Notes

A Concise Preparation of 4-Borono-L-phenylalanine (L-BPA) from L-Phenylalanine

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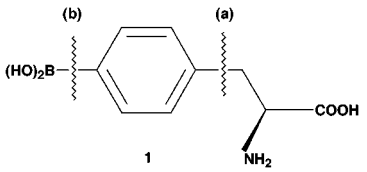
4-Boronophenylalanine, a tyrosine analogue in which the hydroxyl group is replaced by a dihydroboryl group, was the first member to be described[1] of the increasingly important family of boronated analogues of biomolecules.[2] The L enantiomer (L-BPA, **1**) has been shown to accumulate preferentially in melanomic cells,[3−5] which has led to its use in the treatment of malignant melanoma[3] through Boron Neutron Capture Therapy.[6,7] Until recently, **1** was prepared by resolution,[8] the racemic material being prepared in four steps from *p*-bromotoluene.[1] Two enantioselective syntheses of **1** based on asymmetric hydrogenation of a dehydroamino acid derivative have



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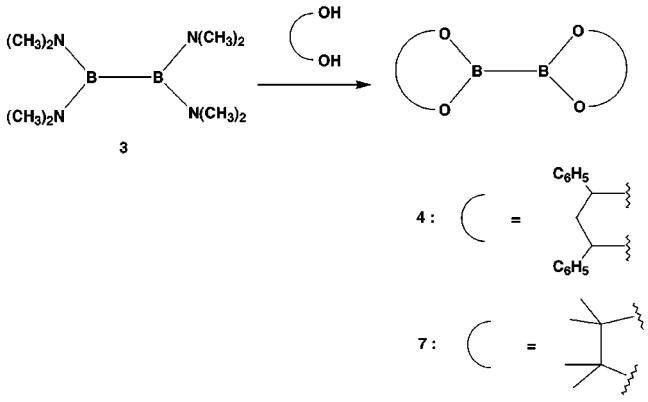
then appeared[9,10] as well as a synthesis which has taken advantage of the chiral pool.[11] In the latter, coupling of an (unstable) L-serine-derived organozinc with a boronated aromatic partner was used as the key reaction (disconnection a). We felt, however, that introduction of a boronic acid moiety in a phenylalanine derivative (disconnection b) would yield a conceptually simple and potentially more straightforward approach to **1**. We now report on such a conversion, which is based on the cross coupling of pinacoldiboronates with aromatic derivatives,[12,13] as well as on the availability of 4-iodo L-phenylalanine **2** which can be prepared[14] by electrophilic iodination of L-phenylalanine.

Tetrakis(dimethylamino)diboron (**3**)[15,16] reacted with *dl*-1,3-diphenyl-1,3-propanediol[17] to give diboronate **4** (72%), in which the boronates are protected by reducible groups.[18] Reaction of **4** with the iodophenylalanine derivatives **5** or **6**, under the conditions developed for such palladium(0)-catalyzed couplings,[12] provided the desired products, however, in low conversion. As large amounts of 1,3-diphenyl-1,3-propanediol were also isolated, the use of a more base-stable boronic acid protecting group seemed indicated and led us to consider Miyaura's reagent (bis-pinacolato diboronate, **7**).[19] In the presence



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4 :

7 :

of **7**, **6** gave the desired coupling product **8**, which could be isolated in 88% yield. However, protection of the carboxylic acid of the phenylalanine partner was not necessary, provided an extra equivalent of base was used, and thus the reaction could be performed *directly* with **5**. Although the isolated yield of the coupled product **9** is somewhat reduced (65%), the synthesis is shortened. Simultaneous deprotection of both the amine and boronic

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(19) Bis(pinacolato)diboron is commercially available from Lancaster.

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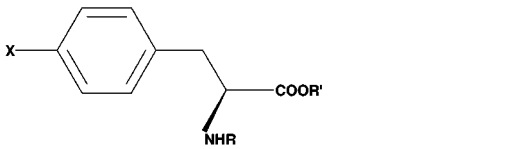
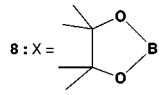
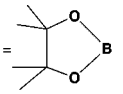
acid protecting groups of **9** could then be effected with boron tribromide (79%) to give pure **1**. Subsequently, it was found that deprotection could be carried out on the unpurified intermediate **9**, as L-BPA can be easily crystallyzed from the crude reaction mixture at its isoelectronic point (pH = 6.2).The overall yield of **1**, identical with an independently prepared sample,[11] from **5** is then 53%.



1 : X = $(HO)_2B$, R=R'=H
2 : X = I, R=R'=H
5 : X = I, R=Boc, R'=H
6 : X = I, R= Boc, R'= $CH_2C_6H_5$

8 : X =  , R= Boc, R'= $CH_2C_6H_5$

9 : X =  , R= Boc, R'= H

Thus, a practical, four-step synthesis of L-BPA (>97% ee)[20] has been developed from L-phenylalanine that proceeds in 22% overall yield and requires no chromatographic purification. The overall transformation consists of a facile replacement of the *para*-hydrogen of L-Phe by a dihydroxyboryl group and should be open to extrapolation for the preparation of other 4-substituted L-phenylalanine derivatives through Suzuki-type couplings, as noted before[11] and recently achieved.[21]

Experimental Section

General Methods. Dry DMSO was stored under Ar on 4 Å molecular sieves, and benzene was distilled over Na before use. After workup, the volatiles were evaporated under reduced pressure without heating. Standard abrevations are used for NMR description of spectra which were recorded on Brucker apparatus at the field indicated; the residual absorption of the NMR solvent ($CDCl_3$) was taken as the internal reference except for ^{11}B NMR spectra for which BF_3/Et_2O was used as an external reference.

Bis(pinacolato)diboron (7). Under argon, to a stirred solution of tetrakis(dimethylamino)diboron **3** (3.45 g, 17.43 mmol) in dry benzene (40 mL) was added via syringe in 30 min a solution of 2,3-dimethylbutane-2,3-diol (4.12 g, 34.86 mmol, 2 equiv) in dry benzene (45 mL). After stirring for 1 h, a solution of hydrogen chloride in diethyl ether (35 mL of a 1 M solution, 35 mmol) was added dropwise via syringe in 30 min and the mixture stirred for 20 h. The white precipitate was filtered off and rinsed with dry benzene (3 × 5 mL); the filtrate was evaporated under reduced pressure, and the residue was taken up in *n*-pentane (150 mL) and filtered and the cake washed several times with dry *n*-pentane. The filtrate was washed with water (3 × 40 mL), dried (sodium sulfate), and evaporated to dryness; the pentane extraction and washing procedure was repeated three times to then give pure **7** (4.06 g − 92%), mp 138 °C (lit.[22] 138 °C), whose spectroscopic properties matched those of ref 22 and were identical with an authentic sample kindly provided by N. Miyaura.

N-(*tert*-Butyloxycarbonyl)-4-iodo-L-phenylalanine (5). To a stirred suspension of 4-iodo-L-phenylalanine **2** (2.44 g, 8.38 mmol) in 1 M aqueous sodium hydroxide (9.25 mL) was added *tert*-butyl alcohol (6.5 mL). Melted (30 °C) di-*tert*-butyl dicarbonate (2 mL, 8.71 mmol) was then added dropwise in 3 min, and the mixture was stirred for 15 h. Water (10 mL) was then added to the clear solution, which was followed by extraction with *n*-pentane. The organic layer was washed with saturated aqueous sodium hydrogenocarbonate, the combined aqueous layers were cooled at 4 °C, and the pH was adjusted to ca. 1.5 with a 1 M aqueous potassium hydrogenosulfate solution and extracted 4 × 10 mL) with diethyl ether. The organic layers were pooled, dried (sodium sulfate), and evaporated. The clear oil was then taken up in *n*-hexane to afford white crystals of **5** (2.77 g, 84%): mp 85−6 °C (*n*-hexane), lit.[23] 120−121 °C. $[\alpha]^{22}_D$ = +21.2 (*c* 1.2, AcOEt). lit.[23] $[\alpha]^{22}_D$ = +21.3 (*c* 1.2, AcOEt). ^{1}H NMR (200 MHz) δ 1.2 (s 9 H), 2.7 (m, 1 H), 2.85 (m, 1 H), 4.15 (m, 1 H), 5.2 (d, J = 7.5 Hz), 6.75 and 7.3 (2 × 2H, AA′XX′ system, J_{app} = 8 Hz). ^{13}C NMR (50 MHz) δ 27.8, 36.0, 55.4, 78.3, 92.2, 130.0, 132.1, 155.2, 168.1.

4-Borono-L-phenylalanine (1). Under argon a solution of **7** (610 mg, 2.4 mmol), 1,1′-bis(diphenylphosphino)ferrocene dichloropalladium (complex with dichloromethane) (52 mg, 0.064 mmol), potassium acetate (825 mg, 8.41 mmol), and *N*-*tert*-Boc-4-iodo-L-Phe **5** (820 mg, 2.1 mmol) in dry dimethyl sulfoxide (25 mL) was stirred at 80 °C for 24 h. After cooling to room temperature, it was diluted with ethyl acetate (150 mL) and washed with 1 M aqueous hydrochloric acid and then water (3 × 20 mL). The aqueous layers were extracted with ethyl acetate (3 × 20 mL), and the combined organic layers were dried (sodium sulfate). For analytical purposes a sample of ***N*-(*tert*-butyloxycarbonyl)-4-pinacolatoborono-L-phenylalanine** could be obtained at this stage by column chromatography on silica gel (CH_2Cl_2/CH_3OH 97.5/2.5). **9**: oil: $[\alpha]^{22}_D$ = +22.5 (*c* 1.4, CH_2Cl_2); IR (NaCl) 3434, 3334, 2971, 1710, 1610,1391, 1354 cm $^{-1}$; ^{1}H NMR (200 MHz) δ 1.2 (s, 9 H), 1.3 (s 12 H), 3.1 (m, 2 H), 4.55 (m, 1 H), 5.1 (d, J = 7.5 Hz, 1 H), 7.1 and 7.7 (2 × 2H, AA′XX′ system, J_{app} = 8 Hz). ^{13}C NMR (50 MHz) δ 24.7, 28.2, 37.8, 53.3, 80.0, 83.7, 128.4, 134.9, 139.3, 155.3, 176.0. ^{11}B NMR (96.3 MHz) 31.5 (large s); MS (EI) *m*/*z* 346 (1): $(M - COOH)^+$, 274 (24): $(M - NHBoc - H)^+$, 217 (100): $(M - CH(COOH)NHBoc)^+$. Anal. Calcd for $C_{20}H_{30}BNO_6$: C 61.40, H 7.73. Found: C 61.78, H 7.89. The preceding crude oil, obtained after evaporation of the volatiles, was dissolved in dry dichloromethane (12 mL) and stirred at −78 °C under argon. Boron tribromide (3.4 mL, 36 mmol) was then added in 2−3 min, and the green reaction mixture was stirred at −78 °C for 2 h before removing the cooling bath; stirring was continued for 20 h before setting again at −78 °C. Methanol (8 mL) was then added dropwise (CAUTION), and after warming to room temperature the mixture was filtered on Celite; the cake was rinsed with methanol (5 × 2 mL) and water (2 mL) added to the filtrate which was then concentrated to ca. 2 mL. The pH was set to 6.2 with 4 M aqueous potassium carbonate, and **1** (233 mg, 53%) crystallized on standing at 4 °C: mp 285−290 °C, lit.[11] 285−290 °C, $[\alpha]^{23}_D$ = −8.0° (*c* = 1.2; 0.1 M HCl), lit.[8] $[\alpha]^{23}_D$ = −8.2° (*c* = 0.7; 0.1 N HCl); the spectral data were identical to those of a sample prepared according to ref 11.

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(20) This value was obtained by comparison of the observed optical rotation with the literature (see Experimental Section).

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