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Development of the first and practical method for enantioselective synthesis of ^{10}B-enriched *p*-borono-L-phenylalanine

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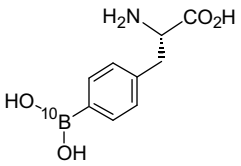
ABSTRACT

At present *p*-(^{10}B)borono-L-phenylalanine (L-^{10}Bpa) is used clinically as an excellent ^{10}B carrier for BNCT; however, its enantioselective synthesis has not been reported yet. The present Letter describes the first and practical method for enantioselective synthesis of ^{10}B-enriched L-Bpa using Z-L-Ser–OMe as the chiral synthon in good total yield and high optical purity.

1. Introduction

Boron neutron capture therapy (BNCT) based on the selective accumulation of ^{10}B compounds in tumor cells and the subsequent irradiation with thermal neutron is highly noted as one of useful techniques for treatment of cancer.[1–3] So far *p*-(^{10}B)boronophenylalanine (^{10}Bpa) (**1**) in which boron atom is enriched with ^{10}B isotope had been developed as an excellent ^{10}B carrier for BNCT (Fig. 1). Since the incorporating amount of L-^{10}Bpa into cancer cells is higher than that of D-^{10}Bpa or DL-^{10}Bpa,[4] L-^{10}Bpa is now being used clinically for the treatment of patients with malignant brain tumor and/or melanoma owing to the selective accumulation and low toxicity.[5] At present, commercially available L-^{10}Bpa is prepared by the enzymatic resolution of the racemic precursor.[6]



L-^{10}Bpa (**1**)

Figure 1. The structure of L-^{10}Bpa (**1**).

2. Results and discussion

To date, three synthetic approaches of L-Bpa with naturally occurring boron atom[7] utilizing the enantioselective method have been known. For example, Kirihata and co-workers reported the enantioselective synthesis of L-Bpa based on the coupling reaction of 4-boronobenzylbromide with the chiral derivative prepared from L-valine.[8] However, this method needs further enzymatic resolution to obtain optically pure L-Bpa, since the enantioselectivity of the coupling reaction is slightly low. Furthermore, Yamamoto and co-workers reported the method based on palladium catalyzed coupling reaction of pinacolborane with 4-iodo-L-phenylalanine derivatives.[9] This method is also not suitable for the synthesis of L-^{10}Bpa, because ^{10}B-enriched pinacolborane is not commercially available and its synthetic method is not reported as well. In another case, Malan and Morin reported an interesting method utilizing the Negishi coupling reaction of iodophenylborate and L-iodoalanine derivatives.[10] However, this method is also unsuitable for the synthesis of L-^{10}Bpa, because both ^{10}B-enriched BI_3 and 1,3-diphenylpropane-1,3-diol used as the protecting group of boron are not commercially available. Consequently, all these methods are not applicable to the synthesis of ^{10}B-enriched L-Bpa.

Therefore, we examined a development of efficient method for enantioselective synthesis of L-^{10}Bpa utilizing the Negishi reaction based on the coupling of 4-(^{10}B)borono-iodobenzene derivative with 3-iodo-L-alanine [L-Ala(3I)] derivative. The most important advantage of the present method is that ^{10}B(OMe)$_3$ as ^{10}B source to prepare 4-(^{10}B)boronoiodobenzene is commercially available. Further L-Ala(3I) can be readily prepared from L-serine. Thus, the synthesis of L-^{10}Bpa was carried out as shown in Schemes 1 and 2.

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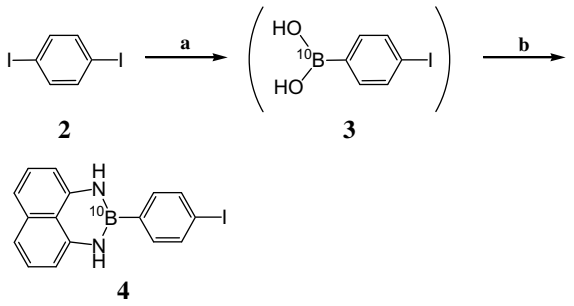


Scheme 1. Reagents and conditions: (a) (i) *n*-BuLi (1.00 equiv), THF, −78 °C, 30 min; (ii) $^{10}B(OMe)_3$, −78 °C, 5 h; (b) 1,8-diaminonaphtalene, THF, rt, 12 h, 57.7% (2 steps from **2**).

First, 1,4-diiodobenzene (**2**) was allowed to react with $^{10}B(OMe)_3$ to give 4-(^{10}B)boronoiodobenzene (**3**). The borono group of **3** was then protected with 1,8-diaminonaphtalene that was developed as a masking agent in the Suzuki–Miyaura cross coupling reaction by Suginome and co-workers[11] to give 4-[2,3-dihydro-1*h*-naphtho[1,8-*de*]-1,3-diaza-2-(^{10}B)borinyl]iodobenzene (**4**) (Scheme 1).

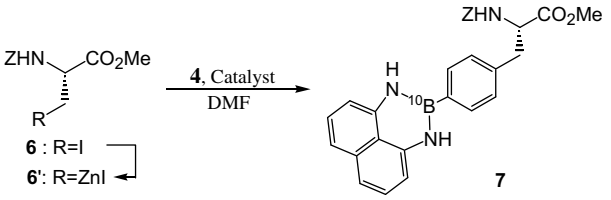
Next, Z-L-Ala(3I)–OMe (**6**)[12] was prepared from Z-L-Ser–OMe (**5**)[13] (Scheme 2), and the compound **6** was coupled with the aryliodide **4** via Zn adduct **6′** by employing the Negishi coupling reaction to give N^{α}-benzyloxycarbonyl-*p*-[2,3-dihydro-1*H*-naphtho[1,8-*de*]-1,3-diaza-2-(^{10}B)borin-yl]-L-phenylalanine methyl ester (**7**). To find the optimal conditions for the Negishi coupling, we examined the relationship between the yields and the catalysts on various reaction conditions as shown in Table 1. The reaction scarcely proceeded in the presence of $Pd(PPh_3)_2Cl_2$ (entries 1 and 2) as a catalyst. When the reaction was carried out at 70 °C with $Pd(PPh_3)_4$ catalyst, L-^{10}Bpa derivative **7** was produced in a 42.7% yield (entry 4), although the reaction did not proceed at room temperature (entry 3). As a result, the reaction proceeded favorably at rt by the use of $Pd_2(dba)_3$ and P(*o*-tolyl)$_3$ as catalysts,[14] although the yield was slightly decreased when the reaction was carried out at 70 °C (entries 5 and 6).

The diaminonaphthyl group of compound **7** was cleaved with 2 M H_2SO_4 in advance to give Z-L-^{10}Bpa–OMe (**8**). The benzyloxycarbonyl and methyl groups were simultaneously removed by acid hydrolysis with 3 M HCl to give L-^{10}Bpa (**1**) (Scheme 2). HPLC analysis of **1** thus obtained with a chiral column revealed the optical purity to be >99% (Fig. 2).

As mentioned above, we have succeeded to develop the first method for the enantioselective synthesis of L-^{10}Bpa (**1**) from Z-L-Ser–OMe (**5**) used as the chiral synthon in 51.0% overall yield. This method is shorter in the reaction step and higher in the overall yield compared to the conventional methods for the synthesis of L-Bpa.[15]

The syntheses of the chiral fluorinated ^{10}Bpa derivatives such as β-[4-(^{10}B)borono-2-trifluoromethylphenyl]alanine and β-[4-(^{10}B)borono-2,6-difluorophenyl]alanine[16–18] using the present method are currently being undertaken, and the results will be reported soon elsewhere.

Table 1
Yields of the Negishi coupling on various reaction conditions



Entry	Catalyst	Conditions	Yield (%)
1	$Pd(PPh_3)_2Cl_2$ (0.06 equiv)	rt, 24 h	Trace
2	$Pd(PPh_3)_2Cl_2$ (0.06 equiv)	70 °C, 12 h	6.88
3	$Pd(PPh_3)_4$ (0.06 equiv)	rt, 24 h	Trace
4	$Pd(PPh_3)_4$ (0.06 equiv)	70 °C, 3 h	42.7
5	$Pd_2(dba)_3$ (0.03 equiv) P(*o*-tolyl)$_3$ (0.10 equiv)	rt, 12 h	78.4
6	$Pd_2(dba)_3$ (0.06 equiv) P(*o*-tolyl)$_3$ (0.10 equiv)	70 °C, 3 h	72.7

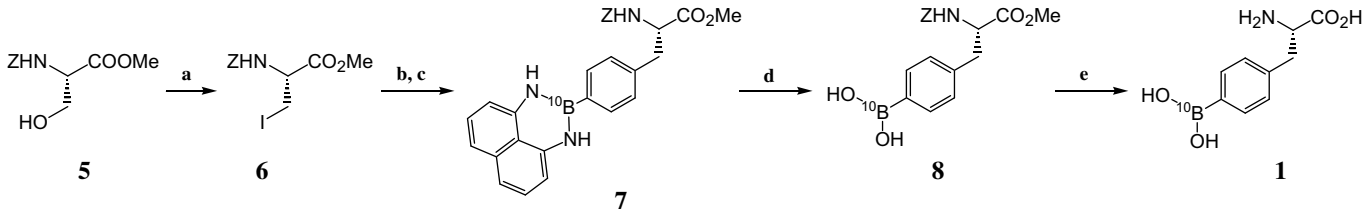
3. Experimental

3.1. General

All of the melting points are uncorrected and were measured by Yanaco MP-J3 (Yanaco Co., Ltd, Kyoto, Japan). Silica-gel column chromatography was carried out with silica gel PSQ100B (Fuji Silysia Chemical Ltd, Aichi, Japan). ^{1}H NMR spectra were measured on a Varian Mercury 300 (300 MHz, Varian Co., Ltd, USA) spectrometer. The chemical shifts in ^{1}H NMR are given in δ values from TMS used as the internal standard. HPLC analysis was performed on a LaChrom Elite (Hitachi high-Technologies Corporation, Tokyo, Japan) instrument equipped with a CROWNPAK AK CR(+) (5 μm, 0.5 × 15 cm) (Daicel Chemical Industries, Ltd, Osaka, Japan) with a flow rate of 0.8 mL/min and detection at 230 nm. Elemental analyses were performed at the Micro Corder JM10 (J-Science Lab. Co. Ltd, Kyoto, Japan). Optical rotations were measured on a Jasco DIP-140 polarimeter (JASCO Co., Tokyo, Japan). $^{10}B(OMe)_3$ was purchased from Stella Chemifa Co. (Osaka, Japan). 1,2-Dibromoethane and *n*BuLi were purchased from Nacalai Tesque Inc. (Kyoto, Japan). 1,8-Diaminonaphtalene, TMS-Cl, and propylene oxide were purchased from Wako Pure Chemical Industries, Ltd (Osaka, Japan), 1,4-diiodo-benzene, tris(dibenzylideneacetone)dipalladium [$Pd_2(dba)_3$] and tri(*o*-tolyl)phosphine [P(*o*-tolyl)$_3$] were purchased from Sigma–Aldrich Co. (USA).

3.2. 4-[2,3-Dihydro-1*H*-naphtho[1,8-*de*]-1,3-diaza-2-(^{10}B)-borinyl]iodobenzene (4)

To a solution of 1,4-diiodo-benzene (**2**) (10.0 g, 30.3 mmol) in THF (100 mL) was added *n*-BuLi (1.6 M solution in hexane,



Scheme 2. Reagents and conditions: (a) I_2, imidazole, PPh_3, CH_2Cl_2, rt, 5 h, 82.7%; (b) activated Zn, DMF, 35 °C, 1.5 h; (c) compound **4**, $Pd_2(dba)_3$, P(*o*-tolyl)$_3$, DMF, rt, 12 h, 78.4% (2 steps); (d) 2 M H_2SO_4, THF, rt, 2 h, 94.6%; (e) (i) 3 M HCl, 80 °C, 17 h; (ii) propylene oxide, *i*PrOH, rt, 14 h, 83.1%.

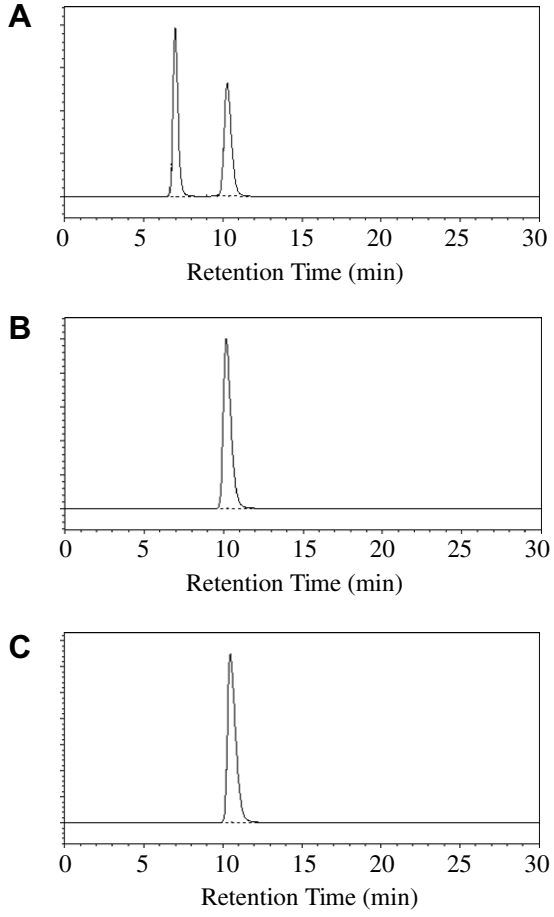


Figure 2. HPLC analysis of ^{10}Bpa with a chiral column; (A) authentic sample of DL-^{10}Bpa, (B) authentic sample of L-^{10}Bpa, (C) synthetic L-^{10}Bpa. Analytical conditions-column: CROWNPAK AK CR(+); eluate: 0.4% aqueous $HClO_4$; flow rate: 0.8 mL/min; detection: UV 230 nm.

18.9 mL, 30.3 mmol) dropwise under cooling at −78 °C, and the solution was stirred for 30 min at −78 °C. To the reaction mixture was added $^{10}B(OMe)_3$ (3.75 g, 36.4 mmol) dropwise under cooling at −78 °C, and the solution was stirred for 5 h at −78 °C. To the reaction mixture was added saturated aqueous NH_4Cl (100 mL), and the solution was extracted with Et_2O (100 mL × 3). The combined extracts were washed with H_2O (100 mL × 3) and brine (100 mL × 3), and dried over anhydrous $MgSO_4$. The dried extract was concentrated in vacuo, and the residue was dissolved in THF. To the solution was added 1,8-diaminonaphtalene (4.79 g, 30.3 mmol), and the mixture was stirred for 12 h. The reaction mixture was concentrated in vacuo, and the residue was purified by silica-gel column chromatography (silica gel: 200 g, hexane/AcOEt = 9:1) to give **4** as brown crystals (7.04 g, 57.7%): mp 171–172 °C. ^{1}H NMR ($CDCl_3$) δ 5.98 (s, 2H), 6.41 (dd, J = 7.5 Hz, 1.2 Hz, 2H), 7.05–7.17 (m, 4H), 7.37 (dd, J = 6.6 Hz, 1.8 Hz, 2H), 7.87 (dd, J = 6.6 Hz, 1.8 Hz, 2H). Anal. Calcd for $C_{16}H_{12}{}^{10}BIN_2$: C, 52.05; H, 3.28; N, 7.59. Found: C, 52.00; H, 3.60; N, 7.46.

3.3. N^{α}-Benzyloxycarbonyl-3-iodo-L-alanine methyl ester (6)

To a solution of I_2 (62.9 g, 248 mmol) and imidazole (16.9 g, 248 mmol) in CH_2Cl_2 (300 mL) was added PPh_3 (65.0 g, 248 mmol) portionwise, and the solution was stirred for 30 min at 0 °C. After stirring for 1 h at room temperature, to the reaction mixture was added the solution of **5** (31.5 g, 124 mmol) in CH_2Cl_2 (300 mL) dropwise, and the mixture was stirred for 5 h. The reaction mixture was filtrated through the Celite, and the filtrate was washed with H_2O (300 mL × 3) and brine (300 mL × 3). The organic layer was dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified by silica-gel column chromatography (silica gel: 400 g, hexane and then hexane/AcOEt = 9:1) to give **6** as colorless amorphous solid (37.2 g, 82.7%): mp 69–71 °C. $[\alpha]_D^{22}$ − 6.1 (c 1.0, $CHCl_3$). ^{1}H NMR (CD_3Cl) δ 3.50 (d, J = 3.6 Hz, 2 h), 3.81 (s, 3H), 4.57–4.62 (m, 1H), 5.13 (s, 2H), 5.66 (d, J = 7.5 Hz, 1H), 7.28 (s, 5H). Anal. Calcd for $C_{12}H_{14}INO_4$: C, 39.69; H, 3.89; N, 3.86. Found: C, 39.92; H, 4.20; N, 3.86.

3.4. N^{α}-Benzyloxycarbonyl-*p*-[2,3-dihydro-1*H*-naphtho[1,8-*de*]-1,3-diaza-2-(^{10}B)borinyl]-L-phenylalanine methyl ester (7)

A solution of 1,2-dibromoethane (310 μL, 3.60 mmol) in DMF (5 mL) was added to zinc dust (4.71 g, 72.0 mmol) under Ar atmosphere, and the suspension was stirred for 30 min at 90 °C. To the suspension was added TMS-Cl (129 μL, 3.60 mmol) at room temperature, and the mixture was stirred for 30 min. A solution of **6** (4.38 g, 12.0 mmol) in DMF (10 mL) was added to the reaction mixture, and the mixture was stirred for 1.5 h at 35 °C. To the reaction mixture were added **4** (4.01 g, 10.0 mmol), $Pd_2(dba)_3$ (274 mg, 0.30 mmol); and P(*o*-tolyl)$_3$ (304 mg, 1.00 mmol), and the mixture was stirred for 12 h at room temperature. The reaction mixture was filtered to remove the excess zinc dust, and the filtrate was diluted with AcOEt (100 mL). The solution was washed with H_2O (40 mL × 3) and brine (40 mL × 3), and dried over $MgSO_4$. The dried extract was concentrated in vacuo, and the residue was purified by silica-gel column chromatography (150 g, benzene and then benzene:acetone = 9:1) to give **7** as colorless crystals (4.00 g, 78.4%): mp 115–117 °C. $[\alpha]_D^{22}$ −0.3 (c 1, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.16 (ddd, J = 26.1 Hz, 14.4 Hz, 6.0 Hz, 2H), 3.75 (s, 3H), 4.62 (dd, J = 14.4 Hz, 6.0 Hz, 1H), 5.11 (s, 2H), 5.28 (d, J = 8.1 Hz, 1H), 6.00 (s, 2H), 6.41 (dd, J = 7.2 Hz, 1.2 Hz, 2H), 7.04–7.17 (m, 6H), 7.32–7.37 (m, 5H), 7.52 (d, J = 7.8 Hz, 2H). Anal. Calcd for $C_{28}H_{26}{}^{10}BN_3O_4{\cdot}0.5CH_3COCH_3$: C, 69.81; H, 5.76; N, 8.28. Found: C, 69.54; H, 5.99; N, 8.47.

3.5. N^{α}-Benzyloxycarbonyl-*p*-(^{10}B)borono-L-phenylalanine methyl ester (8)

To a solution of **7** (3.18 g, 6.23 mmol) in THF (75 mL) was added 2M H_2SO_4 (75 mL), and stirred for 2 h at room temperature. The reaction mixture was filtered, and the filtrate was extracted with AcOEt (50 mL × 3). The combined extracts were washed with 2M H_2SO_4 (50 mL × 3), saturated aqueous $NaHCO_3$ (50 mL × 3) and brine (50 mL × 3). The organic layer was dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified by silica-gel column chromatography (100 g, CH_2Cl_2:MeOH = 19:1) to give **8** as colorless crystals. (2.10 g, 94.6%): mp 190–192 °C. $[\alpha]_D^{22}$ − 12.1 (c1.00, MeOH). ^{1}H NMR (300 MHz, CD_3COCD_3) δ 3.00 (dd, J = 13.5 Hz, 9.0 Hz, 1H), 3.17 (dd, J = 13.5 Hz, 5.4 Hz, 1H), 3.67 (s, 3H), 4.49 (dd, J = 9.0 Hz, 5.4 Hz, 1H), 5.01 (s, 2H), 6.65 (d, J = 9.0 Hz, 1H), 7.14 (s, 2H), 7.24–7.37 (m, 7H), 7.04–7.17 (m, 4H), 7.80 (d, J = 7.8 Hz, 2H). Anal. Calcd for $C_{18}H_{20}{}^{10}BNO_6$: C, 60.67; H, 5.66; N, 3.93. Found: C, 60.26; H, 6.03; N, 3.97.

3.6. *p*-(^{10}B)Borono-L-phenylalanine (1)

A suspension of **8** (1.90 g, 5.33 mmol) in 3 M HCl (200 mL) was stirred for 17 h at 80 °C. The reaction mixture was washed with Et_2O (70 mL × 3), and concentrated in vacuo. The residue was dissolved in *i*PrOH (50 mL), and to the solution was added propylene oxide (621 mg, 10.7 mmol). After stirring for 14 h, the reaction mixture was concentrated in vacuo. The crystalline residue was

recrystallized from water to give **1** as colorless crystals (922 mg, 83.1%): mp 285–298 °C (decomp.). $[\alpha]_D^{25}$ −5.2(c0.50, 1M HCl). ^{1}H NMR (300 MHz, D_2O) δ 2.97 (ddd, J = 18.2 Hz, 14.4 Hz, 5.4 Hz, 2H), 3.80 (dd, J = 14.4 Hz, 5.4 Hz, 1H), 7.15 (d, J = 7.8 Hz, 2H), 7.55 (d, J = 7.8 Hz, 2H). Anal. Calcd for $C_9H_{12}{}^{10}BNO_4{\cdot}0.5H_2O$: C, 49.76; H, 6.03; N, 6.45. Found: C, 49.90; H, 6.27; N, 6.23.

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