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A simple convenient preparation of ω-aminoboronic acids and esters

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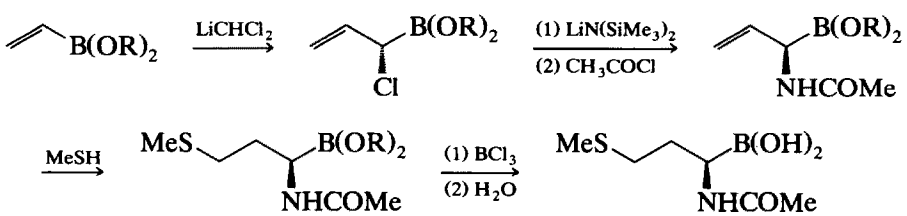
Abstract

The catalytic hydrogenation of ω-azidoboronic esters and, for pinacol derivatives, the reductive alkylation with a dichloroborane, afford with good yields the corresponding ω-aminoboronic acids or esters.

Introduction

Boron analogues of carboxylic aminoacids and peptides have been shown to possess interesting biological activities, in particular as serine protease inhibitors [1]. Hitherto, two principal methods have been used for their preparation.

(1) The conversion of α-chloroboronic esters obtained via an homologation reaction to α-amino derivatives was first described by D.S. Matteson and Cheng [2]. This procedure was successfully used for the preparation of the boronic acid analogue of *N*-acetyl L-methionine **1** [3]:



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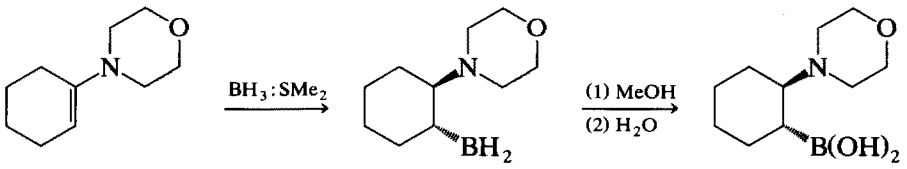
(2) The hydroboration of enamines [4], allylic amines and their *N*-protected derivatives [5] led, after hydrolysis, to β- or γ-aminoboronic acids **2** or **3**:



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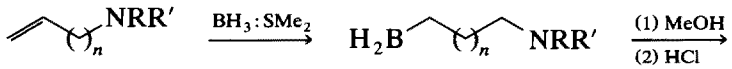
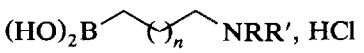


4 **5**



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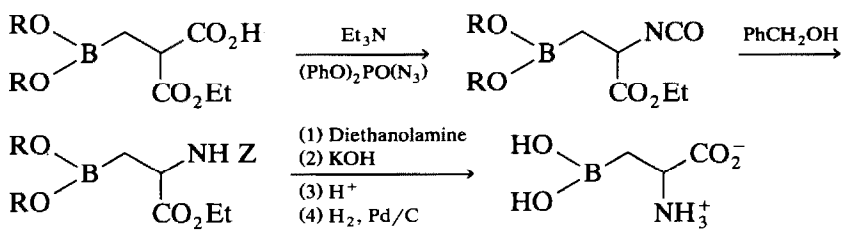
$n = 1$ R or R′ = H, alkyl, Me_3Si, or $PO(OEt)_2$

To our knowledge, the hydroboration of ω-aminoalkenes **4** with $n > 1$ has been observed only for R, R′ = alkyl. The corresponding boranes were mostly oxidized to alcohols [6]. For unsymmetrically substituted olefins, mixtures of regioisomers are usually obtained. In a very few special cases, ω-aminoboronic acids have been isolated as their hydrochlorides.

Among other miscellaneous methods [7], is the recent, noteworthy, synthesis of a boron-containing analogue of aspartic acid. It is, to the best of our knowledge, the only instance where the aminogroup has been introduced *via* a modified Curtius rearrangement [8]:



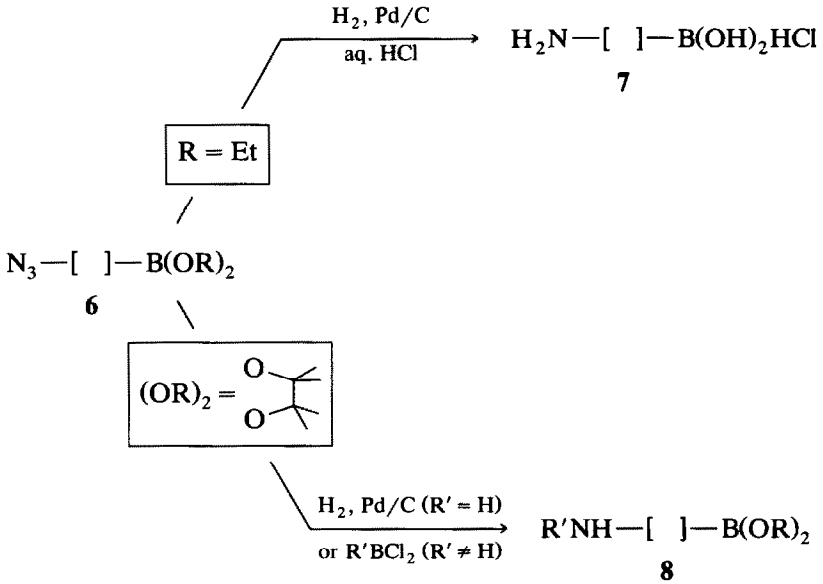
Z = $PhCH_2OCO$

Table 1

Synthesis of ω-aminoboronic acid hydrochlorides **7**

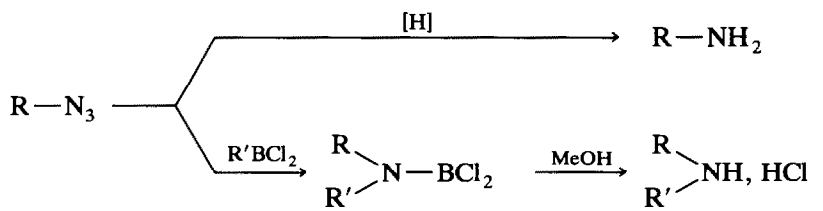
Compound	R^1	R^2	R^3	n	Yield (%)	δ ^{11}B
7a	H	H	H	0	88	32.6
7b	H	H	H	1	93	32.9
7c	H	Me	H	1	87	32.7
7d	H	H	Me	2	89	33.0
7e	H	H	H	2	90	33.2
7f	H	H	H	3	94	32.8

We here report the facile and direct synthesis of ω-aminoboronic acids **7** and esters **8** from the corresponding azides **6**:



Results and discussion

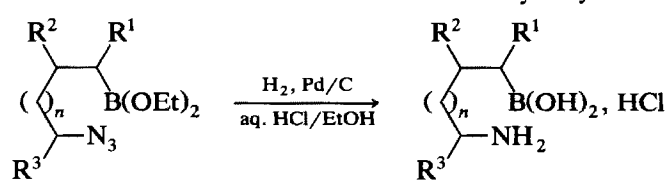
Azides are valuable precursors of primary [9] and secondary amines [10]:



We have previously developed a convenient method for the synthesis of pyrrolidines and piperidines via intramolecular cyclisation of ω-azidoboronic esters **6** [11]. We now investigate another aspect of the reactivity of these compounds, their conversion to ω-aminoboronic acids or esters.

Reduction of boronic esters 6 (R = Et)

Catalytic hydrogenation of **6** (R = Et) in the presence of aqueous HCl gave in good yields ω-aminoboronic acid hydrochlorides **7** (Table 1). The reduction of the azido function occurred with concomitant hydrolysis of the boronic ester:

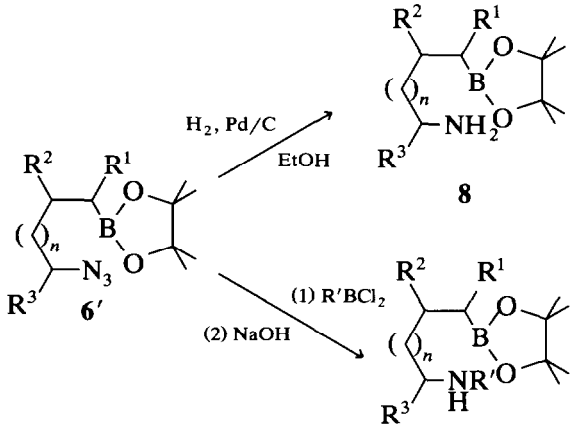


6 **7**

All compounds were characterized by ^{1}H, ^{13}C, and ^{11}B NMR spectra. The ^{11}B chemical shifts ($\delta = 32.6$–33.2 ppm) are consistent with those usually observed for boronic acids [12].

Reduction and alkylation of boronic esters 6′ with $(OR)_2 =$ 

Pinacol boronate esters are stable in aqueous acid. Therefore, it is possible to reduce or to alkylate the azides **6** derived from pinacol without regenerating the corresponding boronic acids. By catalytic hydrogenation in ethanol, or reductive alkylation with a dichloroborane followed by a basic treatment [10], we easily prepared a variety of ω-aminoboronic esters **8** (Table 2):



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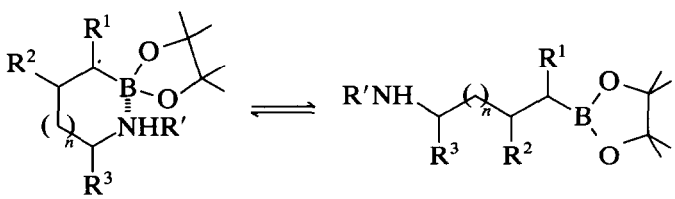
The structural assignments to compounds **8** are consistent with ^{1}H, ^{13}C, ^{11}B NMR spectra, mass spectra, and elementary analysis. **8a**, **8b**, **8d**, **8e** ($n = 0$ or 1) show unusually low chemical shifts for boronic esters (11.4 to 27.5 ppm). ^{11}B Chemical shifts are very sensitive to the coordination around the boron atom [12]. A rapid equilibrium between species containing a tri- and a tetra-coordinate boron atom **8A** and **8B** [13] is possible:



8A **8B**

This intramolecular chelation is highly dependent on the chain length and the nature of the substituents and is not observed when $n > 1$ or $R^1 \neq H$. The boron chemical shifts then lie in the range 32.3–34.0 ppm. For none of the compounds **8**, is more than one set of signals observed in the ^{1}H, ^{13}C and ^{11}B NMR spectra.

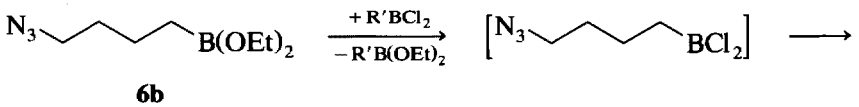
Two further results are worthy of note. First, the reductive alkylation of an ω-azidoboronate with a dichloroborane, and therefore access to *N*-alkylated compounds, can be achieved only with derivatives of pinacol esters. A redistribution

Table 2

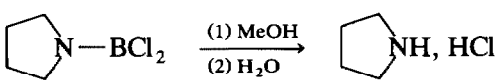
Synthesis of ω-aminoboronic esters **8**

Compound	n	R^1	R^2	R^3	R′	Yield (%)	δ ^{11}B (ppm)
8a	0	H	H	H	H	88	27.5
8b	1	H	H	H	H	93	19.1
8c	1	iPr	H	H	H	84	32.3
8d	1	H	Me	H	H	85	11.4
8e	1	H	Me	H	Hex	72	18.4
8f	2	H	H	H	H	92	33.8
8g	2	H	H	H	Ph	70	33.8
8h	2	H	H	H	Hex	69	33.8
8i	3	H	H	H	H	94	34.0

reaction followed by an intramolecular cyclization occurred with ethyl esters and, for example, the pyrrolidine **9** is the main product of treatment of **6b** with $PhBCl_2$ [11]:



6b



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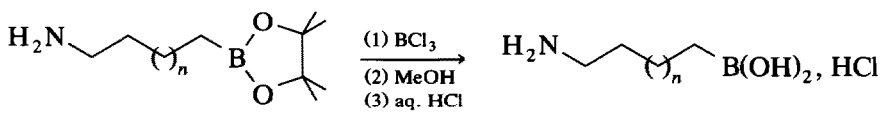
Secondly, it is possible to regenerate the boronic acid from the pinacol ester in good yield. For example, **7a** and **7b** are obtained from the boronates **6′a** and **6′b** by treatment with boron trichloride in methylene chloride [3]:



6′a $n = 0$ — **7a** yield 83%

6′b $n = 1$ — **7b** yield 75%

Thus, ω-azidoboronic esters **6** and **6′** are valuable precursors of the corresponding ω-aminoboronic acids. Ethyl esters are usually the best candidates for this purpose, but for particular structures pinacol esters can be used as temporary boronic acid protective groups.

Experimental

^1H, ^{13}C and ^{11}B NMR spectra were recorded on a Bruker AM 300 spectrometer (75.5 MHz for carbon, 96.3 MHz for boron). Chemical shifts are reported in δ (ppm) and coupling constants are given in hertz. Mass spectra were measured at 70 eV on a Varian MAT 311 spectrometer (Centre Régional de Mesures Physiques de l'Ouest). Elemental analyses were carried out in the Laboratoire Central d'Analyses du CNRS, Lyons. Melting points are uncorrected. The ω-azidoboronic esters **6** were prepared according to a published procedure [11].

Catalytic hydrogenation of boronic esters **6**

The procedure for the catalytic hydrogenation of 3-azidopropyl diethylboronate **6a** is representative. A solution of the boronate **6** (3 mmol) in ethanol (10 ml) and 12 *N* HCl (1 ml) was hydrogenated over 10% palladium on charcoal (50 mg) in a Parr apparatus (4 atm of hydrogen) for 18 h at room temperature. The catalyst was separated by filtration and the solvent was removed under reduced pressure. The residue was washed with ether, leaving a white solid.

7a: yield 88%, m.p. 120–125°C. ^{1}H NMR (D_2O): δ 0.75 (t, 2H, $J = 8.0$), 1.67 (m, 2H), 2.90 (t, 2H, $J = 7.4$). ^{13}C NMR (D_2O): δ 14.0, 24.8, 44.7. ^{11}B NMR (D_2O): δ 32.6. Anal. Found: C, 25.7; H, 8.0; N, 10.1. Calc. for $C_3H_{10}BNO_2$, HCl: C, 25.80; H, 7.88; N, 10.03%.

7b: yield 93%, m.p. 135–140°C. ^{1}H NMR (D_2O): δ 0.78 (t, 2H, $J = 7.6$), 1.87 (m, 4H), 2.96 (t, 2H, $J = 7.1$). ^{13}C NMR (D_2O): δ 17.0, 23.4, 32.2, 42.5. ^{11}B NMR (D_2O): δ 32.9. Anal. Found: C, 30.9; H, 8.7; N, 9.4. Calc. for $C_4H_{12}BNO_2$, HCl: C, 31.27; H, 8.47; N, 9.12%.

7c: yield 87%. ^{1}H NMR (D_2O): δ 0.50–1.12 (m, 2H), 0.93 (d, 3H), 1.37–2.03 (m, 3H), 3.05 (t, 2H, $J = 7.4$). ^{13}C NMR (D_2O): δ 24.0, 25.9, 29.4, 39.1, 40.9. ^{11}B NMR (D_2O): δ 32.7.

7d: yield 89%. ^{1}H NMR (D_2O): δ 0.78 (t, 2H, $J = 7$), 1.26 (d, 3H, $J = 5.6$), 1.30–1.48 (m, 4H), 1.50–1.70 (m, 2H), 3.35 (sext, 1H, $J = 6$). ^{13}C NMR (D_2O): δ 16.7, 20.4, 25.9, 36.5, 50.5. ^{11}B NMR (D_2O): δ 33.0.

7e: yield 90%, m.p. 144–146°C. ^{1}H NMR (D_2O): δ 0.75 (t, 2H, $J = 7.0$), 1.05–1.75 (m, 6H), 2.97 (t, 2H, $J = 6.9$). ^{13}C NMR (D_2O): δ 17.0, 25.8, 29.3, 31.1, 42.5. ^{11}B NMR (D_2O): δ 33.2 Anal. Found: C, 36.0; H, 8.9; N, 8.4. Calc. for $C_5H_{14}BNO_2$, HCl: C, 35.82; H, 8.95; N, 8.35%.

7f: yield 94%, m.p. 161–165°C. ^{1}H NMR (D_2O): δ 0.75 (t, 2H, $J = 7.0$), 1.10–1.75 (m, 8H), 2.98 (t, 2H, $J = 7.0$). ^{13}C NMR (D_2O): δ 17.1, 26.2, 28.2, 29.8, 33.8, 42.7. ^{11}B NMR (D_2O): δ 32.8.

Catalytic hydrogenation of boronic esters **6'**

The same procedure was used, except that no hydrochloric acid was added. The spectral properties of these ω-aminoboronates are as follows.

8a: yield 88%, m.p. 106°C. ^{1}H NMR ($CDCl_3$): δ 0.60 (t, 2H, $J = 7.6$), 1.18 (s, 12H), 1.65 (m, 2H), 2.73 (t, 2H, $J = 6.8$), 2.85 (s, 2H). ^{13}C NMR ($CDCl_3$): δ 12.2, 24.9, 26:8, 43.5, 80.9. ^{11}B NMR ($CDCl_3$): δ 27.5. Anal. Found: C, 43.8; H, 5.6; N, 13.4. Calc. for $C_9H_{20}BNO_2$, $C_6H_3N_3O_7$ (picrate) (m.p. 163°C): C, 43.47; H, 5.55; N, 13.52%.

8b: yield 93%, m.p. 92°C. ^{1}H NMR ($CDCl_3$): δ 0.52 (t, 2H, $J = 6.7$), 1.20 (s, 12H), 1.45–1.70 (m, 4H), 2.95 (t, 2H, $J = 6.0$), 3.05 (s, 2H). ^{13}C NMR ($CDCl_3$): δ 15.9, 22.6, 25.5, 31.3, 42.4, 80.7. ^{11}B NMR ($CDCl_3$): δ 21.6. Anal. Found: C, 44.8; H, 5.9; N, 12.9. Calc. for $C_{10}H_{22}BNO_2$, $C_6H_3N_3O_7$ (picrate) (m.p. 149°C): C, 44.85; H, 5.84; N, 13.08%.

8c: yield 92%, b.p. 80–85°C at 0.1 mmHg, m.p. 25°C. ^{1}H NMR ($CDCl_3$): δ 0.72 (m, 1H), 0.84 (d, 3H, $J = 6.7$), 0.86 (d, 3H, $J = 6.7$) 1.18 (s, 12H), 1.32–1.41 (m, 4H), 1.61–1.76 (m, 3H), 2.64 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 21.8, 22.1, 25.0, 25.1, 26.1, 29.4, 32.0, 33.3, 42.5, 82.5. ^{11}B NMR ($CDCl_3$): δ 32.3. HRMS m/z calc. for $C_{13}H_{28}NO_2{}^{11}B$: 241.2213. Found: 241.222.

8d: yield 85%, m.p. 117°C. ^{1}H NMR ($CDCl_3$): δ 0.15 (t, 1H, $J = 12.7$), 0.55 (d, 1H, $J = 13.0$), 0.94 (d, 3H, $J = 6.4$), 1.16 (s, 12H), 1.50–1.85 (m, 2H), 2.85–3.10 (m, 2H), 3.70 (s, 2H). ^{13}C NMR ($CDCl_3$): δ 25.5, 25.7, 25.9, 29.0, 30.1, 35.9, 41.5, 79.4. ^{11}B NMR ($CDCl_3$): δ 11.4. Anal. Found: C, 46.3; H, 6.2; N, 12.5. Calc. for $C_{11}H_{24}BNO_2$, $C_6H_3N_3O_7$ (picrate) (m.p. 144°C): C, 46.15; H, 6.11; N, 12.67%.

8f: yield 92%, m.p. 20°C, b.p. 45–50°C at 0.01 mmHg. ^{1}H NMR ($CDCl_3$): δ 0.78 (t, 2H, $J = 7.5$), 1.25 (s, 12H), 1.25–1.53 (m, 6H), 2.03 (s, 2H), 2.68 (t, 2H, $J = 7.0$). ^{13}C NMR ($CDCl_3$): δ 11.3, 23.8, 24.7, 29.6, 33.1, 41.9, 82.9. ^{11}B NMR ($CDCl_3$): δ 33.8. Anal. Found: C, 46.2; H, 6.1; N, 12.5. Calc. for $C_{11}H_{24}BNO_2$, $C_6H_3N_3O_7$ (picrate) (m.p. 150°C): C, 46.15; H, 6.11; N, 12.67%.

8i: yield 91%, b.p. 90–100°C at 0.05 mmHg. ^{1}H NMR ($CDCl_3$): δ 0.70 (t, 2H, $J = 7.0$), 1.22 (s, 12H), 1.22–1.87 (m, 8H), 2.97 (t, 2H, $J = 7.5$). ^{13}C NMR ($CDCl_3$): δ 11.1, 23.8, 24.8, 26.4, 27.6, 31.7, 40.0, 82.9. ^{11}B NMR ($CDCl_3$): δ 33.8. HRMS m/z calc. for $C_{12}H_{26}NO_2{}^{11}B$: 227.2056. Found: 227.205.

Reductive alkylation of boronic esters 6'

To a solution of the azide **6'** (4 mmol) in 4 ml of CH_2Cl_2 was added dropwise a solution of the dichloroborane (4 mmol) in CH_2Cl_2 (4 ml). Dinitrogen evolution started after a few seconds. The reaction mixture was kept at room temperature for 18 h. The solution was then cooled to 0°C and carefully hydrolysed by slow addition of 1 ml of water. The reaction mixture was made basic by dropwise addition of 3 ml of 1 *N* NaOH. The free amine was extracted with ether. The ether solution was dried over anhydrous K_2CO_3 and the solvent removed under vacuum. The amine **8** was further purified by bulb-to-bulb distillation.

8e: yield 72%, b.p. 80–85°C at 0.001 mmHg, m.p. 69°C. ^{1}H NMR ($CDCl_3$): δ 0.60 (m, 8H), 1.22 (s, 12H), 1.25–1.95 (m, 11H), 2.92 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 14.0, 22.5, 24.5, 24.8, 25.4, 25.6, 26.7, 28.1, 29.3, 31.5, 33.8, 46.5, 80.5. ^{11}B NMR ($CDCl_3$): δ 18.4. HRMS m/z calc. for $C_{17}H_{36}NO_2{}^{11}B$: 297.2838. Found: 297.283.

8g: yield 70%, b.p. 90–95°C at 0.001 mmHg. ^{1}H NMR ($CDCl_3$): δ 0.73 (m, 2H), 1.22 (s, 12H), 1.25–1.75 (m, 6H), 3.08 (t, 2H, $J = 6.9$). ^{13}C NMR ($CDCl_3$): δ 11.4, 23.8, 29.3, 29.8, 44.0, 82.9, 112.8, 117.1, 129.2, 148.6. ^{11}B NMR ($CDCl_3$): δ 33.8. HRMS m/z calc. for $C_{17}H_{28}NO_2{}^{11}B$: 289.2213. Found: 289.221.

8h: yield 69%, b.p. 70–80°C at 0.001 mmHg. ^{1}H NMR ($CDCl_3$): δ 0.68–1.00 (m, 5H), 1.12–1.75 (m, 26H), 2.57 (t, 4H, $J = 7.0$). ^{13}C NMR ($CDCl_3$): δ 11.5, 14.0, 22.6, 23.9, 24.8, 27.1, 29.9, 30.2, 31.9, 50.1, 50.2, 82.9. ^{11}B NMR ($CDCl_3$): δ 33.8. HRMS calc. for $C_{17}H_{36}NO_2{}^{11}B$: 297.2838. Found: 297.286.

Hydrolysis of ω-aminoboronates 8a and 8b

The conversion of the pinacol esters **8a** and **8b** to the corresponding boronic acids was carried out according to a previously described procedure [3]. To a solution of boron trichloride in CH_2Cl_2 (20 ml of a 1 *M* solution) stirred at −78°C was added dropwise 3 mmol of the boronate **8** in 3 ml of CH_2Cl_2. The mixture was allowed to warm to room temperature and was stirred overnight. The solution was then concentrated under vacuum and the residue was treated with 5 ml of methanol. The remainder of trimethyl borate and the excess of methanol was removed by distillation. This procedure was repeated twice. The residue was then treated with 25 ml of water and 25 ml of ether. The aqueous layer was separated

and washed with 2×15 ml of ether. Removal of water under vacuum gave the ω-aminoboronic acid hydrochloride as a white solid.

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