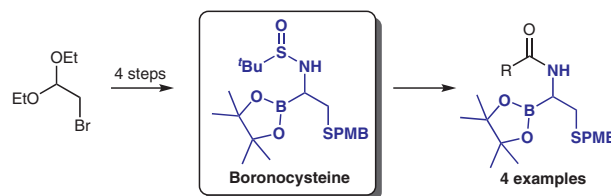


Synthesis of Boronocysteine

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Abstract Herein we report the first synthesis of protected boronocysteine. The target compound was prepared via copper-catalysed diastereoselective nucleophilic borylation of a sulfinimine. After deprotection to give the amine as the hydrochloride salt, four boronocysteine amide derivatives were prepared through reaction with a variety of different active acylating agents.

Key words amino acids, boron, copper, imines, peptides

α -Aminoboronic acids have attracted considerable attention as analogues of amino acids with potential applications in medicinal chemistry.¹ Bortezomib (Velcade®), a peptide analogue incorporating an α -aminoboronic acid used in cancer treatment, became the first drug on the market containing a boron atom (Figure 1). Subsequently, other α -aminoboronic acid derivatives have reached the market including ixazomib and delanzomib. The synthesis of α -aminoboronic acids has proved to be especially challenging, however, as free α -aminoboronate compounds readily undergo rearrangement to *N*-boryl compounds leading to protodeboronation.²

Nevertheless, Matteson was able to carry out the first synthesis of an α -aminoboronic acid derivative in 1966 starting from iodomethylmercuric iodide (Scheme 1).³ He was subsequently able to access a wider range of α -aminoboronic acids via rearrangement reactions of boronate esters using dichloromethyl lithium.⁴ Alternative approaches to α -aminoboronic acid derivatives have included copper-catalysed nucleophilic borylation of imines,⁵ alkylation of α -sulfenyl boronates followed by nucleophilic displacement of the sulfur,⁶ Curtius rearrangement of α -borylcarboxylic acids,⁷ and lithiation/borylation of protected amine deriva-

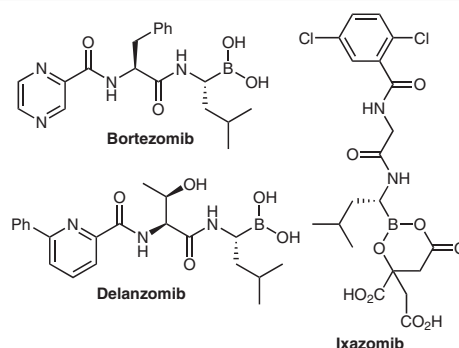
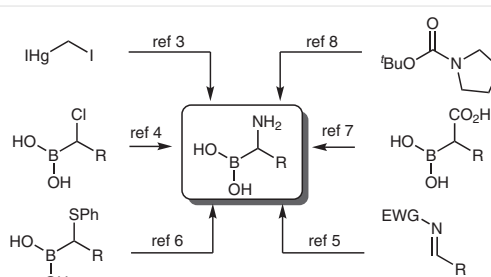


Figure 1 Medicinally useful α -aminoboronic acid derivatives

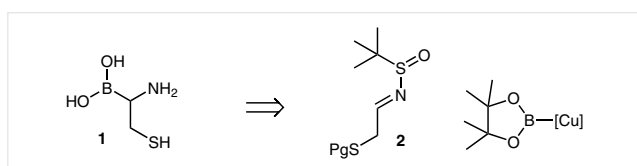
tives.⁸ Notably, whilst a wide range of α -aminoboronic acid derivatives have been reported,^{4–9} there are relatively few examples containing heteroatomic functional groups on the side chain.¹⁰ For an ongoing project involving the study of peptides containing C-terminal cysteine derivatives,¹¹ we required access to the boron analogue of cysteine. Interestingly, no previous synthesis of this compound (or a protected derivative) has been reported in the literature. Herein,



Scheme 1 Synthetic approaches to α -aminoboronic acid derivatives

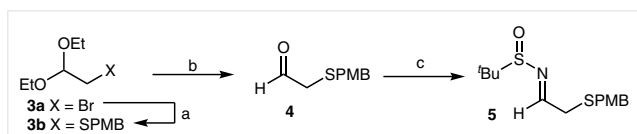
we report a concise synthesis of protected boronocysteine, and its use in the synthesis of *N*-acyl derivatives including dipeptide analogues.

Matteson has previously noted that rearrangement of a thioether-functionalised alkylboronate using dichloromethylithium was unsuccessful, probably due to loss of a sulfur-stabilised carbanion from the 'ate' complex.¹² We therefore envisaged that boronocysteine **1** could readily be constructed by Cu-catalysed borylation of a suitably protected sulfinimine **2** (Scheme 2).⁵ The required imine **2** should be readily available from commercially available bromoacetaldehyde diethyl acetal.



Scheme 2 Proposed synthetic strategy for preparing boronocysteine

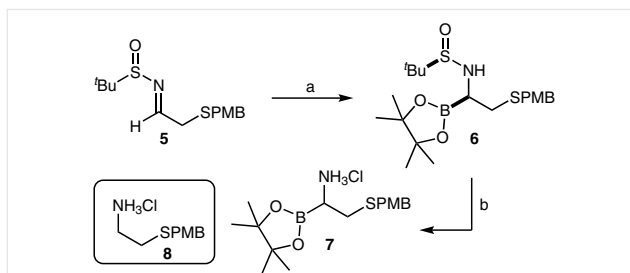
Bromoacetaldehyde dimethyl acetal **3a** was converted into the corresponding sulfide **3b** by reaction with *p*-methoxybenzyl thiol (PMBSH) and sodium hydroxide (Scheme 3).¹³ After deprotection of the acetal, the aldehyde **4**¹⁴ was then converted into sulfinimine **5** through condensation with the sulfinimide.



Scheme 3 Synthesis of imine **5**. Reagents and conditions: a. NaOH, PMBSH, EtOH, 52%; b. HCl, acetone, 99%. c. ^tBuSONH₂, CuSO₄, CH₂Cl₂, 80%.¹⁶

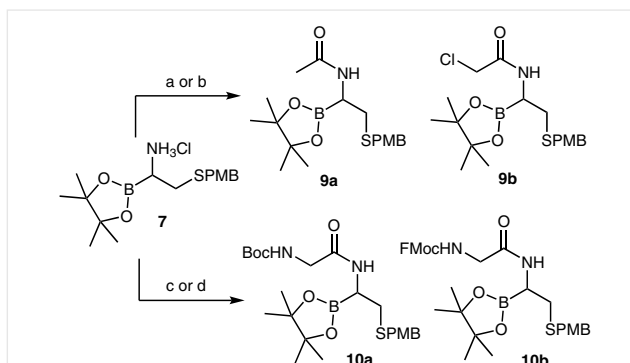
With the required sulfinimide in hand, the Cu-catalysed borylation reaction was investigated. Pleasingly, by using CuCl in the presence of KO^tBu and *rac*-BINAP as a ligand,^{5a} the desired boronate **6** was obtained in 60% isolated yield as a single diastereoisomer (Scheme 4). As reported previously, the sulfinimide could be removed using HCl to give the corresponding α -aminoboronate as the hydrochloride salt **7**.^{5a} This compound required careful handling as it readily underwent protodeboration to give the corresponding 2-aminoethylthio ether **8**.¹⁵ For example, deboronated compound **8** was obtained when **6** was exposed to HCl for 24 h instead of the 3 h reaction time required to produce **7**.

We were, however, able to prepare boronocysteine amides derived from **7** through reaction with appropriate acylating reagents (Scheme 5). Thus, reaction of **7** with acid chlorides provided the acetamide **9a** and chloroacetamide



Scheme 4 Copper-catalysed borylation of imine **5** and sulfinamide deprotection. Reagents and conditions: a. CuCl, (\pm)-BINAP, KO^tBu, B₂pin₂, THF, 60%;¹⁷ b. HCl, dioxane, MeOH, 82%.¹⁸

9b. Dipeptide analogues **10** were obtained through reaction with either an *in situ* generated mixed anhydride **10a**, or a pre-formed acyl fluoride **10b**. These reactions demonstrate that boronocysteine can readily be converted into amide derivatives through reaction with a range of different active acylating agents.



Scheme 5 Synthesis of boronocysteine amides. Reagents and conditions: a. MeCOCl, pyridine, MeCN, 22% (**9a**); b. ClCH₂COCl, *N*-methylmorpholine, CH₂Cl₂, 85% (**9b**); c. Boc-Gly-OH, *N*-methylmorpholine, ^tBuOCOCl, CH₂Cl₂, then **7**, 89% (**10a**);¹⁹ d. FMoc-Gly-F, ^tPr₂NEt, CH₂Cl₂, 60% (**10b**).

In summary, we have described the first synthesis of protected boronocysteine, and demonstrated its application in the formation of amide derivatives.

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Supporting Information

Supporting information for this article is available online at <https://doi.org/10.1055/s-0036-1591491>.

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- (16) (E)-N-[2-[(4-Methoxybenzyl)thio]ethylidene]-2-methylpropane-2-sulfinamide (**5**) Copper(II) sulfate (1.27 g, 7.94 mmol) and aldehyde **4** (779 mg, 3.97 mmol, 1.1 equiv) were added to a solution of (±)-tert-butyl sulfinamide (438 mg, 3.61 mmol) in anhydrous CH₂Cl₂ (7.2 mL). The reaction was stirred at r.t. for 18 h, before filtering through Celite. The solvents were removed *in vacuo* and the residue obtained was purified by column chromatography to give an orange oil (865 mg, 2.89 mmol, 80%). ¹H NMR (600 MHz, CDCl₃): δ = 7.98 (1 H, t, J = 5.6 Hz, NCH), 7.23 (2 H, d, J = 6.5 Hz, ArH), 6.85 (2 H, d, J = 6.5 Hz, ArH), 3.79 (3 H, s, OCH₃), 3.66 (2 H, s, ArCH₂), 3.35 (1 H, dd, J = 14.3, 6.0 Hz, 1 × SCH₂CH), 3.31 (1 H, dd, J = 14.3, 5.3, 1 × SCH₂CH), 1.22 (9 H, s, ^tBu). ¹³C NMR (150 MHz, CDCl₃): δ = 164.2, 158.9, 130.3, 129.2, 114.1, 57.0, 55.4, 35.02, 34.3, 22.5. LRMS (CI): m/z (%) = 420 (100), 300 (37) [M + H⁺], 240 (30), 195 (32) [M - SO^tBu]⁺, 121 (88) [PMB⁺]. HRMS: m/z calcd for C₁₄H₂₂NO₂S₂: 300.10865; found: 300.10877. IR (film): ν_{max} = 2958 (C-H), 1609 (C=C), 1510 (C=N), 1458 (C=C), 1083 (S=O) cm⁻¹.
- (17) N-[2-[(4-Methoxybenzyl)thio]-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethyl]-2-methylpropane-2-sulfinamide (**6**) Using flame-dried glassware under an argon atmosphere, CuCl (38.4 mg, 0.388 mmol), (±)-BINAP (111.1 mg, 0.1784 mmol), and B₂pin₂ (1.331 g, 5.242 mmol) were dissolved in anhydrous THF (4 mL). KO^tBu (1 M in THF, 1.4 mL, 1.4 mmol) was added whilst stirring at r.t. After 10 min, the reaction was cooled to -20 °C, and aldehyde **5** (1.0338 g, 3.4522 mmol) was added followed by MeOH (300 μL, 7.41 mmol) and the reaction stirred overnight. The solvent was removed *in vacuo* and the resultant oil purified by flash column chromatography using EtOAc in CH₂Cl₂ (20 → 35%) to give **6** as an orange oil (878 mg, 2.056 mmol, 60%); R_f = 0.08 (EtOAc/CH₂Cl₂ = 1:4). ¹H NMR (600 MHz, CDCl₃): δ = 7.24 (2 H, d, J = 8.6 Hz, ArH), 6.82 (2 H, d, J = 8.6 Hz, ArH), 3.78 (3 H, s, OCH₃), 3.71 (1 H, d, J = 5.6 Hz, NH), 3.69 (s, 2 H, ArCH₂S), 3.22 (1 H, m, CHB), 2.77 (1 H, dd, J = 13.4, 6.3 Hz, 1 × SCH₂CH), 2.72 (1 H, dd, J = 13.4, 7.9 Hz, 1 × SCH₂CH), 1.25 (s, 6 H, 2 × pinacol-CH₃), 1.23 (s, 9 H, ^tBu), 1.20 (s, 6 H, 2 × pinacol-CH₃). ¹³C NMR (150 MHz, CDCl₃): δ = 158.7, 130.1, 130.0, 114.0, 84.3, 56.2, 55.3, 41.3 (br), 35.2, 34.6, 25.0 (2 C), 22.6. LRMS (CI): m/z (%) = 428 (41), [M + H]⁺, 371 (18) [M⁺ - ^tBu], 322 (38) [M⁺ - SO^tBu], 121 (100) [PMB⁺]. IR: ν_{max} = 2977 (C-H), 2930 (C-H), 1609 (Ar), 1511 (Ar), 1544 (Ar), 1369 (B-O), 1246, 1140 (B-C), 1033 (S=O). HRMS: m/z calcd for C₂₀H₃₄BNO₄S₂: 428.2095; found: 428.2095.
- (18) 2-[(4-Methoxybenzyl)thio]-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethanamine hydrochloride (**7**) A solution of HCl in dioxane (4 M, 585 μL, 2.34 mmol) was added to **6** (99.7 mg, 0.233 mmol) dissolved in anhydrous MeOH (3 mL) to give a pale yellow solution. The reaction was stirred for 3 h. The solvent was removed *in vacuo* to give an orange residue (75.3 mg). The residue was washed with Et₂O, sonicated, and centrifuged to give **7** as a light brown solid (68 mg, 0.190 mmol, 82%). ¹H NMR (400 MHz, MeOD-*d*₄): δ = 7.29 (2 H, d, J = 8.7 Hz, ArH), 6.89 (2 H, d, J = 8.7 Hz, ArH) 3.80 (3 H, s, OCH₃), 3.79 (2 H, s, ArCH₂), 3.01 (1 H, dd, J = 8.7, 4.7 Hz, CHB), 2.85 (1 H, dd, J = 14.3, 4.8 Hz, 1 × CH₂CH), 2.73 (1 H, dd, J = 14.3, 8.8 Hz, 1 × CH₂CH), 1.33 (12 H, s, 4 × CH₃). ¹³C NMR (100 MHz, MeOD-*d*₄): δ = 159.1, 129.9, 129.5, 113.7, 85.5, 74.4, 54.5, 35.1, 30.4, 23.8, 23.7. LRMS (CI): m/z (%) = 323 (100) [M + H]⁺, 198 (18) [M - Bpin]⁺. HRMS: m/z calcd for C₁₆H₂₇BNO₃S: 323.1836; found: 323.18359. IR (solid): ν_{max} = 2975 (C-H), 2958 (C-H), 2831 (C-H), 1607, 1583, 1411 cm⁻¹.
- (19) tert-Butyl [2-[(2-[(4-Methoxybenzyl)thio]-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethyl)amino]-2-oxoethyl]carbamate (**10a**) Using flame-dried glassware under an argon atmosphere, Boc-Gly-OH (87.5 mg, 0.50 mmol) was dissolved in anhydrous CH₂Cl₂ (1.5 mL) and cooled to -20 °C. To this was added NMM (66 μL, 0.60 mmol) followed by IBCF (58 μL, 0.45 mmol), and the mixture stirred for 5 h at -20 °C. HCl salt **7** (23.4 mg, 65.1 μmol)

was added, followed by NMM (7 μ L, 65 μ mol), and the reaction stirred overnight. The reaction mixture was concentrated *in vacuo* and the resultant oil purified by flash column chromatography using deactivated silica (35% water w/w) eluting with MeOH in EtOAc (0 \rightarrow 10%) to give **10a** as a pale yellow oil (28 mg, 58.0 μ mol, 89%). ^1H NMR (600 MHz, CDCl_3): δ = 7.51 (1 H, br s, CHNH), 7.21 (2 H, d, J = 8.7 Hz, ArH), 6.82 (2 H, d, J = 8.7 Hz, ArH), 5.29 (1 H, br s, CH_2NH), 3.93 (2 H, d, J = 5.7, NHCH_2), 3.78 (3 H, s, OCH_3), 3.65 (2 H, s, ArCH_2), 2.81 (1 H, br d, J = 11.5 Hz,

CHB), 2.75 (1 H, dd, J = 14.1, 3.2 Hz, $1 \times \text{SCH}_2\text{CH}$), 2.46 (1 H, dd, J = 14.1, 11.5 Hz, $1 \times \text{SCH}_2\text{CH}$), 1.44 (9 H, s, Bu), 1.18 (6 H, s, $2 \times$ pinacol- CH_3), 1.16 (6 H, s, $2 \times$ pinacol- CH_3). ^{13}C NMR (150 MHz, CDCl_3): δ = 174.9, 158.7, 130.3, 130.1, 114.1, 81.6, 55.4, 54.0, 41.4, 35.2, 33.6, 29.8, 28.4, 25.0, 24.9, 14.3. LRMS (CI): m/z (%) = 481 (100) $[\text{M} + \text{H}]^+$. HRMS: m/z calcd for $\text{C}_{23}\text{H}_{37}\text{BN}_2\text{O}_6\text{S}$: 480.2574; found: 480.2575. IR (film): ν_{max} = 2970 (C-H), 2926 (C-H), 1697 (br, C=O), 1609 (C=O), 1511, 1456 cm^{-1} .