Synthesis of (+)-boronolide and (+)-deacetylboronolide using Pd-catalyzed carbonylation and lactonization

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Abstract: (+)-Boronolide and (+)-deacetylboronolide were synthesized using Pd-catalyzed CO insertion and lactonization as the key step. As to the ^{13}C NMR data of (+)-deacetylboronolide, the assignment at C-6 position should be revised.

Key words: natural products, lactones, asymmetric synthesis, total synthesis, carbonylation

(+)-Boronolide (**1**) was isolated *Tetradenia fruticosa* Benth and *Tetradenia barbera* (N. E. Br.) Codd, respectively.[1,2] The leaves of *Tetradenia barbera* was used as a folk medicine in Madagascar and south Africa.[3] (+)-Deacetylboronolide (**2**) was isolated by Luc Van Puyvelde and co-workers from *Tetradenia riparia* (Hochst) N. E. Br. (Labiatae).[4] Tetradenolide (**3**), which is a related compounds of **1** and **2**, was also isolated from the same plant.[5] As to the biological activity of boronolides, anti-malarial activity was reported (Figure 1).[3,4]

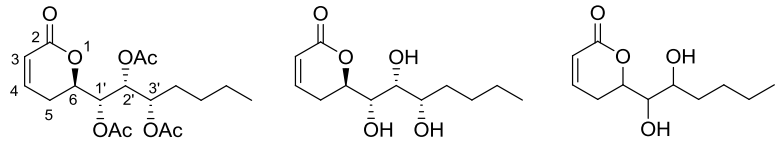
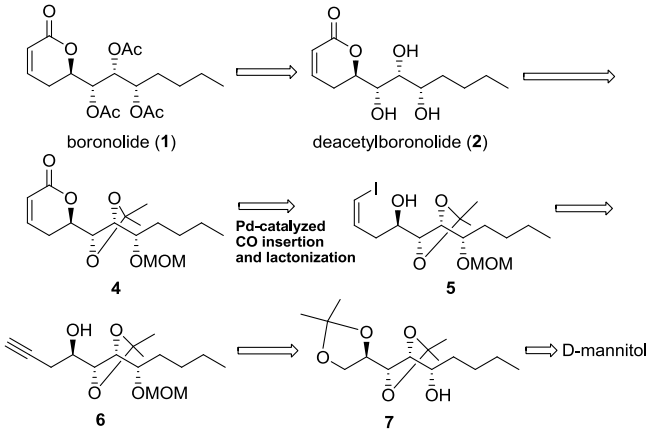


Figure 1. The structures of boronolide (**1**) and deacetylboronolide (**2**).

Due to significant biological activity as well as unique structure, boronolide and its related compounds attracted much attention of many synthetic chemists.[6a-m] In the typical examples of asymmetric syntheses of boronolide, Sharpless asymmetric dihydroxylation,[6b] asymmetric aldol reaction,[6d,6e] and chiral pool approach [6a,6d,6f] were used to construct four chiral centers. The typical example of preparation of α,β-unsaturated δ-lactone was done using elimination of selenoxide[6a,6b,6f] or ring-closing olefin metathesis.[6e] To synthesize α,β-unsaturated δ-lactones, Pd-catalyzed CO insertion and cyclization of (*Z*)-alkenyl halide is one of the most useful tools.[7] In this paper, we wish to describe concise synthesis of (+)-boronolide (**1**) and (+)-deacetylboronolide (**2**) using Pd-catalyzed

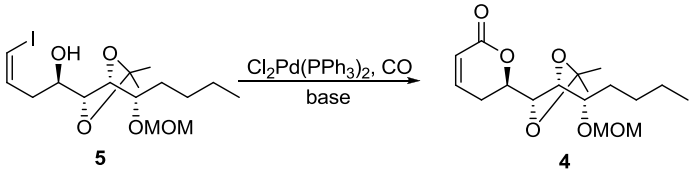
carbonylation. Scheme 1 outlines our synthetic strategy of (+)-boronolide (**1**) and (+)-deacetylboronolide (**2**). The key step is Pd-catalyzed CO insertion and cyclization to form δ-lactone **4**.[7,8] The cyclization precursor **5** can be prepared from terminal alkyne **6**. The alkyne **6** can be synthesized from **7** which could be prepared from D-mannitol using Singh's procedure.[6f]



Scheme 1. Synthetic strategy of boronolide (**1**) and deacetylboronolide (**2**).

Compound **7** was constructed as Singh and co-workers reported with slight modification.[6f] The secondary hydroxy group of **7** was protected as MOM ether to afford **8**. Selective deprotection of the terminal acetonide of **8** was achieved using copper (II) chloride hydrate to give diol **9**.[6f] Conversion of the diol **9** to the terminal epoxide **10** was attained via introducing triisopropylbenzenesulfonyl (Tris) group at primary hydroxy group followed by treatment with NaH. The epoxide **10** was treated with lithium acetylide, an ethylenediamine complex in DMSO afforded terminal acetylene **6**. Introduction of iodine at terminal acetylene was done by treatment with I_2 in the presence of NaOMe to afford **11**. Diimide reduction of **11** with $NsNHNH_2$ in the presence of Et_3N gave *Z*-alkenyl iodide **5**.[9] The geometry of *Z*-alkenyl iodide **5** was confirmed by coupling constant value (J = 8.0 Hz) of olefinic protons in ^{1}H NMR. The iodide **5** was subjected to Pd-catalyzed CO insertion and cyclization. As shown in Table 1, using K_2CO_3 as a base and hydrazine hydrate as an additive was effective in this reaction as Hoye and co-worker reported (Table 1).[10]

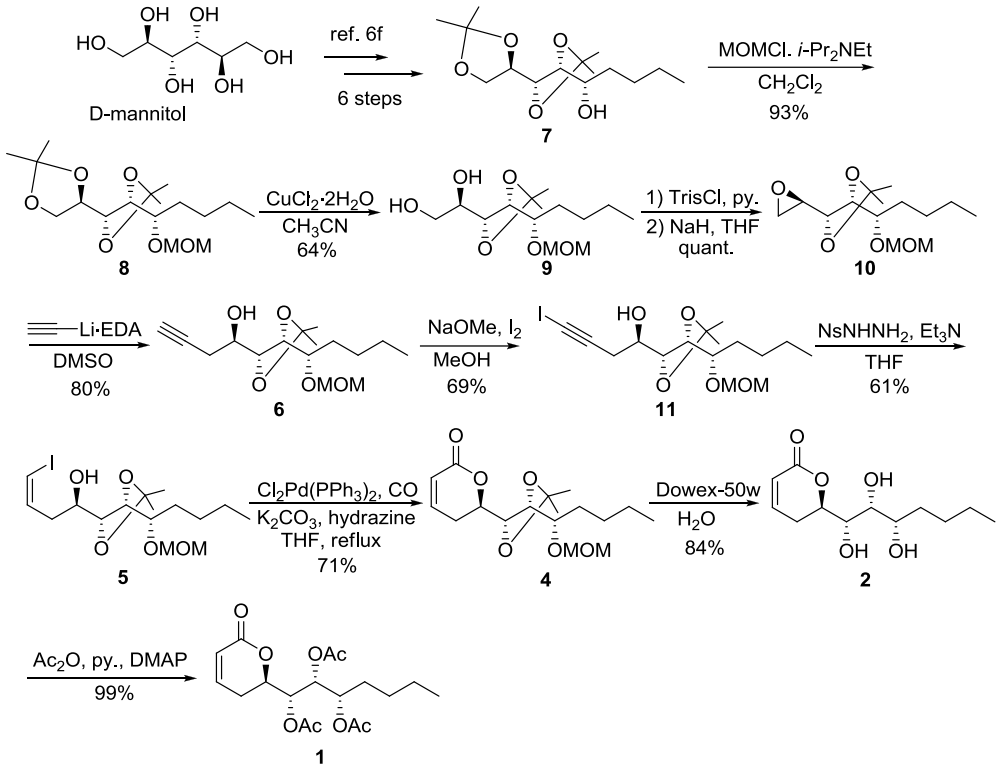
Table 1. Pd-catalyzed CO insertion and cyclization of vinyl iodide **5**.[a]



Entry	solvent	base	temperature	yield of **4** (%)
1	THF	Et_3N	reflux	17
2	DMF	Et_3N	70	20
3	THF	K_2CO_3[b]	reflux	71

[a]The reaction time was 24 h. [b]One drop of hydrazine was added.

Deprotection of both of the acetonide and MOM groups using Dowex 50w gave (+)-deacetylboronolide (**2**). The physicochemical data and spectral data except ^{13}C NMR of **2** were consistent with those of the reported values.[2] As to the ^{13}C NMR data at C-6 carbon, Rivett and co-worker who isolated **2** reported that this signal was overlapped with that of a solvent residual peak of $CDCl_3$ (76.74 ppm).[2] (+)-Deacetylboronolide (**2**) was synthesized by Trost and Singh independently and they also reported the existence of peak at 76.74 ppm.[6d,6f] However, when we measured HMQC NMR, we found that the chemical shift of C-6 carbon was 77.15 ppm and C-1' and C-2' carbons were overlapped at 74.24 ppm (shown in supporting information). Moreover we found that the peak at 76.74 ppm did not exist. The assignment at C-6, C-1' and C-2' carbons should be revised (Figure 2). We also measured ^{13}C NMR using CD_3CN as deuterated solvent, overlapped C-1' and C-2' signals separated and four oxymethine carbons were clearly observed (shown in supporting information). Next, treatment of **2** with Ac_2O in pyridine afforded (+)-boronolide (**1**) in good yield. The physical and spectral data of **1** and **2** were consistent with those of the reported values (Scheme 2).



Scheme 2. Syntheis of boronolide (**1**) and deacetylboronolide (**2**).

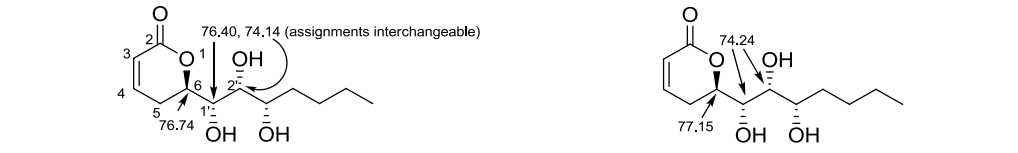


Figure 2. Assignment of the ^{13}C NMR at C-6 carbon of deacetylboronolide (**2**) by HMQC experiment.

In conclusion, we have accomplished the total synthesis of (+)-boronolide (**1**) and (+)-deacetylboronolide (**2**) using Pd-catalyzed carbonylation and lactonization strategy. This study will be adopted for the synthesis of natural products which contain an α,β-unsaturated lactone rings.

Acknowledgements

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