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Two Efficient Methods For The Cleavage Of Pinanediol Boronate Esters Yielding The Free Boronic Acids

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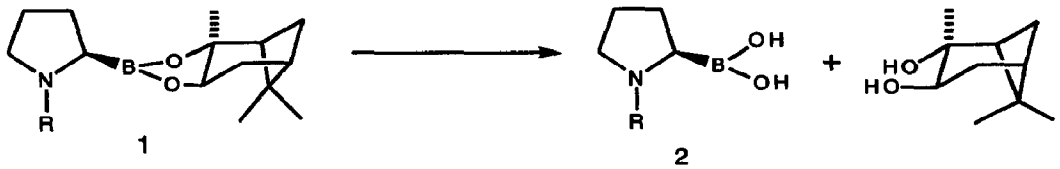
Abstract: *Two synthetic methods for the preparation of boronic acids from their corresponding pinanediol boronate esters are reported. The key to success of the procedures relies on removal of the liberated pinanediol from the reaction mixture.*

It has recently been shown[1] that dipeptides of proline boronic acid are excellent inhibitors of the post-proline cleaving enzyme dipeptidyl peptidase IV (CD 26). Inhibition of this enzyme *in vivo* has been demonstrated to suppress the immune response[2a] and has recently been implicated in the entry of HIV-1 into T-cells.[2b] Given the obvious importance of these processes, and our need to produce large quantities of optically active proline boronic acid dipeptides **2** for *in vivo* evaluation as immunosuppressive agents, we investigated the preparation of this class of inhibitors. Until recently syntheses of these compounds have been hampered by two factors: 1) the lack of an efficient route to enantiomerically pure proline boronic acid and 2) the boronic acid dipeptides are generally prepared as their pinanediol or pinacol esters.[3] The esters are believed to hydrolyze under the biological assay conditions yielding the active boronic acid inhibitor.[3b] However, results from our laboratories show that pinanediol hydrolysis does not occur under hydrolytic conditions with BOC protected dipeptides and fails to go to completion with the free terminal amino dipeptides.[4]



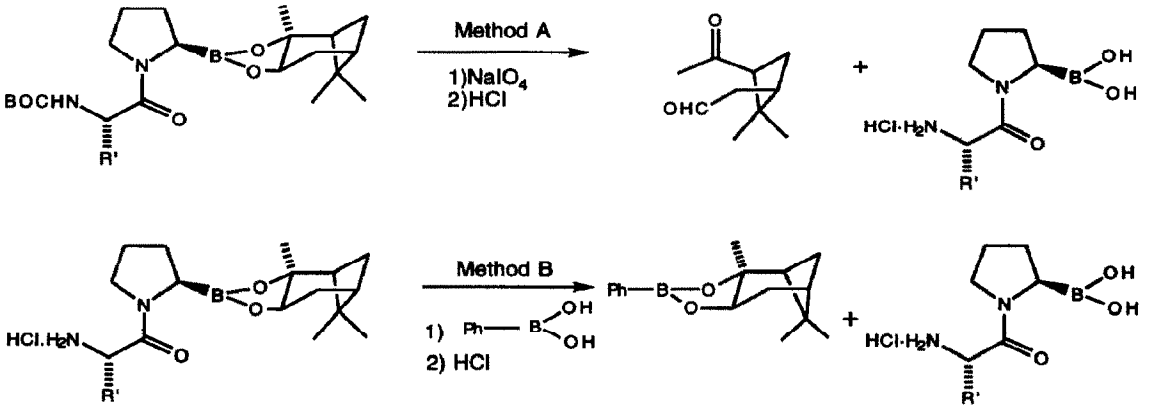
1 **2**

R = amino acid

In a previous communication[5] we outlined the synthesis of proline boronic acid pinanediol ester as a single enantiomer. The selection of pinanediol as a protecting group not only allowed for the preparation of optically pure material but also simplified the handling of the boronic acids affording compounds that were readily isolable and stable to chromatography (compared to pinacol and other esters, which are lost to varying extents on chromatography). The cleavage of the pinanediol group from amino boronate esters (*e.g.* **1**) is known to be difficult and successful procedures have only been developed for simple hydrocarbon based substrates.[6]

Application of these methods, including hydrolytic, reductive,[7] and destructive techniques such as boron trichloride,[8] to our esters led to either material destruction or recovery of starting material. We suspected the problem was not that the hydrolysis did not occur, but that the equilibrium strongly favors the starting boronate ester. If this hypothesis were correct removal of the liberated pinanediol from the equilibrium should drive the reaction to completion. Based on this theory we developed two complementary techniques for application to either the BOC protected dipeptide or the free amine salt.

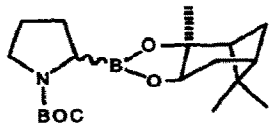
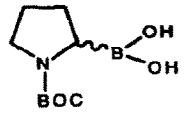
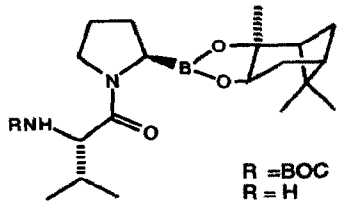
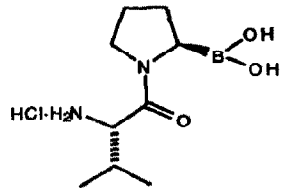
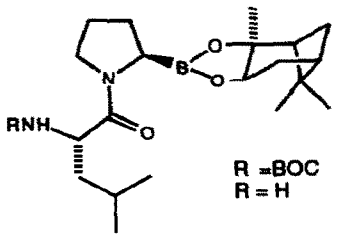
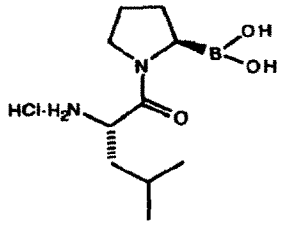
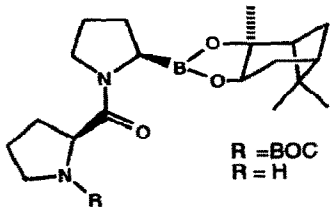
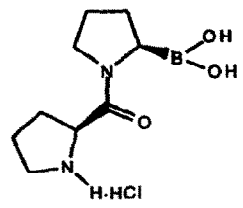
Scheme 1



Method A relies on the oxidative cleavage of the liberated pinanediol using sodium metaperiodate. Whilst we were aware of the susceptibility of boronic acids to oxidation, on consideration of the mechanism we reasoned that boronic acids are oxidized by nucleophilic oxidants such as alkaline hydrogen peroxide, whereas periodate is an eletrophilic oxidant. Indeed treatment of the BOC protected dipeptide with periodate in acetone at neutral pH smoothly afforded the free boronic acid which was readily separated from the ketoaldehyde. Method A, although destructive, is the only procedure available for removal of the pinanediol group that is compatible with BOC protected dipeptides and allows for the isolation of the BOC protected dipeptide boronic acid after the first step (*i.e.* $NaIO_4$).

Method B is based on transesterification with phenylboronic acid and removes the pinanediol as the phenylboronate ester, (see scheme 1). The procedure uses a biphasic system which takes advantage of the solubility differences in the starting pinanediol ester, the free boronic acid (both soluble in the aqueous phase) and the pinanediol phenylboronate ester (soluble only in the organic phase). This procedure allows for the recovery of the valuable chiral auxiliary pinanediol[9] from the phenylboronate ester simply by treatment with hydrogen peroxide (affording the boric acid ester which can be used directly for transesterification of other boronic acids). These two methods have been applied to a variety of substrates as shown in the table.

Table

SUBSTRATE	METHOD	PRODUCT	YIELD[a]
	A		65%[b]
 R =BOC R = H	A B		65%[c] 83%
 R =BOC R = H	A B		71%[c] 84%
 R =BOC R = H	A B		55%[c] 85%

a) all compounds gave satisfactory elementary analysis and spectral data.
b) isolated as the pinacol ester for ease of purification.
c) products typically deprotected (BOC cleaved) to aid purification.

In summary two methods for the removal of pinanediol from boronate esters have been developed. Method A allows for mild removal of the boronate ester which should be general, and compatible with a wide variety of functional groups including BOC protected amines. Method B is particularly applicable to water soluble boronates and allows for the recovery of the chiral auxiliary as the phenylboronate ester. These methods offer significant advancement over current literature protocols and allow for the preparation of multigram quantities of chemically and optically pure boronic acids.

General Experimental Procedures

Method A

To a stirred solution of the boronate ester (2.3 mmol) in acetone (60 mL) was added NH_4OAc (aq) (50 mL, 0.1N) and $NaIO_4$ (6.9 mmol). The mixture was stirred at room temperature for 24-48 h, the acetone was removed (*in vacuo*) and the aqueous phase was diluted with NaOH (aq) (75 mL, 2N), washed with CH_2Cl_2 and acidified cautiously to pH=3 with HCl (aq) (2N). Extraction with CH_2Cl_2 (4 x 50 mL) followed by filtration and concentration afforded the crude product. This was treated with HCl / Et_2O (4.5N) for 3-4 h and the solvent was removed. The solid residue was crystallized from an appropriate solvent to afford the desired product as the hydrochloride salt.

Method B

To a stirred solution of the boronate ester (8.54 mmol) in water (100 mL) at pH=3 (adjusting as necessary with 2N aq HCl) was added phenyl boric acid (8.54 mmol) and hexanes (100 mL). After 30 min at room temperature the hexane layer was removed and replaced with fresh hexane (100 mL). After a further 30 min, the hexane layer was again removed and the combined organic layers were dried (Na_2SO_4), filtered and concentrated to afford a quantitative yield of pinanediol phenylboronate. The aqueous phase was passed through an ion exchange column (Dowex 50X2-200) eluting with water until neutral and then with NH_4OH (aq) (1.0%). The relevant fractions were lyophilized, treated with HCl (aq) (2.0N) and lyophilized again to afford the desired hydrochloride salt.

References

1. Flentke, G. R. ; Munoz, E. ; Huber, B. T. ; Plaut, A. G. ; Kettner, C. A. ; Bachovchin, W. W. *Proc. Natl. Acad. Sci.*, USA **1991**, 88, 1556-1559.
2. (a) Kubota, T. ; Flentke, G. R. ; Bachovchin, W. W. ; Stollar, B. D. *Clin. Exp. Immunol.*, **1992**, 89 , 192-197. (b) Callebaut, C. ; Krust, B. ; Jacotot, E. ; Hovanessian, A. G. *Science*, **1993**, 262, 2045-2050.
3. (a) Kettner, C. A. ; Shenvi, A. B. *J. Biol. Chem.*, **1984**, 259, 15106-15114. (b) Bachovchin, W.W. ; Plaut, A. G. ; Flentke, G. R. ; Lynch, M. ; Kettner, C. A. ; *J. Biol. Chem.*, **1990**, 265, 3738-3743.
4. Snow, R. J. *et al* manuscript in preparation.
5. Kelly, T. A. ; Fuchs, V. U. ; Perry, C. W. ; Snow, R. J. *Tetrahedron*, **1993**, 49, 1009-1016.
6. (a) Matteson, D. S. ; Ray, R. ; Rocks, R. R. ; Tsai, D. J. S. *Organometallics*, **1983**, 2, 1536-1543. (b) Matteson, D. S. *Tetrahedron*, **1989**, 45, 1859-1885. (c) Brown, H. C. ; Rangaishenvi, M. V. ; *J. Organomet. Chem.*, **1988**, 358, 15-30. (d) Matteson, D. S. ; Ray, R. *J. Am. Chem. Soc.*, **1980**, 102, 7590-7591.
7. (a) Rangaishenvi, M. V. ; Singaram, B. ; Brown, H. C. *J. Org. Chem.*, **1991**, 56, 3286-3294. (b) Brown, H. C. ; Bakshi, R. K. ; Singaram, B. *J. Am. Chem. Soc.*, **1988**, 110, 1529-1534. (c) Brown, H. C. ; Singaram, B. ; Cole, T. E. *J. Am. Chem. Soc.*, **1985**, 107, 460-464. (d) Brown, H. C. ; Cole, T. E. ; Bakshi, R. K. ; Srebnik, M. ; Singaram, B. *Organometallics*, **1986**, 5, 2303.
8. (a) Matteson, D. S. ; Michnick, T. J. ; Willett, R. D. ; Patterson, C. D. *Organometallics*, **1989**, 8, 726-729. (b) Matteson, D. S.; Sadhu, K. M. ; Lienhard, G. E. *J. Am. Chem. Soc.*, **1981**, 103, 5241-5242.
9. For a review of chiral ligands see Narasaka, K. *Synthesis*, **1991**, 1-11.

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