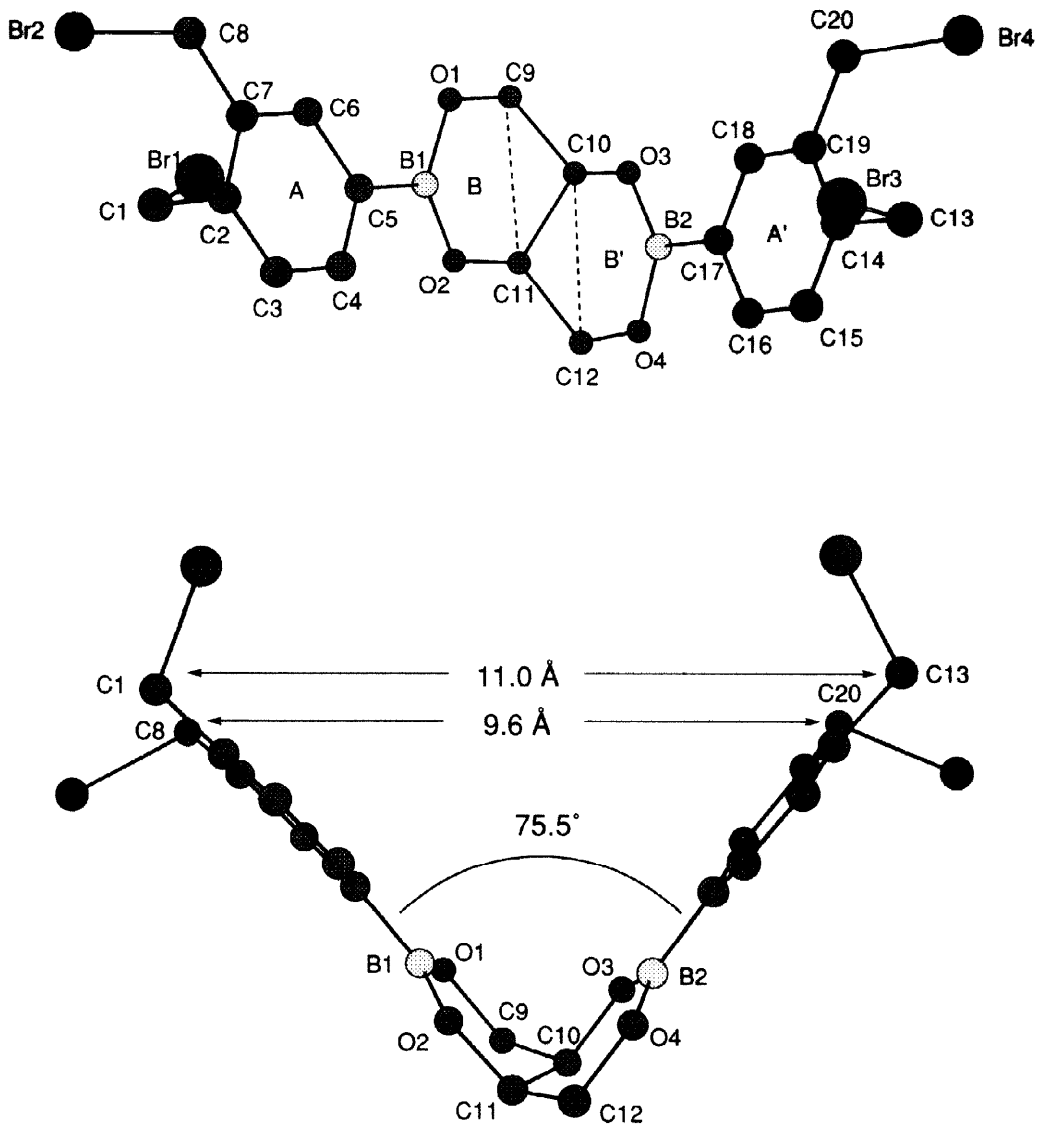


Fig. 1 Stereo view drawings of **4**. Selected bond lengths (Å) and bond angles (°): C(5)-B(1) 1.54(3), C(9)-C(10) 1.47(4), C(9)-O(1) 1.41(2), C(10)-C(11) 1.58(4), C(10)-O(3) 1.39(3), C(11)-C(12) 1.51(4), C(11)-O(2) 1.41(3), C(12)-O(4) 1.43(2), C(17)-B(2) 1.53(3), B(1)-O(1) 1.39(2), B(1)-O(2) 1.34(2), B(2)-O(3) 1.33(3), B(2)-O(4) 1.37(3), C(10)-C(9)-O(1) 112(2), C(9)-C(10)-C(11) 108(1), C(9)-C(10)-O(3) 110(2), C(11)-C(10)-O(3) 108(2), C(10)-C(11)-C(12) 111(1), C(10)-C(11)-O(2) 107(2), C(12)-C(11)-O(2) 109(2), C(11)-C(12)-O(4) 110(1), C(5)-B(1)-O(1) 116(1), C(5)-B(1)-O(2) 119(1), O(1)-B(1)-O(2) 123(1), C(17)-B(2)-O(3) 119(2), C(17)-B(2)-O(4) 116(2), O(3)-B(2)-O(4) 123(2), C(9)-O(1)-B(1) 116(1), C(11)-O(2)-B(1) 123(2), C(10)-O(3)-B(2) 122(2), C(12)-O(4)-B(2) 119(2).

The side view drawing of **4** shows V shape structure with the angle of 75.5°. The intramolecular carbon-carbon distances (C(1)•••C(13) and C(8)•••C(20)) between the corresponding two bromomethyl groups were

11.0 and 9.6 Å. We noticed that the distance between the two bis(bromomethyl)phenyl groups in the V shape structure of **4** is too long to react with [60]fullerene (with the size of *ca.* 8 Å). Hence, the distance between the two bis(bromomethyl)phenyl groups in **4** should be shortened in the double addition with [60]fullerene of Scheme 1. This opinion is experimentally supported by the result reported in previous communication: the regioselectivity was achieved in the intramolecular double addition between [60]fullerene and **4**.[4]

In conclusion, the present study has demonstrated that boronic acids react with 1,3-diol moieties of threitol affording two six-membered boronate rings.[13] The formation of six-membered rings in **4** is consistent with the general concept, in which six-membered boronate rings are more stable than five-membered rings.[8] However, the [6,6]bicyclo structure constructed by the two boronate rings in **4** is formed for the first time in this study. We believe that this study provides fruitful information in the field of saccharide chemistry including saccharide-recognition.

EXPERIMENTAL

All melting points are uncorrected. IR spectra were recorded on a SHIMAZU FT-IR 8100M and measured as KBr pellets. ^{1}H, ^{13}C, and ^{11}B NMR spectra were determined in $CDCl_3$ or DMSO-d_6 with a BRUKER ARX300. Mass spectra were measured on a HITACHI M-2500 Mass Spectrometer. D-Threitol (**1**) was purchased from SIGMA Co., Ltd.. 4-Bromo-*o*-xylene (**5**) (purity >75%) was purchased from Tokyo Chemical Industry Co., Ltd..

3,4-Dimethylphenylboronic acid (6).

To a suspension of megnesium-ribbon (4.38 g, 180 mmol) in dry tetrahydrofurane (30 ml) added dropwise a solution of 4-bromo-*o*-xylene (**5**) (purity >75%, 30.14 g, 22.0 ml, 163 mmol) in dry tetrahydrofurane (120 ml) for 40 min at room temperature under nitrogen. The reaction mixture was added to trimethylborate (22.86 g, 24.7 ml, 220 mmol) for 1 h at -60°C under nitrogen. The reaction mixture was stirred for an additional 2 h, allowed to warm to room temperature, and stirred for an additional 14 h. Then, 10% sulfuric acid (100 ml) was added at 0°C and the reaction mixture was stirred for 2 h at room temperature. It was extracted with ether, washed with brine and water, dried over anhydrous magnesium sulfate, and evaporated *in vacuo*. The residue was washed with hexane to give **6** in 69% yield (purity >75%, 16.77 g, 112 mmol). Without further purification, **6** was used to the next reaction.

4-(2,6-Dioxa-1-boracyclohexanyl)-*o*-xylene (7).

A solution of **6** (1.50 g, 10.0 mmol) and propane-1,3-diol (913 mg, 12.0 mmol) in toluene (50 ml) was heated under reflux with azeotropic removal of water (Dean-Stark) for 2 h under nitrogen. After the reaction mixture was cooled to room temperature, it was evaporated *in vacuo*. The residue was washed with methanol to give **7** in 71% yield (1.38 g, 7.09 mmol): colorless prisms; mp 85–86°C; IR (KBr) ν 2973, 1615, 1482, 1437, 1420, 1312 (ν_{BO}), 1183, 1132, 831, 723, 664, 448 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.05 (quint, J = 5.6 Hz, 2 H, $OCH_2\underline{CH_2}$), 2.27 (s, 6 H, Me), 4.16 (t, J = 5.6 Hz, 4 H, OCH_2), 7.12, 7.50 (d, J = 7.6 Hz, each 1 H, ArH), 7.53 (s, 1 H, ArH). Anal. Calcd. for $C_{11}H_{15}BO_2 \cdot 1/5(CH_3OH)$: C, 68.47; H, 8.11%. Found: C, 68.63; H, 7.98%.

α,α'-Dibromo-4-(2,6-dioxa-1-boracyclohexanyl)-*o*-xylene (8).

To a solution of **7** (760 mg, 4.0 mmol) and NBS (1.57 g, 8.8 mmol) in carbon tetrachloride (60 ml) was added AIBN (33 mg, 0.2 mmol) under nitrogen. The mixture was heated under reflux for 2 h. After the reaction mixture was cooled to room temperature, it was filtered to remove succinimide and washed with carbon tetrachloride. The filtrate was evaporated *in vacuo*. The residue was washed with ether to give **8** in 50% yield (692 mg, 1.99 mmol): colorless prisms; mp 114–115°C; IR (KBr) ν 1609, 1483, 1439, 1428, 1318 (ν_{BO}), 1275, 1186, 1125, 936, 845, 743, 683, 608, 594, 558 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.07 (quint, J = 5.4 Hz, 2 H, $OCH_2C\underline{H_2}$), 4.16 (t, J = 5.4 Hz, 4 H, OCH_2), 4.67, 4.68 (s, each 2 H, CH_2Br), 7.34, 7.69 (d, J = 7.6 Hz, each 1 H, ArH), 7.76 (s, 1 H, ArH); ^{11}B NMR ($CDCl_3$, $(MeO)_3B$ as external standard) δ 26.53. Anal. Calcd. for $C_{11}H_{13}BBr_2O_2$: C, 37.98; H, 3.77%. Found: C, 38.00; H, 3.83%.

2,4,6-[3,4-Bis(bromomethyl)phenyl]boroxin (2).

To a solution of **8** (3.99 g, 11.47 mmol) in tetrahydrofurane (23 ml) was added 1.2 N hydrochloric acid (6 ml) at 0 °C. After the mixture was stirred for 2 h at room temperature, water was added. The reaction mixture was extracted with ether, washed with water, dried over anhydrous magnesium sulfate, and evaporated *in vacuo*. The residue was washed with dichloromethane to give **2** in 90% yield (2.99 g, 3.44 mmol): colorless prisms; mp 294–296°C; IR (KBr) ν 1609, 1404, 1350 (ν_{BO}), 1215, 849, 723, 617 cm^{-1}; ^1H NMR (DMSO-d_6) δ 4.82 (s, 4 H, CH_2), 7.43, 7.73 (d, J = 7.5 Hz, each 1 H, ArH), 7.84 (s, 1 H, ArH), 8.19 (s, D_2O-exchange, 2 H, $B(OH)_2$). Anal. Calcd. for $C_{24}H_{21}B_3Br_6O_3$: C, 33.16; H, 2.44%. Found: C, 33.73; H, 2.54%.

α,α'-Dibromo-4-(2,5-dioxa-1-boracyclopentyl)-*o*-xylene (9).

A suspension of **2** (145 mg, 0.167 mmol) and ethylene glycol (37 mg, 0.6 mmol) in toluene (15 ml) was heated under reflux with azeotropic removal of water (Dean-Stark) for 40 min under nitrogen. After the reaction mixture was cooled to room temperature, it was evaporated *in vacuo* to give **9** in 96% yield (160 mg, 0.479 mmol). An analytical sample was obtained by recrystallization from hexane as colorless prisms: mp 95–96°C; IR (KBr) ν 2979, 2909, 1609, 1507, 1478, 1464, 1439, 1410, 1393, 1370, 1339 (ν_{BO}), 1237, 1094, 1001, 945, 847, 781, 681, 610, 550 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.39 (s, 4 H, CH_2O), 4.67, 4.68 (s, each 2 H, CH_2Br), 7.39, 7.74 (d, J = 7.5 Hz, each 1 H, ArH), 7.81 (s, 1 H, ArH); ^{11}B NMR ($CDCl_3$, $(MeO)_3B$ as external standard) δ 31.12. Anal. Calcd. for $C_{10}H_{11}BBr_2O_2$: C, 35.98; H, 3.32%. Found: C, 36.34; H, 3.37%.

D-Threitol-1,3:2,4-bis[-3,4-bis(bromomethyl)phenylboronate] (4).

A suspension of D-threitol (**1**) (31 mg, 0.25 mmol) and **2** (145 mg, 0.167 mmol) in dry toluene (100 ml) was heated under reflux with azeotropic removal of water (Dean-Stark) for 4 h under nitrogen. After the reaction mixture was cooled to room temperature, it was evaporated *in vacuo*. The residue was purified by recrystallization from hexane/dichloromethane to give **4** in 82% yield (136 mg, 0.204 mmol) as colorless prisms: mp 176–177°C; IR (KBr) ν 2973, 1609, 1464, 1441, 1420, 1320 (ν_{BO}), 1233, 1217, 1190, 1127, 847, 820, 750, 698, 612, 552 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.32, 4.43 (d, J = 12.4 Hz, each 2 H, CH_2), 4.51 (s, 2 H, CH), 4.63, 4.65 (s, each 4 H, CH_2Br), 7.31, 7.72 (d, J = 7.6 Hz, each 2 H, ArH), 7.77 (s, 2 H, ArH); ^{13}C NMR ($CDCl_3$) δ 29.82, 30.27 (CH_2Br), 65.67 (CH_2), 66.66 (CH), 130.29, 135.07 (CH), 135.51 (C),

136.67 (CH), 139.14 (C), CB was missing; ^{11}B NMR ($CDCl_3$, $(MeO)_3B$ as external standard) δ 27.71; MS (SIMS, positive, NBA) m/z 590, 588, 586, 584 [(M - Br + H)$^+$], 589, 587, 585, 583 [(M - Br)$^+$]. Anal. Calcd. for $C_{20}H_{20}B_2Br_4O_4$: C, 36.09; H, 3.03%. Found: C, 36.40; H, 3.06%.

X-ray Crystallographic Analysis of 4.

$C_{20}H_{20}O_4B_2Br_4$, M = 665.61, monoclinic, space group $P2_1$ (No. 4), a = 6.463 (2) Å, b = 27.789 (3) Å, c = 7.126 (2) Å, β = 111.18 (1)°, V = 1193.4 (4) Å^3, Z = 2, D_C = 1.852 g/cm^3, monochromated Cu-Kα radiation, λ = 1.54178 Å. A colorless prism of compound **4** (from hexane/dichloromethane, approximate dimensions of 0.30 x 0.10 x 0.10 mm), mounted on a glass fiber in a random orientation, was used for X-ray data collection. Data were collected on a Rigaku AFC7R diffractometer using ω-2θ scan at a temperature of 20 ± 1°C. Total of 1998 reflections were collected, of which 1826 were unique. The structure was solved by heavy-atom Patterson methods[14] and refined by full-matrix least-squares calculation to give R = 0.040, R_W = 0.041 for 1444 observed independent reflections ($I > 3.00\sigma(I)$). The non-hydrogen atoms were located in succeeding difference Fourier syntheses and anisotropically treated. Hydrogen atoms were included but not refined. All calculations were performed using the teXsan[15] crystallographic software package of Molecular Structure Corporation.

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