A High-Yield Synthesis of 4-Borono-DL-phenylalanine

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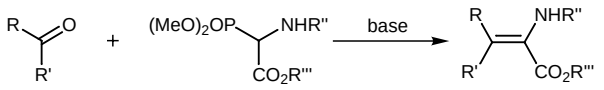
Received 5 July 1999; revised 27 August 1999

Abstract: A high-yield synthesis of 4-borono-DL-phenylalanine has been achieved by a route which features a highly diastereoselective formation of the *Z*-isomer of a boron-containing dehydroamino acid derivative.

Key words: boron neutron capture therapy, 4-boronophenylalanine, Horner–Emmons Wittig reaction, phosphonoglycine ester, diastereoselectivity

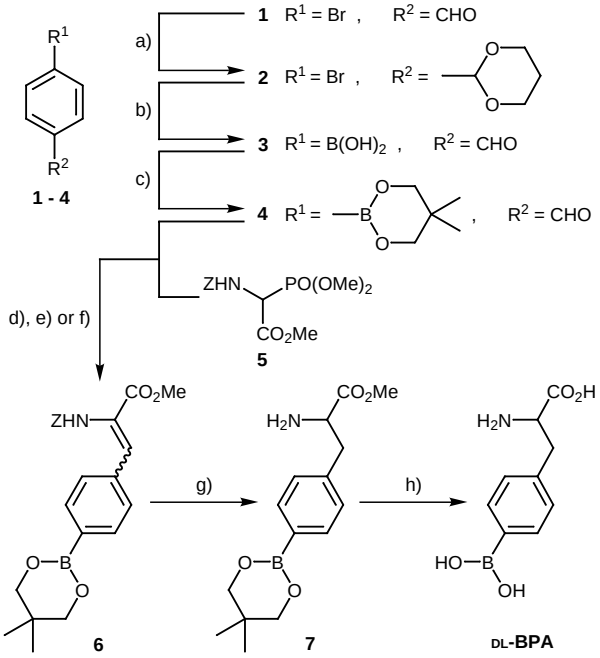
4-Boronophenylalanine (BPA)[1] is a boronated amino acid which exhibits a highly specific affinity for tumors, and its boron-10 labelled racemate has been clinically used for Boron Neutron Capture Therapy (BNCT) of malignant melanomas as an effective boron carrier.[2] In recent years, the use of BPA in clinical trials has been extended to treatment for brain tumors,[3] which increases further the significance of BPA as a BNCT agent. Therefore, an efficient synthesis of BPA is an important goal for BNCT research groups.[4–8] Herein, we describe the details of a high-yield synthesis of DL-BPA focused on the construction of an amino acid moiety.

The present synthesis of BPA is based on the Horner–Emmons Wittig reaction of carbonyl compounds with *N*-acylphosphonoglycine esters (Scheme 1).[9–11] Schmidt and co-workers reported that for phosphonoglycine ester condensations, the use of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) or tetramethylguanidine (TMG) in an appropriate solvent provided (*Z*)-dehydroamino acid derivatives diastereoselectively in excellent yields and with high purity.[12] In our approach to the synthesis of BPA, we examined the condensation of the boron-containing carbonyl compound **4** with *N*-(benzyloxycarbonyl)phosphonoglycine ester **5**[9] in the presence of NaH, DBU and TMG, respectively (Scheme 2). To the best of our knowledge, this is the first report on the application of this modified Horner–Emmons Wittig reaction to the synthesis of a boron-containing amino acid.



Scheme 1

To accomplish the desired total synthesis, it was necessary to prepare the general synthon **3** as simply as possible. Commercially available 4-bromobenzaldehyde (**1**) was treated with propane-1,3-diol in the presence of a catalytic amount of BF_3•OEt_2 in refluxing toluene to provide the acetal **2**. Subsequently, the boronated carbonyl compound **3** was prepared from **2** by a Grignard reaction with trimethyl borate in THF at –78 °C followed by stepwise hydrolysis. As a result, the facile preparation of **3** was achieved in a two-step yield of 64%.



Reagents and conditions: a) Propane-1,3-diol/BF_3•OEt_2/toluene, reflux, 4.5 h, (96%); b) (i) Mg/1,2-dibromoethane/THF, reflux, 30 min, (ii) $B(OCH_3)_3$/THF, –78 to –45 °C, 6 h, (iii) 3 M aq NH_4Cl, evaporation, H_2O, 2 M aq HCl (pH 3–4), reflux, 15 min, concd HCl, (67%); c) 2,2-Dimethylpropane-1,3-diol/THF, r.t., 10 min, (98%); d) DBU/CH_2Cl_2, r.t., 3 h, (95%, *E*/*Z* = 9/91); e) TMG/THF, –70 °C to r.t., 30 h, (94%, *E*/*Z* = 6/94); f) 60% NaH/THF, r.t., 31 h, (85%, *E*/*Z* = 48/52); g) 10% Pd–C/H_2/MeOH–CH_2Cl_2 (2:1), r.t., 3 atm, 19 h, (quant.); h) (i) 1 M aq NaOH, 45–50 °C, 2 h, (ii) 2 M aq HCl, 30 °C, 3 h, 1 M aq NaOH (pH 6.2), (83%).

Scheme 2

In the direct condensation of **3** with **5**, it was considered that the reactive boronic acid group would prevent the nucleophilic C–C bond forming reaction.[13] Actually the reaction of **3** with **5** under the same conditions as adopted in the preparation of **6** using DBU gave a poor result. Thus, the boronic acid group was protected by esterification with 2,2-dimethylpropane-1,3-diol.

The resulting compound **4** was allowed to react with **5** in the presence of NaH in THF at ambient temperature to provide an *E*/*Z* mixture of **6** in a modest yield of 85%. The mixture was separated by repeated silica gel chromatography ($CHCl_3$: hexane: EtOAc, 6:4:1) to identify each diastereomer. The *E*/*Z* configurational assignment was made by a Nuclear Overhauser Enhancement (NOE) difference spectroscopy.[14] Based on the results, the *E*/*Z* ratios of all the condensation products were estimated by the ^{1}H NMR integration of the amide protons of the *E*- and *Z*-isomers. Consequently, the use of NaH was found to have provided **6** with the *E*/*Z* ratio of 48/52.

The condensation of **4** with **5** using DBU was successfully achieved in CH_2Cl_2 at ambient temperature to provide **6** in an excellent yield of 95% and predominantly in the form of the *Z*-isomer as indicated with the *E*/*Z* ratio of 9/91. Similarly, the use of TMG in THF at –70 °C provided **6** in a 94% yield and with the *E*/*Z* ratio of 6/94. From these results, the phosphonoglycine ester condensations using DBU and TMG proved to be not only excellent in yields but also effective for the diastereoselective preparation of (*Z*)-**6**. With the boronic acid groups protected appropriately, this beneficial condensation could be applied to the preparation of other boronated *(Z)*-dehydroamino acid derivatives. In addition, the combination with enantioselective hydrogenation using a rhodium chiral bisphosphine catalyst gives the possibility of efficiently obtaining optically active boronated amino acid derivatives.[6,15]

In the present work, compound **6** was hydrogenated with concomitant debenzylation using 10% Pd–C at 3 atmospheres for 19 hours to provide **7** in quantitative yield. Finally, compound **7** was hydrolyzed by the successive treatment with sodium hydroxide and hydrochloric acid to provide DL-BPA in an 83% yield.

In summary, the efficient construction of an amino acid moiety using a phosphonoglycine ester condensation led to a high-yield synthesis of DL-BPA, and the overall yield was 49% (the yield based on **3**:77%). The present procedure could meet the high requirements of BNCT clinical groups for more convenient availability of BPA.

Mps were determined using a Yanaco Model MP-J3 apparatus and are uncorrected. IR spectra were recorded on JEOL JIR-Diamond 20 M FT-IR and Hitachi Model 270-30 spectrophotometers for KBr discs and Nujol mulls, respectively, and are reported as cm^{-1}. NMR spectra were recorded on a JEOL JNM-LA300WB spectrometer. Unless otherwise stated, ^{1}H and ^{13}C chemical shifts are reported in ppm downfield from internal TMS, and ^{11}B NMR chemical shifts are in ppm relative to external BF_3•OEt_2. Spectral assignments were made with the aid of DEPT, ^{1}H–^{1}H COSY, ^{13}C–^{1}H COSY and ^{13}C–^{1}H COLOC experiments (the signals of carbons bonded to borons are not detected owing to quadrupolar relaxation). Half-height widths ($\Delta\nu_{1/2}$) of ^{11}B NMR signals were calculated by fitting Lorentzian function to the baseline-corrected spectra (software: multipeak fit package ver. 1.20 in IGOR Pro ver. 3.12, Wave Metrics Inc.). Low resolution mass spectra (*m/z*) were recorded at 70 eV on a Shimadzu GCMS-QP1000EX spectrometer. Elemental analyses were performed on a Perkin-Elmer Model 240 elemental analyser.

2-(4-Bromophenyl)-1,3-dioxane (2)[16]

To a solution of 4-bromobenzaldehyde (**1**) (31.8 g, 172 mmol) and propane-1,3-diol (14.5 g, 191 mmol) in toluene (200 mL) was added BF_3 •OEt_2 (0.5 mL). The mixture was refluxed for 4.5 h in a Dean-Stark apparatus to remove the theoretical amount of H_2O. The solution was washed with 1 M aq $NaHCO_3$ (100 mL) and then with H_2O (100 mL), dried ($MgSO_4$) and concentrated in vacuo to give **2** (40.1 g, 96%) as a white solid, which was sufficiently pure to be employed in the next step, mp: 63.5–64.5 °C (from EtOH).

IR (KBr): ν_{max} = 2970 (s, C–H), 1595 (m, C=C ring str.), 1105, 1012 (s, C–O asym., sym. str.).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.38–1.45 (m, 1H, C*H*H), 2.11–2.27 (m, 1H, C*H*H), 3.90–3.99 (m, 2H, OCH_2), 4.21–4.26 (m, 2H, OCH_2), 5.43 (s, 1H, OC*H*O), 7.32–7.50 (m, 4H, arom. H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 25.6 (C-5), 67.3 (C-4, C-6), 100.7 (C-2), 122.7, 137.8 (C-1', C-4'), 127.8, 131.3 (other arom. C).

EIMS: *m/z* = 242/244 (M^+, 41/41%), 185 (100%).

Anal. Calcd for $C_{10}H_{11}BrO_2$: C, 49.41; H, 4.56. Found: C, 49.11; H, 4.52.

4-Formylphenylboronic Acid (3)[17]

To magnesium turnings (1.65 g, 67.9 mmol) was added one third of a solution of **2** (15.0 g, 61.7 mmol) in anhyd THF (60 mL). The mixture was heated with stirring, followed by addition of 1,2-dibromoethane (5 drops) to initiate the reaction. The remaining aryl halide solution was added dropwise under reflux. After being refluxed for a further 30 min, the solution was cooled to ambient temperature. The prepared Grignard reagent and a solution of trimethyl borate (6.41 g, 61.7 mmol) in anhyd THF (60 mL) were added simultaneously, dropwise, to pre-cooled (–78 °C) anhyd THF (150 mL) over 1.5 h. The mixture was stirred for another 6 h, during which the temperature was allowed to rise slowly to –45 °C. After removal of the cooling bath the mixture was stirred for a further 10 min, and 3 M aq NH_4Cl (22 mL) was added dropwise. The mixture was concentrated in vacuo to give a green viscous residue. To the residue was added H_2O (400 mL), and the suspension was adjusted to pH 3–4 with 2 M aq HCl. After being refluxed for 15 min, the hot solution was filtered through filter paper. The hot filtrate was collected, and the residue on the filter paper was extracted with boiling H_2O (1 L containing 8 drops of 2 M aq HCl). To the combined hot filtrates was added concd HCl (200 mL). The solution was cooled to ambient temperature and maintained in an ice bath over 24 h. The resulting solid was suction filtered, washed with a large amount of H_2O and dried in vacuo at ambient temperature to give **3** (6.19 g, 67%) as pale green needles (from hot H_2O), mp: 252.5–259 °C (dec.), (lit.[1] mp: 240 °C).

IR (KBr): ν_{max} = 3210 (br s, O–H), 1666 (s, C=O), 1506 (m, C=C ring str.).

^{1}H NMR (300 MHz, acetone-d_6): δ = 7.47 (s, 2H, B(O*H*)$_2$), 7.89–8.09 (m, 4H, arom. H), 10.08 (s, 1H, C*H*O).

^{13}C NMR (75.5 MHz,acetone-d_6): δ = 129.2, 135.5 (arom. *C*H), 138.9 (C-4), 193.3 (*C*HO).

^{11}B NMR (96.3 MHz,acetone-d_6): δ = 27.7 ($\Delta\nu_{1/2}$ = 154 Hz).

2-(4-Formylphenyl)-5,5-dimethyl-1,3,2-dioxaborane (4)

A mixture of **3** (6.27 g, 41.8 mmol) and 2,2-dimethylpropane-1,3-diol (4.95 g, 47.5 mmol) in anhyd THF (60 mL) was stirred for 10 min at ambient temperature. The solvent was then evaporated under reduced pressure. The resulting residue was dissolved in CH_2Cl_2 (150 mL), washed with H_2O (3 × 100 mL), dried ($MgSO_4$) and concentrated in vacuo. To the residue was added hexane (80 mL) with shaking, and the suspension was concentrated in vacuo to give **4** (8.95 g, 98%) as a white solid, which was employed in the next step without further purification; mp 68–68.5 °C.

IR (KBr): ν_{max} = 2956 (m, C–H), 1703 (s, C=O), 1483 (s, C=C ring str.).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.02 (s, 6H, 2CH_3), 3.78 (s, 4H, 2CH_2), 7.82–7.96 (m, 4H, arom. H), 10.02 (s, 1H, C*H*O).

^{13}C NMR (75.5 MHz, acetone-d_6): δ = 21.8 (*C*H$_3$), 31.8 (C-5), 72.4 (C-4, C-6), 128.6, 134.3 (arom. CH), 137.8 (C-4'), 192.7 (*C*HO).

^{11}B NMR (96.3 MHz, acetone-d_6): δ = 25.9 ($\Delta\nu_{1/2}$ = 292 Hz).

EIMS: *m/z* = 218 (M^+, 35%), 56 (100%).

Anal. Calcd for $C_{12}H_{15}BO_3$: C, 66.10; H, 6.93. Found: C, 66.00; H, 7.06.

Methyl (*E*/*Z*)-2-(Benzyloxycarbonylamino)-3-[4-(5,5-dimethyl-1,3,2-dioxaboran-2-yl)phenyl]acrylate ((*E*/*Z*)-6)

f) Use of NaH: A solution of **5**[9] (3.42 g, 10.3 mmol) in anhyd THF (10 mL) was added dropwise, with stirring to a slurry of 60% NaH (0.454 g, 11.4 mmol) suspended in anhyd THF (5 mL). The mixture was stirred at ambient temperature for 10 min, until hydrogen evolution had ceased. A solution of **4** (2.18 g, 10.0 mmol) in anhyd THF (15 mL) was added dropwise to the mixture, and stirring was continued for 31 h. Then, THF (20 mL) containing a few drops of H_2O was added to decompose an excess amount of NaH, and the solvent was evaporated under reduced pressure. The light yellow/green residue was dissolved in CH_2Cl_2 (70 mL), washed with H_2O (4 × 25 mL), dried (Na_2SO_4) and concentrated in vacuo. The resulting residue was filtered through silica gel ($CHCl_3$), and the crude product was purified by silica gel chromatography ($CHCl_3$: hexane, 3:2) to give an *E*/*Z* mixture of **6** (3.60 g, 85%, *E*/*Z* = 48/52) as a white solid. Separation of the *E*- and *Z*-isomers was made by repeated silica gel chromatography ($CHCl_3$: hexane: EtOAc, 6:4:1).

***E*-Isomer,** mp: 142.5–143 °C.

IR (KBr): ν_{max} = 3292 (s, N–H), 2958 (m, C–H), 1732 (s, C=O ester), 1695 (s, C=O urethane), 1631 (m, C=C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.02 (s, 6H, CH_3), 3.60 (s, 3H, OCH_3), 3.77 (s, 4H, 2CH_2OB), 5.17 (s, 2H, OCH_2C$_6$H$_5$), 7.00 (br s, 1H, N*H*), 7.21, 7.73 (2d$_{app.}$ of AA'XX' system, 2 × 2H, $J_{app.}$ = 8.3 Hz, BC$_6$H$_4$), 7.33–7.40 (m, 5H, OCH$_2$C$_6$H$_5$), 7.63 (br s, 1H, BC$_6$H$_4$C*H*).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 21.9 (*C*H$_3$), 31.9 [*C*(CH$_3$)$_2$], 52.3 (O*C*H$_3$), 67.3 (O*C*H$_2$Ph), 72.3 (*C*H$_2$OB), 124.3 (C-3), 125.8, 137.7 (C-2, C-1'), 127.9, 128.3, 128.4, 128.6, 133.3 (arom. CH), 135.8 ($C_{quat.}$–CH$_2$OC), 153.4 (NH*C*O), 165.1 (C-1).

^{11}B NMR (96.3 MHz, $CDCl_3$): δ = 26.2 ($\delta\nu_{1/2}$ = 793 Hz).

EIMS: *m/z* = 315 (M^+ – 108, 44%), 243 (68%), 228 (100%).

Anal. Calcd for $C_{23}H_{26}BNO_6$: C, 65.27; H, 6.19; N, 3.31. Found: C, 65.21; H, 6.47; N, 3.46.

***Z*-Isomer**, mp: 126.5–127 °C.

IR (KBr): ν_{max} = 3305 (s, N–H), 2951 (m, C–H), 1736 (s, C=O ester), 1691 (s, C=O urethane), 1626 (s, C=C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.02 (s, 6H, 2CH_3), 3.76, 3.79 (baseline-unresolved 2s, 7H, 2CH_2OB, OCH_3), 5.10 (s, 2H, OCH_2C$_6$H$_5$), 6.40 (br s, 1H, N*H*), 7.31 (br m, 6H, OCH$_2$C$_6$H$_5$ overlapping with BC$_6$H$_4$C*H*), 7.47, 7.77 (2d$_{app.}$ of AA'XX' system, 2 × 2H, $J_{app.}$ = 8.1 Hz, BC$_6$H$_4$).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 21.8 (*C*H$_3$), 31.8 (*C*(CH$_3$)$_2$), 52.6 (O*C*H$_3$), 67.5 (O*C*H$_2$Ph), 72.3 (*C*H$_2$OB), 124.5, 135.6, 135.9 (C-2, C-1', $C_{quat.}$–CH$_2$OC), 128.2, 128.5, 128.7, 134.0 (arom. CH), 131.4 (C-3), 153.7 (NH*C*O), 165.7 (C-1).

^{11}B NMR (96.3 MHz, $CDCl_3$): δ = 25.9 ($\Delta\nu_{1/2}$ = 686 Hz).

EIMS: *m/z* = 315 (M^+ –108, 57%), 243 (75%), 228 (100%).

Anal. Calcd for $C_{23}H_{26}BNO_6$: C, 65.27; H, 6.19; N, 3.31. Found: C, 65.52; H, 6.33; N, 3.26.

d) Use of DBU: To a solution of **5** (3.76 g, 11.4 mmol) in anhyd CH_2Cl_2 (8 mL) was added DBU (1.60 g, 10.5 mmol). After being stirred at ambient temperature for 10 min, a solution of **4** (2.18 g, 10.0 mmol) in anhyd CH_2Cl_2 (16 mL) was added dropwise to the mixture over 10 min (the temperature rose to 33 °C). The reaction mixture was stirred for 1 h, during which the temperature was lowered to ambient temperature, and stirring was continued for a further 2 h. Then, the solution was diluted with CH_2Cl_2 (200 mL), washed with 0.5 M aq H_2SO_4 (50 mL) and then with H_2O (4 × 100 mL), dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified by silica gel chromatography ($CHCl_3$) to give (*E*/*Z*)-**6** (4.02 g, 95%, *E*/*Z* = 9/91) as a white solid. The spectroscopic data were in good accordance with those of the *E*- and *Z*-isomers obtained by the condensation using NaH.

e) Use of TMG: a solution of **4** (2.18 g, 10.0 mmol) in anhyd THF (20 mL) was added dropwise to a pre-cooled (–70 °C) solution of **5** (3.96 g, 12.0 mmol) and TMG (1.38 g, 12.0 mmol) in anhyd THF (80 mL). The reaction mixture was allowed to warm to ambient temperature overnight and stirred for a further 30 h at ambient temperature. Then, the solvent was evaporated under reduced pressure. The light yellow/green residue was dissolved in CH_2Cl_2 (200 mL), washed with 0.5 M aq H_2SO_4 (50 mL) and then with H_2O (3 × 100 mL), dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified by silica gel chromatography ($CHCl_3$: hexane, 15:1) to give (*E*/*Z*)-**6** (3.99 g, 94%, *E*/*Z* = 6/94) as a white solid. The spectroscopic data were in good accordance with those of the *E*- and *Z*-isomers obtained by the condensation using NaH.

Methyl 2-Amino-3-[4-(5,5-dimethyl-1,3,2-dioxaboran-2-yl)phenyl]propionate (7)

To a solution of **(*E*/*Z*)-6** (*E*/*Z* = 9/91) (1.69 g, 4.00 mmol) in anhyd MeOH-CH_2Cl_2 (2:1, 30 mL) was added 10% Pd–C (84.3 mg). After being stirred under hydrogen at 3 atm for 19 h, the mixture was filtered through a membrane filter (White Mitex LSWP02500, Millipore Co.), and the filtrate was concentrated in vacuo to give **7** (1.16 g, 100%) as an amorphous solid. The product was employed in the next step without purification, (lit.[5]: no spectroscopic data reported).

IR (Nujol): ν_{max} = 3386 (br m, N–H), 1740 (s, C=O ester).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.01 (s, 6H, 2CH_3), 2.99 (dd, 1H, *J* = 13.6, 7.4 Hz, ArC*H*H), 3.15 (dd, 1H, *J* = 13.6, 5.6 Hz, ArC*H*H), 3.36 (br s, 2H, NH_2), 3.69, 3.75 (baseline-unresolved 2s, 7H, OCH_3, 2CH_2OB), 3.87 (dd, 1H, *J* = 7.4, 5.6 Hz, C*H*CH$_2$), 7.19, 7.74 (2d$_{app.}$ of AA'XX' system, 2 × 2H, $J_{app.}$ = 8.0 Hz, arom. H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 21.9 (*C*H$_3$), 31.9 (*C*(CH$_3$)$_2$), 40.1 (C-3), 52.2 (O*C*H$_3$), 55.3 (C-2), 72.3 (*C*H$_2$OB), 128.6, 134.2 (arom. CH), 139.0 (C-1'), 173.9 (C-1).

^{11}B NMR (96.3 MHz): δ = 26.2 ($\Delta\nu_{1/2}$ = 863 Hz).

4-Borono-DL-phenylalanine

A mixture of **7** (1.16 g, 4.00 mmol) and 1 M aq NaOH (15 mL) was stirred at 45–50 °C for 2 h, and then 2 M aq HCl (20 mL) was added slowly to the solution in an ice bath. After being stirred at 30 °C for 3 h, the solution was adjusted to pH 6.2 with 1 M aq NaOH and concentrated in vacuo to 17 mL to form a white solid. After storage overnight in a refrigerator the solid was separated and washed (chilled H_2O) to give practically pure DL-BPA (0.691 g, 83%) as a white powder, mp 284–287 °C (dec.); lit.[4] mp: 284–287 °C (dec.).

IR (KBr): ν_{max} = 3585 (s, O–H), 2906 (br s, N–H aminium), 1608 (s, C=O carboxylate).

^{1}H NMR (300 MHz, D_2O+DCl, int. ref.: sodium 3-(trimethylsilyl)propionate-d_4 (TSP-d_4)): δ = 3.26 (dd, 1H, *J* = 14.5, 7.6 Hz, C*H*H), 3.39 (dd, 1H, *J* = 14.5, 5.7 Hz, C*H*H), 4.42 (dd, 1H, *J* = 7.6,

5.7 Hz, C*H*CH_2), 7.37, 7.76 ($2d_{app.}$ of AA'XX' system, 2 × 2H, $J_{app.}$ = 8.0 Hz, arom. H).

^{13}C NMR (75.5 MHz, D_2O +DCl ext. ref.: TSP-d_4): δ = 38.4 (*C*H_2), 56.8 (*C*HCH_2), 131.8, 137.2 (arom. CH), 139.6 ($C_{quat.}$–CH_2), 174.1 (*C*O).

^{11}B NMR (96.3 MHz, D_2O +DCl): δ = 28.3 ($\Delta\nu_{1/2}$ = 849 Hz).

Acknowledgement

The authors are grateful to Drs. Tomoshige Kobayashi and Akira Ohta of the Department of Chemistry at Shinshu University for the elemental analysis and mass spectral data, respectively.

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Article Identifier:
1437-210X,E;1999,0,12,2041,2044,ftx,en;F04399SS.pdf