Regioselective Synthesis of $[1\text{-}B_{10}H_9(SH)]^{2-}$ and $[2\text{-}B_{10}H_9(SH)]^{2-}$: Potential Agents for Boron–Neutron Capture Therapy of Brain Tumours

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The substitution reaction of $[1\text{-}B_{10}H_9(N_2)]^-$ with *N,N*-dimethylthioformamide and the acid-catalyzed nucleophilic substitution of $[B_{10}H_{10}]^{2-}$ with tetramethylthiourea gave $[1\text{-}B_{10}H_9(SCH{=}NMe_2)]^-$ and $[2\text{-}B_{10}H_9\{SC(NMe_2)_2\}]^-$, respectively. The basic hydrolysis of these thioamide complexes yielded the 1- and 2-isomers of $[B_{10}H_9(SH)]^{2-}$ respectively. Their stereochemistry was determined by ^1H n.m.r. spectroscopy from the S–Me chemical shift values of their *S*-methyl derivatives.

Boron–neutron capture therapy of malignant brain tumours is being clinically tested by Hatanaka[1] using the sodium salt of ^{10}B-enriched $[B_{12}H_{11}(SH)]^{2-}$ (**1**) synthesized by this company.[2] The divalent anion (**1**) is a monomercapto derivative of $[B_{12}H_{12}]^{2-}$ (**2**), which is a polyhedral borane anion with high-boron content, high solubility in water, high chemical stability, and low toxicity. Another potential agent for the boron–neutron capture therapy, $[B_{10}H_9(SH)]^{2-}$, is a monomercapto derivative of $[B_{10}H_{10}]^{2-}$ (**3**), which is one of the polyhedral borane anions with similar properties to those of (**2**).[3]

In view of the symmetrical structure of (**3**), the isomers $[1\text{-}B_{10}H_9(SH)]^{2-}$ (**4**) and $[2\text{-}B_{10}H_9(SH)]^{2-}$ (**5**) would exist for the $[B_{10}H_9(SH)]^{2-}$ anion. Thus, synthetic routes were developed to (**4**) and (**5**) by basic hydrolysis of $[1\text{-}B_{10}H_9(SCH{=}NMe_2)]^-$ (**6**) and $[2\text{-}B_{10}H_9\{SC(NMe_2)_2\}]^-$ (**7**), respectively. This paper reports the preparation of (**6**) by the substitution reaction of $[1\text{-}B_{10}H_9(N_2)]^-$ (**8**) with *N,N*-dimethylthioformamide, and (**7**) by the acid-catalyzed nucleophilic substitution of (**3**) with tetramethylthiourea.

Results and Discussion

Synthesis of Thioamide Complexes (**6**) *and* (**7**), *and their Hydrolysis to Thiols* (**4**) *and* (**5**).—Leyden and Hawthorne[4] have prepared the mono apically-substituted diazonium derivative of (**3**), $[1\text{-}B_{10}H_9(N_2)]^-$ (**8**), by reacting (**3**) with arenediazonium tetrafluoroborate [equation (1)] followed by thermal decomposition [equation (2)]. Apical substitution was determined

$$(3) + RN_2^+ \longrightarrow [1\text{-}B_{10}H_9(NH{=}NR)]^- \quad (1)$$

$$[1\text{-}B_{10}H_9(NH{=}NR)]^- \longrightarrow (8) + RH \quad (2)$$

from the ^{11}B n.m.r. spectrum of (**8**). They[4] also showed that (**8**) was a useful intermediate for synthesizing mono apically-substituted derivatives because the nitrogen molecule could easily be displaced by a wide variety of nucleophiles.

When (**8**) is heated in *N,N*-dimethylthioformamide (dmtf) at 100 °C for several hours, the thioamide complex anion (**6**) is obtained as shown in the Scheme. The presence of B–S bonding in (**6**) is suggested from the ^1H n.m.r. spectrum, which shows the two methyl groups of dmtf placed in magnetically different environments.

Compound (**3**) can react with Lewis bases (L) under acidic conditions to eliminate hydrogen and give $[2\text{-}B_{10}H_9(L)]^-$ [equation (3)] [*L* = sulphone, sulphonamide, amide, or urea].[3]

$$(3) + L \xrightarrow{H^+} [2\text{-}B_{10}H_9(L)]^- + H_2 \quad (3)$$

Equatorial substitution predominates in this acid-catalyzed nucleophilic substitution reaction. This suggested that (**3**) might react with a thiourea to give an equatorially-substituted thiourea complex anion. In fact, when (**3**) is treated with tetramethylthiourea (tmtu) containing a small amount of hydrogen chloride, the acid-catalyzed nucleophilic substitution takes place to give monosubstituted tmtu complex (**7**) as shown in the Scheme. The occurrence of a single methyl signal of tmtu in the ^1H n.m.r. spectrum of (**7**) is consistent with B–S bond formation. The position of the S atom of tmtu in (**7**) was confirmed by comparing the S–Me chemical shift value of $[B_{10}H_9(SMe_2)]^-$, derived from (**7**) *via* $[B_{10}H_9(SH)]^{2-}$, with those of authentic samples prepared by other routes (see later).

When (**6**) or (**7**) is subsequently refluxed in aqueous acetone containing excess NMe_4OH or in aqueous CsOH for several hours, cleavage of the S–C bond occurs to form (**4**) or (**5**) along with *N,N*-dimethylformamide or tetramethylurea [equations (4) and (5)].

$$(6) + OH^- \longrightarrow (4) + Me_2NCHO \quad (4)$$

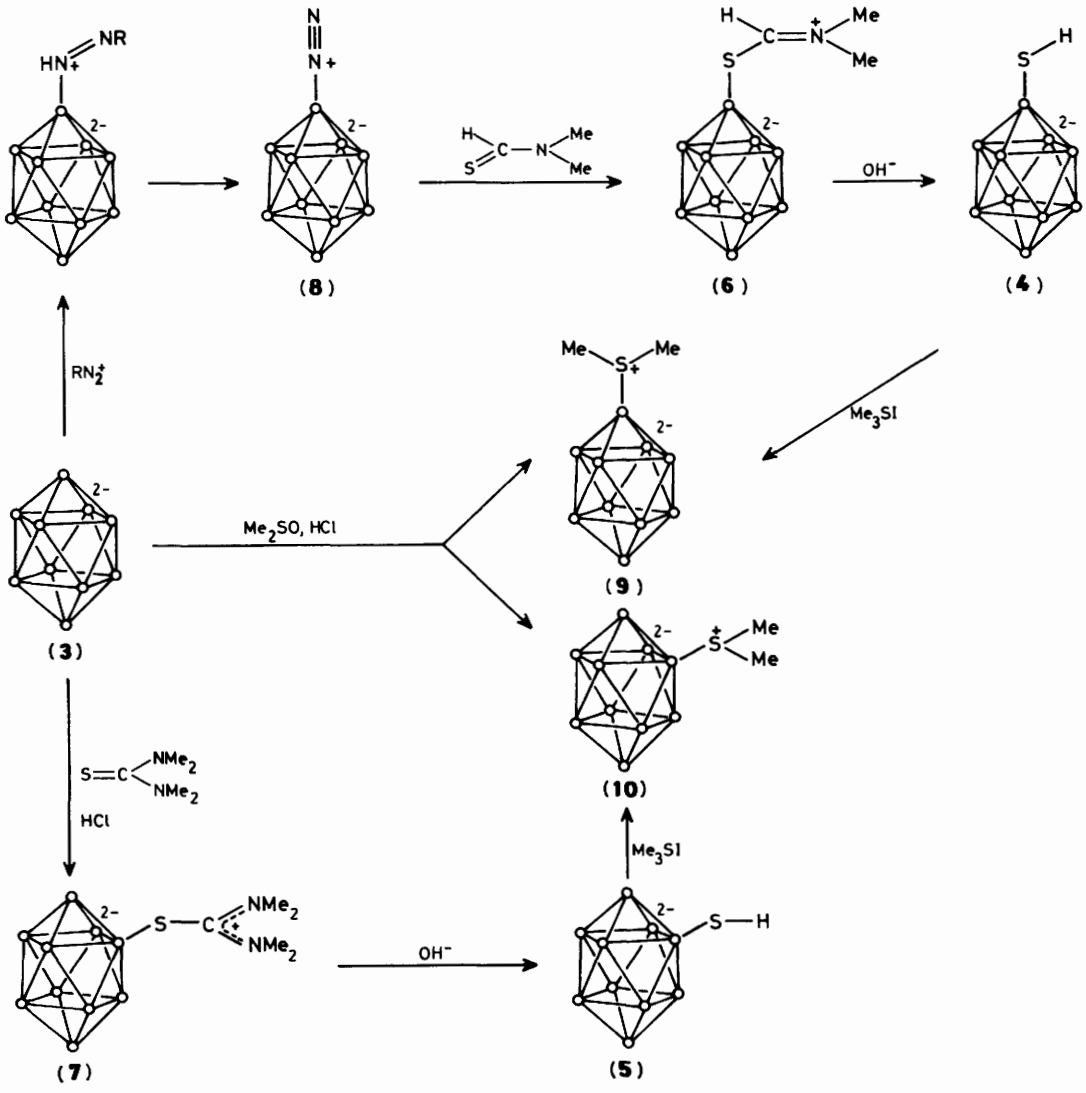
$$(7) + OH^- \longrightarrow (5) + (Me_2N)_2CO \quad (5)$$

The ^1H n.m.r. spectra show an SH proton signal at δ 0.4 for (**4**) and −0.3 for (**5**). There appears no N–Me proton signal of dmtf or tmtu in both spectra. In addition, (**4**) and (**5**) display no band characteristic of either the C=N or NCN moiety, and a sharp SH stretching band is found at 2 555 cm^{-1} in the i.r. spectrum of (**5**). These results show that cleavage of the S–C bonds of (**6**) and (**7**) occurs to give the thiols (**4**) and (**5**). Although no ν(S–H) band has been found in the spectrum of (**4**), the deuteriated analogue $[1\text{-}B_{10}H_9(SD)]^{2-}$ exhibited the ν(S–D) band at 1 852 cm^{-1}, suggesting that the S–H band of (**4**) is obscured by the strong ν(B–H) band.

Conversion of $[B_{10}H_9(SH)]^{2-}$ *to* $[B_{10}H_9(SMe_2)]^-$, *and the Stereochemistry of the Thiols* (**4**), (**5**) *and the Thioamide Complexes* (**6**), (**7**).—Knoth *et al.*[5] found that when (**3**) was treated with a large excess of dimethyl sulphoxide (dmso) in the presence of hydrogen chloride $[1\text{-}B_{10}H_9(SMe_2)]^-$ (**9**) and $[2\text{-}B_{10}H_9(SMe_2)]^-$ (**10**) were formed in an approximate mole ratio of 3:1, the stereochemistry of which was determined from their ^{11}B n.m.r. spectra [equation (6)]. The ^1H n.m.r. spectra of

$$(3) + Me_2SO \xrightarrow{H^+} [B_{10}H_9(SMe_2)]^- + H_2O \quad (6)$$

analytically pure NMe_4^+ salts of (**9**) and (**10**), obtained by fractional recrystallization of the crude products from hot



Scheme. R = aryl

water, in [$^2H_6$]dmso ($SiMe_4$ as the internal standard) show an apical SMe_2 signal at δ 2.99 and an equatorial one at δ 2.20. The ^1H n.m.r. spectra of sodium salts of the isomeric anions in D_2O ($NaO_3S(CH_2)_3SiMe_3$ as the internal standard) show apical and equatorial SMe_2 signals at δ 3.02 and 2.28, respectively.

When $[NMe_4]_2[1\text{-}B_{10}H_9(SH)]$ was treated with Me_3SI in boiling water, *S*-methylation at the thioether sulphur occurred readily. The ^1H n.m.r. spectrum in D_2O for the sodium salt obtained by cation exchange of the reaction mixture shows only one peak at δ 3.02, assignable to the apical SMe_2 protons. This result confirms that both $[NMe_4]_2[1\text{-}B_{10}H_9(SH)]$ and its precursor $[NMe_4][1\text{-}B_{10}H_9(SCH{=}NMe_2)]$ may be apically substituted derivatives, and no thermal rearrangement occurs throughout the synthetic processes from $[1\text{-}B_{10}H_9(N_2)]^-$ to $[1\text{-}B_{10}H_9(SH)]^{2-}$. A similar *S*-methylation reaction of $[NMe_4]_2[2\text{-}B_{10}H_9(SH)]$ affords $[NMe_4][2\text{-}B_{10}H_9(SMe_2)]$, which gives a ^1H n.m.r. spectrum in [$^2H_6$]dmso ($SiMe_4$ as the internal standard) having only an equatorial SMe_2 signal at δ 2.20. This indicates that the acid-catalyzed nucleophilic substitution of (**3**) with tetramethylthiourea gives the equatorial isomer selectively.

An *X*-ray study of one of these isomers, (**5**), also confirmed the SH group to be at the equatorial position.[6]

Experimental

Apparatus, Materials, and Procedures.—Infrared spectra were recorded on a Hitachi 215 spectrophotometer. ^1H N.m.r. spectra were measured with a Varian T-60 spectrometer ($SiMe_4$ as internal standard unless otherwise stated). Thin-layer chromatography (t.l.c.) was carried out as described in the literature[7] using Baker-Flex PEI-Cellulose t.l.c. sheets, where 3N aqueous ammonium hexafluorophosphate was used as the solvent system. Spots were detected by spraying 2% palladium chloride in 0.1 N hydrochloric acid. Elemental analyses were done in these laboratories. The triethylammonium salt of (**3**) was prepared from decaborane, purchased from the Callery Chemical Company, by a literature method.[8] Conversion to the K^+, Na^+, or NH_4^+ salt was carried out using the column with a cation exchange resin. $[NMe_4][1\text{-}B_{10}H_9(N_2)]$ was prepared by a procedure reported previously.[4] *N,N*-Dimethylthioformamide was purchased from E. Merck Darmstadt, dried over molecular sieves, and distilled at 72—74 °C [2.5—3.0

mmHg (*ca.* 332—399 Pa)]. All other materials were of reagent grade, and were used without purification.

Synthesis and Characterization of $[NMe_4][1\text{-}B_{10}H_9(SCH{=}NMe_2)]$.—A mixture of $[NMe_4][1\text{-}B_{10}H_9(N_2)]$ (5.65 g, 25.8 mmol) and *N,N*-dimethylthioformamide (72.8 g, 817 mmol) was heated with stirring at 103 °C to cause mild gas evolution. When the evolution ceased, the resulting mixture was cooled to room temperature and added to benzene (1 l) with vigorous stirring. The yellow solid that separated immediately was collected by filtration. This crude product was dissolved in 80% ethanol (420 cm^3) at 70 °C, filtered while hot, and allowed to stand overnight at 0 °C. The yellow crystals which formed were collected by filtration and dried *in vacuo* at 80 °C to obtain $[NMe_4][1\text{-}B_{10}H_9(SCH{=}NMe_2)]$ (5.27 g, 18.8 mmol, 73% yield). m.p. 254—256 °C (Found: C, 29.80; H, 10.00; N, 9.50; S, 11.30 Calc. for $C_7H_{28}B_{10}N_2S$: C, 30.00; H, 10.05; N, 10.00; S, 11.45%). I.r. (Nujol mulls): 3 022m, 2 461vs, 1 601s, 1 483s, 1 418m, 1 286m, 1 000s, 948s, 927s, 858w, and 812w cm^{-1}. ^1H N.m.r. ($[^2H_6]$dmso): δ 3.10 (s, N–Me of NMe_4^+, relative intensity 12), 3.43, 3.60 (s, N–Me of dmtf, relative intensity 3), and 9.73 (s, C–H of dmtf, relative intensity 1). T.l.c.: R_f 0.41 (aqueous 3N NH_4PF_6). These results are compatible with the formation of $[NMe_4][1\text{-}B_{10}H_9(SCH{=}NMe_2)]$ with B–S bonding.

Synthesis and Characterization of $Cs[2\text{-}B_{10}H_9\{SC(NMe_2)_2\}]$.—A large excess of dry HCl gas was introduced into tmtu (1.73 g, 13.1 mmol) for 30 min to form 2.84 g of the liquified tmtu hydrochloride containing 30.4 mmol of HCl. Heating a mixture of $Na_2[B_{10}H_{10}]$ (2.31 g, 14.1 mmol) and tmtu (25.6 g, 194 mmol) at 95 °C gave a pale yellow slurry, to which was added dropwise 1.61 g of the liquified tmtu hydrochloride (containing 17.3 mmol of HCl) with vigorous stirring over a period of 40 min. Vigorous gas evolution occurred and the temperature rose to 99—102 °C. The resulting pale orange slurry was heated for an additional 35 min at 100 °C and then left to cool at ambient temperature. The slurry was diluted with 45% ethanol (120 cm^3) at 75 °C, and excess CsCl in 45% ethanol was added to cause separation of a yellow solid which was collected by filtration. Recrystallization of the resulting product from hot water gave yellow needle-like crystals, which were collected by filtration, washed with a small amount of chilled water, and dried *in vacuo* at 100 °C, yielding the first crop of pure $Cs[2\text{-}B_{10}H_9\{SC(NMe_2)_2\}]$ (3.03 g). The filtrate and washings were combined, and concentrated to obtain a second crop of 0.52 g. The overall yield was 66% (Found: C, 15.80; H, 5.85; N, 7.35; S, 8.20. Calc. for $C_5H_{21}B_{10}CsN_2S$: C, 15.70; H, 5.55; N, 7.35; S, 8.40%). T.l.c.: R_f 0.36 (aqueous 3N NH_4PF_6). I.r. (Nujol mulls): 2 526s, 2 486vs, 1 588s, 1 496w, 1 265m, 1 208w, 1 164m, 1 118m, 1 055m, 1 005w, 947m, 875m, 830w, and 787m cm^{-1}. ^1H N.m.r. ($[^2H_6]$dmso): δ 3.15 (s, N–Me of tmtu).

Basic Hydrolysis of Thioamide Complexes (**6**) *and* (**7**), *and Characterization of the Cs Salts of* (**4**) *and* (**5**).—A mixture of $[NMe_4][1\text{-}B_{10}H_9(SCH{=}NMe_2)]$ (8.61 g, 30.70 mmol) and 50% aqueous acetone (280 cm^3) was heated at 65 °C with stirring to give a transparent solution, to which was added dropwise 10% NMe_4OH (31 cm^3) over a period of 30 min, followed by refluxing for an additional 9 h, and subsequent cooling. The resulting mixture was neutralized with 1N H_2SO_4 and evaporated to dryness under reduced pressure. The residue was dissolved in water (850 cm^3) and the solution passed through excess SK-1B (H^+), a cation exchange resin. The acid effluent was neutralized with 1N CsOH and evaporated to dryness. The residue was fractionally recrystallized from hot water to give $Cs_2[1\text{-}B_{10}H_9(SH)]\cdot H_2O$ (1.94 g, 4.47 mmol, 15%). It was very soluble in water, soluble in dmso, but only sparingly soluble in acetone, ethanol, diethyl ether, or hydrocarbons (Found: H, 2.85; B, 25.20; S, 7.35; H_2O, 3.40. Calc. for $H_{12}B_{10}Cs_2OS$: H, 2.80; B, 24.90; S, 7.40; H_2O, 4.15%). I.r. (Nujol mulls): 3 605w, 3 540w, 2 452s, 1 605w, 1 139w, 1 111m, 1 019m, and 867w cm^{-1}. ^1H N.m.r. ($[^2H_6]$dmso): δ 0.4 (s, br, S–H).

A mixture of $Cs[2\text{-}B_{10}H_9\{SC(NMe_2)_2\}]$ (9.50 g, 24.9 mmol) and water (750 cm^3) was refluxed to give a transparent pale yellow solution, to which was added dropwise 0.96N CsOH (30 cm^3) with stirring over a period of 15 min. After refluxing for an additional 6.5 h, the solution was cooled to room temperature, neutralized with 1 N H_2SO_4, and evaporated under reduced pressure to produce a wet solid. The product thus obtained was dissolved in hot water (45 cm^3) and cooled. The yellow crystals which formed were removed by filtration and the filtrate concentrated to 6 cm^3. The pale yellow crystals produced were collected by filtration, washed three times with chilled water (1 cm^3), and air-dried under nitrogen to obtain $Cs_2[2\text{-}B_{10}H_9(SH)]\cdot 0.5H_2O$ (3.61 g, 8.49 mmol, 34%) (Found: H, 2.55; B, 25.25; S, 7.05; H_2O, 2.35. Calc. for $H_{22}B_{20}Cs_4OS_2$: H, 2.60; B, 25.45; S, 7.55; H_2O, 2.10%). I.r. (Nujol mulls): 3 627w, 3 547w, 2 555m, 2 467s, 1 597w, 1 034(sh), 1 012m, 955s, 888w, and 857w cm^{-1}. ^1H N.m.r. ($[^2H_6]$dmso): δ −0.3 (s, br, S–H).

S-*Methylation of* (**4**) *and* (**5**).—$[NMe_4]_2[2\text{-}B_{10}H_9(SH)]$ (0.60 g, 2.0 mmol) and trimethylsulphonium iodide (2.60 g, 12.5 mmol) were mixed in water (15 cm^3) and the solution refluxed for 3 h under nitrogen. Cooling the solution to room temperature yielded microcrystals, which were collected by filtration, washed with water and then ethanol, and air-dried. The crude product thus obtained was dissolved in H_2O–MeCN (5:1), and the solution passed through Amberlite IR-120 (H^+ form) (30 cm^3). The acid effluent was collected, neutralized with 10% NMe_4OH, and evaporated to one-tenth its volume under reduced pressure. Subsequent cooling to 0 °C produced colourless needle-like crystals which were collected by filtration and dried *in vacuo* at 70 °C to give $[NMe_4][2\text{-}B_{10}H_9(SMe_2)]$ (0.30 g, 1.19 mmol, 71%)) (Found: C, 28.80; H, 11.15; N, 5.35; S, 12.80. Calc. for $C_6H_{27}B_{10}NS$: C, 28.45; H, 10.75; N, 5.55; S, 12.65%). ^1H N.m.r. ($[^2H_6]$dmso): δ 3.13 (s, N–Me, intensity 2) and 2.20 (s, equatorial SMe_2, intensity 1).

$[NMe_4]_2[1\text{-}B_{10}H_9(SH)]$ (0.27 g, 0.90 mmol) was treated with Me_3SI (1.32 g, 6.34 mmol) as described above. The product obtained was dissolved in H_2O–MeCN (1:1), and the solution passed through Amberlite IR-120 (Na^+) (10 cm^3). Evaporation of the effluent to dryness under reduced pressure gave a pale yellow solid, $Na[1\text{-}B_{10}H_9(SMe_2)]$ (0.07 g, 0.35 mmol). ^1H N.m.r. (D_2O; $NaO_3S(CH_2)_3SiMe_3$ as the internal standard): δ 3.02 (s, apical SMe_2).

Preparation of (**9**) *and* (**10**) *by Reaction of* $[B_{10}H_{10}]^{2-}$ *with Dimethyl Sulphoxide*.—The acid-catalyzed substitution of $[NH_4]_2[B_{10}H_{10}]$ (2.0 g) with dmso (20 cm^3) was carried out according to a literature method.[5] A mixture of the reactants was poured into water (50 cm^3). After filtration to remove the insoluble materials, the filtrate was mixed with an aqueous solution of excess NMe_4Cl. The precipitate, which was produced immediately, was collected by filtration, washed with ethanol, and dried *in vacuo* at 70 °C, to yield crude $[NMe_4][B_{10}H_9(SMe_2)]$ (2.60 g). The crude product (0.1 g) was dissolved in H_2O–MeCN (3:1), and the solution passed through Amberlite IR-120 (H^+ form) (24 cm^3). The acid effluent was neutralized with 0.01N NaOH and evaporated to dryness under reduced pressure to give $Na[B_{10}H_9(SMe_2)]$ (0.06 g) (mixture of 1- and 2-isomers). ^1H N.m.r. of the Na salt (D_2O; $NaO_3S(CH_2)_3SiMe_3$ as the internal standard): δ 3.02 (s, apical SMe_2, relative intensity 4) and 2.28 (s, equatorial SMe_2, relative

intensity 1). The remaining crude product was refluxed in water (500 cm^3) and on leaving to stand overnight at room temperature, pale yellow crystals formed. These were collected by filtration and dried *in vacuo* at 80 °C, yielding the first crop (A, 1.61 g) of $[NMe_4][1\text{-}B_{10}H_9(SMe_2)]$. Fractional recrystallization from the filtrate gave a second crop (0.46 g) and a third crop (B, 0.28 g) of $[NMe_4][2\text{-}B_{10}H_9(SMe_2)]$ (Found for A: C, 28.10; H, 10.85; N, 5.10; S, 12.30. Found for B: C, 28.65; H, 10.75; N, 5.15; S, 12.65. Calc. for $C_6H_{27}B_{10}NS$: C, 28.45; H, 10.75; N, 5.55; S, 12.65%). ^1H N.m.r. ($[^2H_6]$dmso; $SiMe_4$ as the internal standard): for A, δ 2.99 (s, apical SMe_2, relative intensity 1) and 3.13 (s, N–Me, relative intensity 2); for B, δ 2.20 (s, equatorial SMe_2, relative intensity 1) and 3.13 (s, N–Me, relative intensity 2).

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