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A Practical Synthesis of L-Valyl-pyrrolidine-(2*R*)-boronic Acid: Efficient Recycling of the Costly Chiral Auxiliary (+)-Pinanediol

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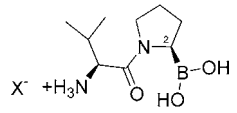
Abstract:

A practical synthesis of L-valyl-pyrrolidine-(2*R*)-boronic acid (1) is detailed. A previously disclosed synthesis of 1 (Snow, R.; Kelly, T. R.; Adams, J.; Coutts, S.; Perry, C. (Boehringer Ingelheim Pharmaceuticals, Inc.). WO 93/10127, 1993) was significantly improved by developing an efficient process for recycling the costly chiral auxiliary (+)- pinanediol.

Introduction

Peptides containing boronic acid analogues of amino acids have recently been investigated for their anticancer and serine protease inhibiting activities.[2] Evidence suggests that these types of compounds could also be useful as immunosuppressants.[3] The proline surrogate pyrrolidine-2-boronic acid imparts significant proteinase inhibitory activity towards bacteria when present as a C-terminus residue in certain peptides.[4] Our interest was focused on developing a practical synthesis of L-valyl-pyrrolidine-(2*R*)-boronic acid **1** (Figure 1). This compound is an immunostimulant and may serve as a potential adjuvant to standard chemotherapy.

Scale-up of the reported synthesis of **1**[1] was challenging due to the use of a number of hazardous reagents as well as inefficient and tedious purification steps. Furthermore, expensive (+)-pinanediol was utilized as an unrecovered resolving agent. At a bulk price of nearly $10 000 per kg, and without an efficient recycle in place, this material initially comprised >90% of the overall API cost. Because our production of **1** was projected to be less than 2 kg/yr due to microgram-dosing levels, it was unlikely the price of bulk pinanediol could be significantly reduced, as would normally be the case for typical manufacturing volumes. Additionally, the HCl salt **1a** was not suitable for further development because of its amorphous and deliquescent nature. An extensive search for a more suitable salt form eventually led to the selection of methanesulfonic acid (MSA) salt **1b**, which was highly crystalline and exhibited good physicochemical properties.



1a: X = Cl
1b: X = CH_3SO_3

Figure 1. **L-Valyl-pyrrolidine-(2*R*)-boronic acid.**

Results and Discussion

The previously disclosed synthesis[1] of the key intermediate **6a** was demonstrated on >100-g scale with several modifications as outlined in Scheme 1. THF was an acceptable substitute for diethyl ether as the solvent in the lithiation of **2**, and TMEDA was not required as an additive.

With appropriate precautions, we were able to safely handle *sec*-butyllithium on multiliter scale. Attempts to employ a less hazardous reagent for the α-metalation were unsuccessful.[5] The boronic acid **3** was condensed with (+)-pinanediol, and after removal of the Boc group under acidic conditions, **6a** was obtained as a crystalline solid with diastereomeric excess (de) of 92%. A single recrystallization from IPA produced **6a** with de >99%.[1b] Initial supplies of HCl salt **1a** were prepared using the previously reported synthesis as outlined in Scheme 2. EDAC-mediated coupling of **6a** with Boc-valine gave **8a,** which was subsequently deprotected using anhydrous HCl. The pinanediol auxiliary was then removed by an exchange process using phenylboronic acid. Salt-exchange to the more desirable MSA salt **1b** was accomplished by the addition of 1 equiv of MSA to a solution of **1a** in acetone−water, resulting in the crystallization of **1b**.

While preparing the initial supplies of the API, we recognized that to devise a safe, scalable, and cost-effective synthesis of the preferred salt form **1b**, we needed to address the following issues: (1) recycling of the (+)-pinanediol to reduce the overall cost of goods, (2) elimination of other costly or environmentally unfriendly reagents and solvents (e.g., EDAC and dichloromethane), and (3) development of a process for the direct isolation of **1b** without going through **1a**.

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(1) (a) Snow, R.; Kelly, T. R.; Adams, J.; Coutts, S.; Perry, C. (Boehringer Ingelheim Pharmaceuticals, Inc.). WO 93/10127, 1993. (b) Kelly, T. A.; Fuchs, V. U.; Perry, C. W.; Snow, R. J. *Tetrahedron* **1993**, 1009. (c) Martina, S.; Enkelmen, V.; Wegner, G.; Schluter, A. D. *Synthesis* **1991**, 613.

(2) (a) Matteson, D. S.; Sadhu, H. M.; Lienhard, G. E. *J. Am. Chem. Soc.* **1981**, 5241. (b) Kettner, C. A.; Shenvi, A. B. *J. Biol. Chem.* **1984**, 15106. (c) Kinder, K. H.; Katzenellenbogen, J. A. *J. Med. Chem.* **1985**, 1917.

(3) Flentke, G. R.; Munoz, E.; Huber, B. T.; Plaut, A. G.; Kettner, C. A.; Bachovchin, W. W. *Proc. Natl. Acad. Sci. U.S.A.* **1991**, 1556.

(4) Bachovchin, W. W.; Plaut, A. G.; Flentke, G. R.; Lynch, M.; Kettner, C. A. *J. Biol. Chem.* **1990**, 3738.

(5) (a) Beak, P.; Zajdel, W. J.; Reitz, D. B. *Chem. Rev.* **1984**, 471. (b) Meyers, A. I. *Aldrichimica Acta* **1985**, 59. (c) Comins, D. L.; Weglarz, M. A. *J. Org. Chem.* **1988**, 4437. Beak, P.; Lee, W. K. *J. Org. Chem.* **1990**, *55*, 8.

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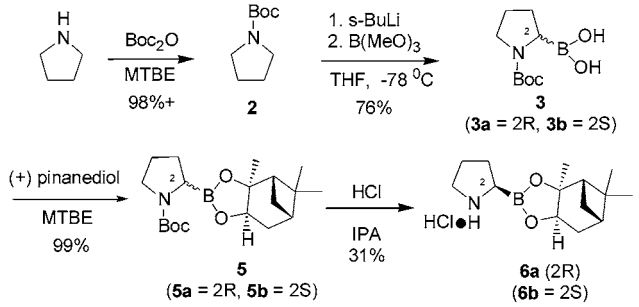
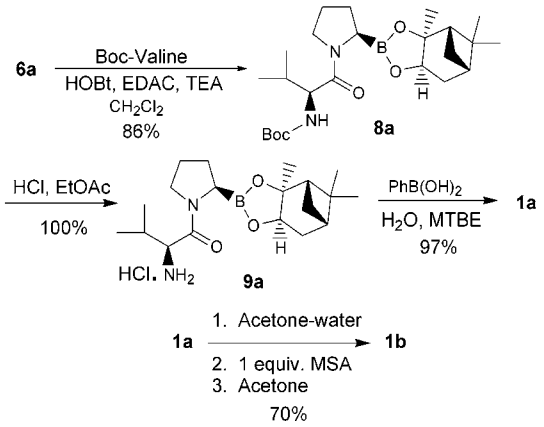
Scheme 1



Scheme 2

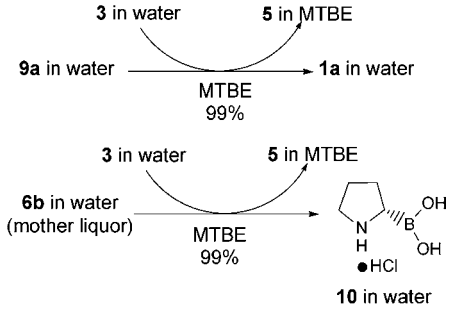


Recycling of (+)-Pinanediol. We investigated a variety of hydrolytic and oxidative methods for the removal of the pinanediol auxiliary[6] from **8a** and **9a**; however, none of these was as effective as the reported exchange method using phenylboronic acid in terms of quality and yield. All attempts to reclaim pinanediol from the resulting phenylboronic acid pinanediol ester also failed. To recycle the expensive auxiliary, we eventually envisioned that the exchange of (+)-pinanediol from **9a** would likely be successful with any fairly organic-soluble boronic acid and recognized that intermediate **3** (in racemic form) might be the perfect choice, for two important reasons. First, the use of **3** to effect the transesterification would eliminate the need for phenylboronic acid and, of greater importance, would in fact result in an efficient recycling of the pinanediol, delivering early intermediate **5** as the only byproduct. It was also recognized that **3** would likely be able to recapture much of the (+)-pinanediol lost with the mother liquor containing **6b** during the crystallization of **6a**. If successful, almost all of the pinanediol used could be recycled, dramatically reducing the cost of API.

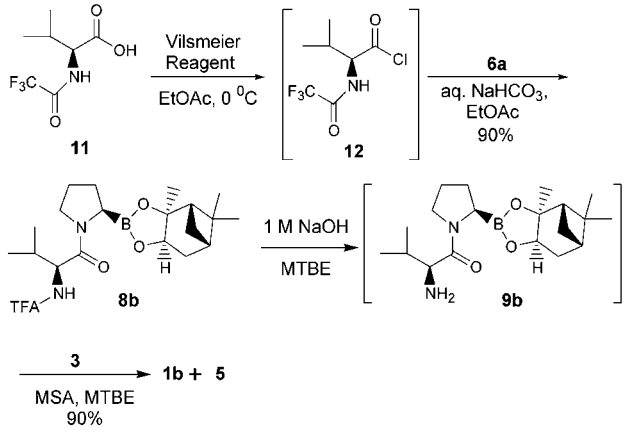
When examined experimentally, both exchange reactions proved to be completely successful. Treatment of **9a** with **3** in aqueous MTBE generated the desired **1a** and **5** in less than 1 h in near quantitative yield. Furthermore, reaction of **3** with the mother liquor containing **6b** rapidly produced **5** and prolineboronic acid **10** (Scheme 3). The efficiency of these exchanges is due to the fact that **5** is completely insoluble in water and completely partitions to the MTBE layer, driving the process to completion. Compound **5** produced in either exchange reaction required no further

(6) (a) Matteson, D. S.; Sadhu, K. M. *J. Am. Chem. Soc*. **1981**, 5241. (b) Matteson, D. S.; Majumdar, D. *J. Am. Chem. Soc*. **1980**, 7590.

Scheme 3. **Recycling of (+)-pinanediol**



Scheme 4



purification and was successfully used to repeat the sequence leading to **1b**. **1b** produced from recycled pinanediol showed no difference in quality from **1b** derived from fresh reagents, even after three iterations. Trace impurities carried through with the recycle are effectively purged during the crystallization of **6a**.

***N*-Trifluoroacetyl-valine Route to 1b.** Having developed a process for the recycling of (+)-pinanediol, we turned our efforts towards improving the coupling of **6a** with a suitable valine derivative and the subsequent isolation of **1b**. From previous experience, we had learned that simple dipeptide formation could be easily promoted, with minimal racemization, using the acid chloride of an *N*-TFA protected amino acid. If this coupling method succeeded here, removal of the TFA group would be easily telescoped with isolation of desired **1b**. Consequently, TFA-valine (**11**)[7] was treated with the Vilsmeier reagent (chloromethylene−dimethylammonium chloride) in ethyl acetate at 0 °C to generate **12**, which was added to a solution of **6a** in aqueous $NaHCO_3$ at 0 °C to produce **8b** in 90% yield and >98% purity after crystallization (Scheme 4).

HPLC analysis of the crude product indicated about 1.5% of the undesired val-(2*R*) epimer, while the crystallized material had less than 0.15%.

The coupled product **8b** was then hydrolyzed to **9b** with 1 N NaOH−MTBE at 50 °C. To the product-rich MTBE layer, **3** and methanesulfonic acid were each added. The transesterification was driven to completion due to crystallization of **1b** from MTBE as it formed. The desired **1b** was collected by filtration in 90% yield and 99.7% purity. The

(7) Curphey, T. J. *J. Org. Chem.* **1979**, *44*, 5 and references therein.

pinanediol ester **5** was recovered in 98% yield from the MTBE filtrate.

Conclusions

The new synthesis of **1b** using the TFA-valine route is a significant improvement over the previously disclosed synthesis.[1] The overall cost of goods was reduced to nearly one-tenth of the initial cost by efficient recycling of pinanediol. The overall route was made more environmentally friendly by eliminating phenylboronic acid, dichloromethane, EDAC, HOBt, diethyl ether, and hexane, which were key reagents and solvents used in the original synthesis. The cycle time was improved by elimination of unit operations such as chromatography and lyophilization.

Experimental Section

The TFA-valine route to **1b** and recycling of (+)-pinanediol are described below. Compounds **2**, **3**, **5**, **6**, **8a**, and **9a** were prepared according to the previously disclosed procedures with some modification as described above.

Solvents and reagents were obtained from commercial sources and used without further purification. Moisture content was determined by coulometric titration on a Mitsubishi CA-06 moisture meter on a weight/volume basis. NMR data was collected on a Bruker 400 MHz spectrometer at 300 MHz for proton and 75 MHz for carbon in $CDCl_3$.

TFA-valyl-pyrrolidine-(2*R*)-boronic Acid Pinanediol Ester (8b). TFA-valine (**11)** (65.1 g, 1 equiv) was dissolved in 650 mL of ethyl acetate. The solution was cooled to 0 °C, and Vilsmeier reagent (39 g, 1.3 equiv) was added. The cold reaction mixture was stirred for about 2 h. In another flask, amine pinanediol ester hydrochloride **6a**, (83 g, 0.29 mol) was combined with water (800 mL) and sodium bicarbonate (100 g, 4 equiv), and the resulting mixture was cooled to 0 °C. The acid chloride solution was then transferred to the aqueous solution, and the resulting biphasic mixture was stirred vigorously at 0 °C for 1.5 h. The organic layer was separated and washed with 300 mL of 0.1 M phosphoric acid, dried over sodium sulfate, and concentrated to give **8b** in 97% yield (125 g), in 98.7% purity (HPLC). The solid product was dissolved in acetone (375 mL, 3 mL/g) with warming to 45 °C, and water (375 mL, 3 mL/g) was added to the resulting solution with stirring. The resulting slurry was stirred at ambient temperature for 3 h, and the product was collected by filtration to give 116 g of **8b** in 90% yield and 99.7% purity (HPLC). Mp 134−136 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 0.8 (s, 3 H), 0.9 (d, 3 H), 1.0 (d, 3 H), 1.27 (s, 3 H), 1.3 (d, 1 H), 1.4 9s, 3 H), 1.7−2.0 (m, 5 H), 2.2−2.1 (m, 4 H), 2.3 (t, 1 H), 3.2 (t, 1 H), 3.5 (q, 1 H), 3.7 (t, 1 H), 4.2 (d, 1 H), 4.6 (q, 1 H), 7.2 (d, 1 H). ^{13}C NMR (400 MHz, $CDCl_3$): δ (ppm) 18.0, 19.8, 24.7, 26.9, 27.7, 27.9, 29.2, 32.3, 36.0, 38.7, 40.0, 45.1, 47.5, 51.6, 56.3, 78.2, 86.2, 116.0 (q), 156.7 (q), 167.4.

Valyl-pyrrolidine-(2*R*)-boronic Acid MSA Salt (1b). Compound **8b** (100 g, 0.225 mol) was dissolved in 1 L of MTBE. Sodium hydroxide (1 N, 450 mL, 2 equiv) was added, and the biphasic mixture was stirred vigorously and heated to 50 °C. After 1 h, HPLC analysis indicated no **8b** remained. The organic layer was reserved, and the aqueous layer was extracted with one 500 mL portion of MTBE. The organic layers were combined, and 700 mL of MTBE was distilled off at atmospheric pressure. *N*-Boc-pyrrolidine-2-boronic acid (**3**) (48.4 g, 1 equiv) was dissolved in 600 mL of MTBE and added to the previous solution. To this mixture was added dropwise methanesulfonic acid (14.6 mL, 1 equiv). The resulting clear solution was stirred at ambient temperature. After 15 min, a white crystalline precipitate began to form. The reaction mixture was filtered after 4 h, and 63 g of **1b** was isolated in 90% yield and 99.7% HPLC purity. The material showed ^{1}H, ^{13}C NMR, and MS data identical to those of previously reported material.[1]

Recycling of (+)-Pinanediol from the Resolution Step. Compound **3** (254 g, 1.18 mol) was suspended in 2 L of heptane and 1 L of water. Mother liquor from the resolution step containing 336 g of mostly **6b** and some **6a** (total 1 equiv) were added, and the reaction mixture was stirred vigorously at ambient temperature for 1 h. The heptane layer was removed from the biphasic mixture, dried over sodium sulfate, and concentrated to give 400 g (97%) of **5** as a clear oil, which could be converted to **6a** without further purification.

Recycling of (+)-Pinanediol from the Final Step. After the isolation of **1b**, the MTBE mother liquor was washed with 500 mL of water and evaporated to afford **5** (77 g, 98% yield), which could be converted to **6a** without further purification.

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