Synthesis of a Boronic Acid Analogue of L-Ornithine

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Received 11 April 1996; revised 18 June 1996

The asymmetric synthesis of (R)-1,4-diaminobutane-1-boronic acid dihydrochloride, the amino boronic acid analogue of L-ornithine, is described. The key step of our approach utilized the Matteson boronic ester homologation of (+)-pinanediol 3-azidopropanoborionate to create and control the stereochemistry of the chiral center.

Boronic acid analogues of z-amino acids represents an exciting class of enzymes inhibitors. Main results were hitherto reported in the field of serine proteases 1 where the mechanism of inhibition appears to involve the coordination of the active site nucleophilic serine on the boron atom. The resulting negatively charged complex then mimics the tetrahedral transition state formed during the hydrolysis of a natural substrate. 2 For other classes of enzymes, the inhibition process is less clear. For example, the inactivation by boronalanine of two enzymes of the peptidoglycan biosynthesis, an alanine racemase and a D-Ala-D-Ala ligase, suggests that other mechanistic enzyme types may indeed be susceptible to inhibition. 3 In connection with our ongoing programmes related to polyamines 4 and amino boronic acids, 5 we synthesized the (R)-borornithine dihydrochloride 1·2 HCl as a potential inhibitor of ornithine decarboxylase. This key enzyme for regulating the metabolism of polyamines 5 uses, as the previously mentioned alanine racemase, 3 pyridoxal 5'-phosphate as cofactor.

The discovery of a practical synthesis of chiral z-chloro boronic esters has resulted in valuable application to the preparation of various boron analogues of z-amino carboxylic acids. However, it is noteworthy that the great majority of these compounds were isolated as their N-acyl derivatives or (and) as their boronic esters. To prepare 1 as its dihydrochloride, which was necessary to test the ornithine decarboxylase activity, we selected the following retrosynthetic approach based on the homologation of the 3-azidopropaneboronic ester which can be easily prepared from allyl bromide (Scheme 1).

### Scheme 1

Hydroboration of allyl bromide with diisopinocampheylborane followed by treatment with excess of acetaldehyde resulted in the facile elimination of the pinanyl group providing, after hydrolysis, the boronic acid with high regioselectivity. Simultaneous esterification and displacement of bromide using sodium azide then afforded the corresponding ethyl ester 8 which was converted to the optically active (+)-pinanediol derivative 2. This diol was preferred because of the stability of its esters, the high level of stereoinduction in the homologation process, and its availability in either enantiomeric form from commercial (+)- or (−)-z-pinene. Using lithium diisopropylamine to generate the lithium dichloromethanide and zinc chloride, 9 the homologation of 2 yielded the z-chloro boronic ester 3. The diastereoisomeric purity of this pinanediol derivative was determined after treatment of a sample with lithium 2-pyridinylthiolate. 10,11 The 1H NMR spectrum analysis of the stable resulting z-thio boronic ester 4 indicated that the homologation occurred with 93% de. A parallel experiment conducted with a
racermic mixture had previously showed the important discrimination of the protons $H_a$ and $H_b$ for the two diastereoisomers ($\Delta \delta = 0.14$ ppm for $H_a$ and 0.26 ppm for $H_b$).\textsuperscript{12} To introduce the amino function to the boron, we first decided to realize the displacement of chloride using lithium hexamethyldisilazanide.\textsuperscript{7} The silyl protecting groups of the amine 5 were then cleaved using anhydrous hydrochloric acid in diethyl ether to afford the amine hydrochloride 6. Unfortunately under catalytic hydrogenation conditions followed by an acidic hydrolysis, attempts to prepare the expected boroornithine 1 from 6 were unsuccessful (Scheme 2).

Concurrently, the synthesis of the bisazido derivative 7 was effected by displacement of chloride from 3 using sodium azide in dimethyl sulfoxide.\textsuperscript{13} As previously for 6, we did not succeed in obtaining 1 by catalytic hydrogenation of 3 (Scheme 3). In both cases, examination of the $^1$H and $^{13}$C NMR spectra of the crude reaction revealed the presence of substantial amounts of putrescine.\textsuperscript{14}

**Scheme 3**

After these disappointing results, we anticipated that a nitrogen protected boronic ester such as 8 in which the $N$-protective group is compatible with the reduction of azido function\textsuperscript{15} and can be removed under acidic conditions, could be a suitable precursor of 1. Desilylation of 5 was carried out with a single equivalent of methanol and the amino boronic ester intermediate was treated with benzyl chlororfoformate.\textsuperscript{16} (+)-Pinanediol (R)-4-azido-1-(benzoyloxy)butane-1-boronic acid was obtained in 70% yield from 2. Selective reduction of the azido function over PtO$_2$ was performed in 70% yield, thus giving the monoprotected boroornithine derivative 9 which could also be a good precursor of the boronic acid analogue of arginine. Simultaneous removal of the benzoyloxyboronyl protecting group and pinanediol by aqueous hydrochloric acid hydrolysis afforded unprotected boroornithine 1 (Scheme 4).

**Scheme 4**

- (R)-1,4-Diaminobutane-1-boronic acid 1 was thus obtained as its dihydrochloride in 12% overall yield starting from allyl bromide. It can be stored in aqueous solution several days (> one week) without decomposition. Biological studies of 1 will be reported in due course.

Et$_2$O, THF and CH$_2$Cl$_2$ were dried immediately prior to use by distillation under N$_2$ from sodium benzophenone ketyl and P$_2$O$_5$, respectively. BuLi (1.3 M in hexane) was titrated against i-PROH to the 1,10-phenanthroline end point. ZnCl$_2$ was vacuum dried at 100°C/0.1 Torr. The (+)-pinanediol (used as purchased from Aldrich Company) was 98% ee. All melting points were determined on a Kofler apparatus and are uncorrected. IR spectra were obtained from a Midac M 2000 model. NMR spectra were measured on a Bruker AC 200 (200 MHz for $^1$H and 50.3 MHz for $^{13}$C) and Bruker AC 300 (300 MHz for $^1$H, 75.5 MHz for $^{13}$C and 96 MHz for $^{11}$B). For $^1$H and $^{13}$C NMR, TMS was used as internal standard ($\delta = 0$). For $^{11}$B NMR, the chemical shifts are in ppm relative to BF$_3$-OEt$_2$. Optical rotations were measured using a Perkin-Elmer 241 spectrophotometer. HRMS were obtained on a Varian MAT 311 (Centre Régional de Mesures Physiques, Université de Rennes 1). Microanalysis were performed at the Central Laboratory for Analysis, CNRS, Lyon, (France). Silica gel 50F$_{254}$ was used for column chromatography.

(+) Pinanediol 3-Azidopropenboronate (2): To a stirred solution of diethyl 3-azidopropenecarbonate (3.70 g, 20 mmol) in heptane (20 mL), was added (+)-pinanediol (3.40 g, 20 mmol). After stirring for 12 h at r.t., the reaction mixture was concentrated in vacuo and subjected to flash column chromatography (1% EtOAc/heptane, $R_f$ 0.33) to afford pure 2 as a colorless oil; yield: 4.68 g (89%); $\delta$H$_{2}$C$_{2}$Cl$_{2}$). IR (nent): $\nu$: 2905, 2069, 1379, 1280 cm$^{-1}$.

$^1$H NMR (200 MHz, CDCl$_3$): $\delta$ = 4.26 (dd, $J$ = 1.8 and 8.7 Hz, 1H, $H_2$), 2.37 (t, $J$ = 7.0 Hz, 2H, $H_3$), 2.32–1.70 (m, 8H, 1H), 1.38 (s, 3H, $CH_3$), 1.29 (s, 3H, $CH_3$), 1.09 (d, $J$ = 11.0 Hz, 1H), 0.90 (t, $J$ = 7.9 Hz, 1H), 0.84 (s, 3H, $CH_3$).

$^{13}$C NMR (50.3 MHz, CDCl$_3$): $\delta$ = 85.6 (C-1), 77.7 (C-2), 53.4 (C-3), 51.3 (C-4), 39.5 (C-5), 38.1 (C-6), 38.0 (C-7), 28.6 (C-8), 27.0 (C-9), 26.5, 24.0, 23.7 (C-7, C-2').

Anal. Calc. for C$_{13}$H$_{19}$BN$_2$O$_2$ (263.1): C, 59.34; H, 8.43; found: C, 59.5; H, 8.5.

(+) Pinanediol (S)-4-Azido-1-chlorobutane-1-boronic (3): A solution of 2 (1.59 g, 6.04 mmol) and CH$_2$Cl$_2$ (1.48 g, 17.5 mmol) in THF (12 mL) was stirred at -78°C during the dropwise addition of 0.86 M LDA in THF (7.67 mL, 6.64 mmol). The mixture was treated with a solution of ZnCl$_2$ (1.4 g, 12.1 mmol) in a solution of THF (12 mL) and then allowed to warm r.t. overnight. Workup by treatment with aq NH$_4$Cl and Et$_2$O was followed by the concentration at -40°C of the ether layer under vacuum. For optimum stereoselectivity, the whole operation was done as quickly as possible and the residue was used as such immediately in the next step. For an analytical sample, the Et$_2$O solution was concentrated, and the residue was chromatographed (silica gel, 5% EtOAc/ heptane, $R_f$ 0.48) to afford pure 3 as a colorless oil; yield: 1.54 g (82%).

$^1$H NMR (200 MHz, CDCl$_3$): $\delta$ = 4.37 (dd, $J$ = 1.9 and 8.9 Hz, 1H, $H_2$), 3.49 (m, 1H, $H_1$), 3.33 (t, $J$ = 6.5 Hz, 2H, $H_3$), 2.31–1.81 (m, 9H), 1.42 (s, 3H, $CH_3$), 1.30 (s, 3H, $CH_3$), 1.15 (d, $J$ = 10.5 Hz, 1H), 0.85 (s, 3H, $CH_3$).

$^{13}$C NMR (50.3 MHz, CDCl$_3$): $\delta$ = 86.9 (C-4), 79.0 (C-2), 51.5 (C-6), 51.3 (C-4), 39.5 (C-3), 38.2 (C-5), 35.2 (C-6), 31.2 (C-3), 28.4 (C-10), 27.0 (C-9), 26.7, 26.4, 23.9 (C-8, C-7, C-2').

Anal. Calc. for C$_{14}$H$_{17}$BCl$_2$O$_2$ (311.6): C, 53.96; H, 7.44; N, 13.48; found: C, 54.1; H, 7.6; N, 13.3.

(+) Pinanediol (R)-4-Azido-1-(2-pyridinylthio)butane-1-boronic (4): A solution of crude 3 (prepared from 6.04 mmol of 2) in THF (12 mL) was added to a stirred solution of lithium 2-pyridinylthiolate (6.04 mmol from BuLi (6.04 mmol) and 2-pyridinethiol.
(670 mg) in THF (16 mL) at −78 °C. The mixture was allowed to warm to r.t. slowly and stirred overnight. The mixture was worked up by addition of NH₄Cl and Et₂O. The ether phase was washed with water, brine and then dried (MgSO₄). The solution was concentrated and the diastereoisomeric purity was determined by examination of the 1H NMR spectrum of the crude reaction. The residue was subjected to flash chromatography (silica gel, 50% EtOAc/heptane, Rₜ 0.5) to give 4 as white crystals; yield: 1.63 g (70% from 2); mp 110−111°C; [α]D²⁰ = −125 (c = 1.28, CH₂Cl₂).

IR (CHCl₃): ν = 2915, 2709, 1603, 1558, 1463, 1434, 1368, 1280, 735 cm⁻¹.

1H NMR (200 MHz, CDCl₃): δ = 8.42 (m, 1.5 epimer, 3%), 8.28 (m, 1 H), 7.71 (m, 1 H), 7.34 (m, 1 H), 7.19 (m, 1 H), 5.98 (dd, J = 1.4 and 8.0 Hz, 1 H, H-2), 4.19 (dd, epimer, 3%), 3.26 (td, J = 3.5 and 7.0 Hz, 2 H, H-4), 2.49−1.76 (m, 14.15 H, 10.45 H, J = 1.01 Hz, 1 H), 1.28 (s, 3 H, CH₃), 1.26 (s, 3 H, CH₃), 0.84 (s, 3 H, CH₃).

13C NMR (50.3 MHz, CDCl₃): δ = 162.4, 141.8, 140.2, 122.8, 119.3 (C₁₀ reasonably), 83.4 (C-1), 78.1 (C-2), 53.3 (C-5), 51.4 (C-4), 40.0 (C-4), 38.0 (C-5), 37.8 (C-3), 30.5 (C-3), 30.1 (C-10), 28.7, 27.4, 26.9 (C-9), 24.3 (C-8).

1B NMR (96 MHz, CDCl₃): δ = 14.36.

Anal. Calcd. for C₂₃H₂₈N₂O₇S (386.3): C, 59.07; H, 7.04; N, 14.50; found: C, 59.1; H, 7.2; N, 14.7.

(+)-Pinanediol (R)-1-Amino-4-azidobutane-1-boronic acid hydrochloride (6): A solution of crude 3 prepared from 2 (6.04 mmol) in THF (12 mL) at −78 °C was treated with lithium hexamethyldisilazanide (6.04 mmol) in THF (1.6 mL). After stirring overnight at 20 °C, the resulting solution of (+)-pinanediol 4-azido-1-[bis(trimethylsilyl)amino]butane-1-boronic acid was cooled to −78 °C, treated with MeOH (0.24 mL, 6.04 mmol), stirred 1.5 h at −78 °C, and treated with benzyl chlorofororm (26.59 mg, 0.13 mg, 6.64 mmol). After 14 h at 20 °C, the solution was concentrated and subjected to flash chromatography (silica gel, 20% EtOAc/heptane, Rₜ 0.4) to give 8 as a colorless oil; yield: 1.8 g (70% from 2); [α]D²⁰ +127; [α]D²⁰ +39.8 (c = 0.9, CH₂Cl₂).

1H NMR (200 MHz, CDCl₃): δ = 7.34 (m, 5 H, H₁₃), 5.2−5.08 (m, 3 H, NH, CH₂Ph), 4.32 (m, 1 H, H-2), 3.32−3.18 (m, 18 H, H-4, H-1), 2.32−1.63 (m, 9 H, H-3, H-4, H-6, H-7, H-2, H-3), 1.38 (s, 3 H, CH₃), 1.26 (s, 3 H, CH₃), 1.10 (d, 1 H, J = 10.8 Hz, H-7), 0.86 (s, 3 H, CH₃).

13C NMR (50.3 MHz, CDCl₃): δ = 156.8 (C = O), 136.6, 127.5, 127.3, 127.1, 127.0 (C₁₀ reasonably), 86.7 (C-1), 78.4 (C-2), 66.7 (CH₂Ph), 51.4 (C-6), 51.2 (C-4), 39.4 (C-4'), 38.2 (C-5), 35.3 (C-3), 28.9 (C-3), 28.5 (C-10), 27.0 (C-9), 26.4 (2, C-7, C-2), 24.0 (C-6).


(+)-Pinanediol (R)-4-Amino-1-(benzoxycarbonyl)amino)butane-1-boronic acid Hydrochloride (9): (+)-Pinanediol (R)-4-azido-1-(benzoxycarbonyl)amino)butane-1-boronic acid (8, 205 mg, 0.48 mmol) was dissolved in abs EtOH (10 mL). PO₄(10 mg) was added and H₂ was passed over the mixture for 12 h, at which time the mixture was filtered and evaporated to give an oil (200 mg). It was triturated with 0.1 N HCl and concentrated in vacuo. After successive washings with Et₂O, the pure amine hydrochloride 9·HCl was obtained as an amorphous, hygroscopic solid; yield: 153 mg (73%); [α]D²⁰ +10.3; [α]D²⁰ +12.9 (c = 0.6, MeOH).

1H NMR (200 MHz, CDCl₃): δ = 8.21 (br s, 3 H, NH₂), 7.32 (m, 5 H, H₁₃), 5.58 (m, 1 H, NHCO), 5.06 (m, 2 H, CH₂Ph), 4.36 (dd, 1 H, J = 1.9 and 5.8 Hz, H-2), 3.15−2.80 (m, 3 H, H-4, H-1), 2.40−1.62 (m, 9 H, H-3, H-4, H-6, H-7, H-2, H-3), 1.36 (s, 3 H, CH₃), 1.26 (s, 3 H, CH₃), 1.15 (d, 1 H, J = 10.9 Hz, H-7), 0.81 (s, 3 H, CH₃).

13C NMR (50.3 MHz, CDCl₃): δ = 157.0 (C = C), 137.2, 128.5, 128.1, 128.0 (C₁₀ reasonably), 100.7 (C-1), 78.4 (C-2), 66.3 (CH₂Ph), 51.4 (C-6), 51.2 (C-4'), 39.5 (C-4), 38.1 (C-5), 35.5 (C-3), 28.6, 28.5, 27.0, 26.5, 26.4, 24.0 (C-2', C-3, C-7, C-8, C-9, C-10).

Anal. Calcd. for C₂₁H₂₁N₂ClO₄ (436.8): C, 60.49; H, 7.84; N, 6.41; found: C, 60.7; H, 8.0; N, 6.6.

(R)-1,4-Diaminobutane-1-boronic Acid Dihydrochloride (1·2 HCl): A mixture of (+)-pinanediol (R)-4-amino-1-(benzoxycarbonyl)amino)butane-1-boronic acid hydrochloride (9·HCl, 100 mg, 0.23 mmol) in 6 N HCl (2.8 mL) was refluxed for 1 h. The solution was cooled, washed with CHCl₃ (3 x 2 mL) and evaporated to dryness to afford 1 as an amorphous solid; yield: 40 mg (56%); [α]D²⁰ +39.5; [α]D²⁰ +42.6 (c = 0.95, H₂O).

1H NMR (300 MHz, D₂O): δ = 2.97 (m, 2 H, H-4), 2.82 (m, 1 H, H-1), 1.73 (m, 4 H, H-2, H-3).

13C NMR (75.5 MHz, CDCl₃): δ = 41.7 (C-4'), 28.7, 26.8 (C-2, C-3).

1B NMR (96 MHz, D₂O): δ = 28.72.

FAB MS: m/z = 403 (M + H⁺) for ester of 1 with matrix 3-nitrobenzyl alcohol.

(1) For a review, see: Morin, C. Tetrahedron 1994, 50, 12521.
For other leading references on polyamines, see: Inhibition of Polyamine Metabolism; Mc Cann, P.P.; Pegg, A.E.; Sjoerdasma, A. Eds.; Academic: San Diego, 1987.
(10) The diastereoisomer ratio was usually determined by direct examination of the 400 MHz 1H NMR spectrum of the crude homologated boronic ester (different chemical shift of one of the pinanyl protons that appears as a doublet near δ = 1.10–1.15. See for example: Matteson, D.S.; Sadhu, K.M.; Peterson, M.L. J. Am. Chem. Soc. 1986, 108, 810. In our hands, we observed that it was quite difficult to measure the diastereomeric purity with a good precision.
(11) This method was generalized to other α-chloro boronic esters. Ollivault, M.; Monnier, L.; Carboni, E. manuscript in preparation.
(12) The diastereoselectivity of the homologation reaction was confirmed by the synthesis of the acetamido derivative from 5 (Ac₂O, HOAc) and analyzing the product (NH peak) with 200 MHz 1H NMR. Determination of diastereoisomeric purity was based on the 1H NMR spectrum of the crude reaction (integration of the NH peaks at δ = 8.94 and 8.22 indicated an R/S isomer ratio of 32:1). Flash column chromatography (silica gel, 10% MeOH/ EtOAc) gave the pure acetamido compound as white crystals; mp 114–116 °C; [α]D 10° = –31.2 (c = 1.55, CH₂Cl₂).
1H NMR (200 MHz, CDCl₃): δ = 8.94 (br, s, 1 H, NH), 8.22 (NH, 1 S, epimer, 3 %), 4.19 (dd, 1 H, J = 2.1 and 8.7 Hz, H-2), 3.31 (m, 2 H, H-4'), 2.73 (m, epimer, 3 %), 2.49 (m, 1 H, H-1'), 1.41–2.31 (m, 13 H, H-3, H-4, H-6, H-7, H-2', H-2', CH₂), 1.39 (s, 3 H, CH₃), 1.27 (s, 3 H, CH₃), 0.86 (s, 3 H, CH₃).
13C NMR (50.3 MHz, CDCl₃): δ = 174.4 (C = O), 83.5 (C-1), 76.3 (C-2), 52.4 (C-6), 51.6 (C-4'), 40.1 (C-4), 38.2 (C-5), 36.7 (C-3'), 29.4 (C-10), 28.6 (C-3), 27.3 (C-9), 27.0 (C-7), 26.6 (C-2'), 24.2 (C-8), 18.2 (COCH₃).
Anal. Calc. for C₁₇H₂₃BN₂O₅: (334.2 C) 57.50; H, 8.14; N, 16.76; found: C, 57.4; H, 8.3; N, 16.9.
(13) This sequence was realized with a racemic α-chloro boronic ester.
(14) Similar decomposition of α-amino boronic acids or esters have been already reported: Matteson, D.S.; Sadhu, K.M. Organometallics 1984, 3, 614.