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A stereoselective synthesis of (+)-boronolide

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Abstract

A stereoselective synthesis of (+)-boronolide is described. The key steps involve a stereoselective reduction of an α-hydroxy ketone, allylation of an α-hydroxy aldehyde and a ring-closing olefin metathesis of a homoallylic alcohol derived acrylate ester utilizing Grubbs' catalyst.

The bark and branches of *Tetradenia fruticosa* and the leaves of *Tetradenia barberae* are traditional folk medicines in Madagascar and Southern Africa.[1] The active principle, boronolide (**1**), an α-pyrone derivative containing a polyacetoxylated side chain, has been isolated from these species since 1971.[1a,b] The deacetylated boronolide (**2**) and 1′,2′-dideacetylated boronolide (**3**) have also been isolated from *Iboza riparia*, a central-African species ubiquitously used in tribal medicine.[2] The root extract of these plants is traditionally used by the Zulu as an emetic agent and is known to be effective against malaria.[1c] The absolute configuration of (+)-boronolide was determined through X-ray crystallographic analysis and chemical degradation.[1b,3b]

The biological properties of boronolide and its deacetylated derivatives have fostered significant interest in their synthesis. Three total syntheses of boronolide have now been reported in the literature.[4–6] The first synthesis was carried out in racemic form utilizing acrolein dimer as the starting material.[4] The synthesis by Nagano and co-workers utilized the chiral centers of D-glucose.[5] The recent synthesis by Honda et al. utilized Sharpless dihydroxylation as the key steps, however, the synthesis lacks stereochemical control.[6] Herein we report an asymmetric synthesis of (+)-boronolide from diethyl D-tartrate. The key steps involve a stereoselective allylation of an α-hydroxy aldehyde, asymmetric reduction of an α-hydroxy ketone and ring-closing olefin metathesis of a homoallylic alcohol derived acrylate ester utilizing Grubbs' catalyst.[7]

A key structural feature of (+)-boronolide is the presence of a substituted α,β-unsaturated δ-lactone moiety. As shown in Fig. 1, we planned to construct this unsaturated lactone unit by a ring-closing olefin metathesis of the acrylate ester **4**. The syntheses of such α,β-unsaturated γ- and δ-lactones have been recently developed by both Nicolaou and us.[8] Stereoselective synthesis of the acrylate ester **4** would be achieved from the key starting material, 1-*O*-benzyl-2,3-*O*-isopropylidene-D-threitol derivative **5**.

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Preparation of **5** in multigram quantities was carried out from diethyl-D-tartrate utilizing the protocol described by Seebach et al.[9]

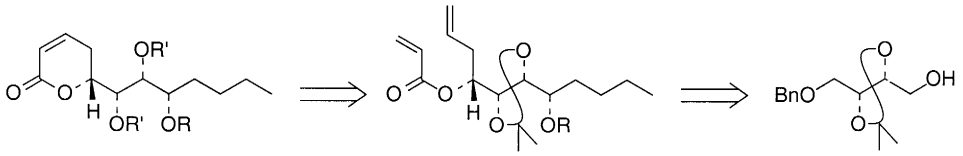
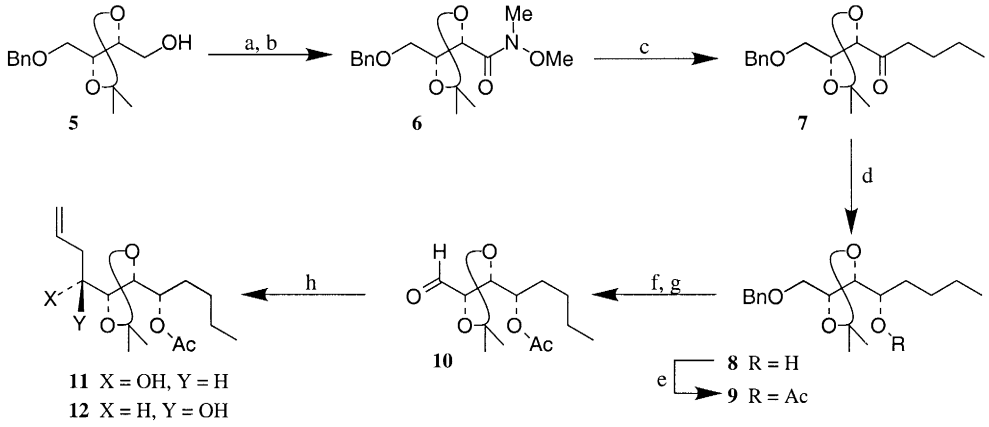


Fig. 1.

Isopropylidene derivative **5** was first converted to Weinreb amide **6** (Scheme 1). Thus, oxidation of alcohol **5** by Jones' reagent in aqueous acetone at 0°C afforded the corresponding carboxylic acid in 68% yield.[10] The resulting carboxylic acid was then converted into the Weinreb amide **6** by treatment with isobutyl chloroformate and *N*-methylpiperidine in a mixture (10:1) of CH_2Cl_2 and THF followed by subsequent treatment of the reaction mixture with *N*-methoxy-*N*-methylamine and *N*-methylpiperidine in CH_2Cl_2.[11] Weinreb amide **6** was isolated in 83% yield after silica gel chromatography. To install the butyl side chain of (+)-boronolide, Weinreb amide **6** was treated with butylmagnesium bromide in THF at −20°C to afford the ketone **7** in 96% yield. Reduction of the ketone **7** by L-selectride in THF at −78°C provided the (*S*)-alcohol **8** stereoselectively (12:1 by 500 MHz ^{1}H NMR and ^{13}C NMR analysis) in near quantitative yield.[12] Alternatively, Swern oxidation of **5** followed by the treatment of the resulting aldehyde with *n*BuLi in THF at −78°C, afforded the (*S*)-alcohol **8** and its epimer as a 1:1 mixture in 80% yield. Of particular interest, the reaction of the above aldehyde with *n*BuLi in the presence of $ZnBr_2$ has been shown to provide the corresponding (*R*)-carbinol selectively.[13] The (*S*)-alcohol **8** so obtained from the L-selectride reduction, was reacted with acetic anhydride in the presence of triethylamine and a catalytic amount of DMAP in CH_2Cl_2 to furnish the acetate derivative **9** in 98% yield.

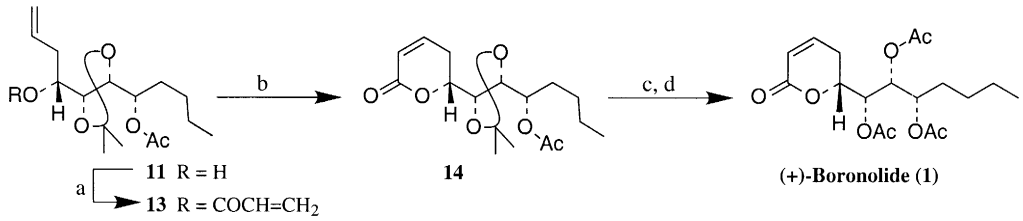


Scheme 1. (a) CrO_3, H_2SO_4, Me_2CO–H_2O, 0°C (68%); (b) Me_2CHCH_2OCOCl, *N*-methylpiperidine, CH_2Cl_2–THF (10:1); (MeO)NHMe·HCl, *N*-methylpiperidine, CH_2Cl_2 (83%); (c) $CH_3(CH_2)_3MgBr$, THF, −20°C (96%); (d) L-selectride, THF, −78°C (99%); (e) Ac_2O, Et_3N, DMAP (cat), CH_2Cl_2 (98%); (f) H_2, $Pd(OH)_2$ (cat), EtOAc–MeOH (4:1), (quant.); (g) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, −78°C; (h) allylmagnesium bromide, $ZnCl_2$, THF, −78°C (53% from **8**)

For conversion of **9** to aldehyde **10**, the benzyl protecting group was removed by a catalytic hydrogenation of **9** with Pearlman's catalyst ($Pd(OH)_2$) in a mixture of ethyl acetate and methanol (4:1) under a hydrogen filled balloon at 23°C for 12 h. Swern oxidation of the resulting alcohol provided the aldehyde

10. The elaboration of the α-pyrone unit with appropriate stereochemistry of (+)-boronolide then required the stereoselective allylation of **10**. Thus, attempted allylation of **10** with allyltrimethylsilane in CH_2Cl_2 in the presence of $TiCl_4$ at −78°C provided the homoallylic alcohol **11** selectively (selectivity ratio 4:1 by 500 MHz ^{1}H NMR) however, the reaction was sluggish and the conversion was poor (30–35%). The reaction with allyltributyltin in the presence of $SnCl_4$ at −78°C has also resulted (4:1 mixture of alcohol **11** and **12)** in comparable diastereoselectivities and conversion. The best result was obtained when the allylation of **10** was carried out with diallyl zinc at −78°C utilizing Kishi's protocol.[14] Thus, $ZnCl_2$ (7.2 equiv., 1 M solution in Et_2O, Aldrich) was added to allylmagnesium bromide (5 equiv., 1 M solution in Et_2O, Aldrich) in THF at 0°C and the mixture was stirred for 30 min, warmed to 23°C and stirred for an additional 1 h. The resulting diallyl zinc was cooled to −78°C and the aldehyde **10** in THF was added dropwise over a period of 3 min. The mixture was stirred at −78°C for 12 h and quenched with water followed by standard work up to furnish the homoallylic alcohol **11** stereoselectively (isomer ratio 5:1) in 53% yield (from **8**). The isomers were separated by silica gel chromatography to provide diastereomerically pure **11**.

The alcohol **11** was converted to its acrylate ester **13**, the RCM precursor. Acryloyl chloride followed by triethylamine were added dropwise to alcohol **11** in CH_2Cl_2 at 0°C. The mixture was warmed to 23°C for 30 min to furnish the ester **13** in 80% isolated yield. Olefin metathesis of **13** with commercially available Grubbs' catalyst (10 mol%) in the presence of $Ti(O^iPr)_4$ (30 mol%) in refluxing CH_2Cl_2 (0.007 M solution) for 12 h, afforded the α,β-unsaturated-δ-lactone **14** in 84% yield after silica gel chromatography (Scheme 2).[15] In the absence of $Ti(O^iPr)_4$, the reaction was substantially slower (50% conversion after 12 h).[8b] To complete the synthesis, the removal of the isopropylidene group was effected by exposure to Dowex 50 W-X8 (H^+) resin in H_2O at 70°C for 3 h. The resulting crude mixture was treated with acetic anhydride and triethylamine in CH_2Cl_2 in the presence of a catalytic amount of DMAP at 0°C for 30 min to furnish the synthetic (+)-boronolide **1**, $[\alpha]_D^{23}$ +25 *c* 0.2, EtOH; lit.[1b] $[\alpha]_D^{23}$ +28 *c* 0.08, EtOH. Spectral data (IR and 500 MHz ^{1}H NMR) for the synthetic boronolide is identical to that reported for the natural product.[1]



Scheme 2. (a) CH_2=CHCOCl, Et_3N, 0°C to 23°C, CH_2Cl_2 (80%); (b) $Cl_2(PCy_3)_2Ru$=CHPh (10 mol%), $Ti(O^iPr)_4$ (30 mol%), CH_2Cl_2, 40°C (84%); (c) Dowex 50 W-X8 (H^+), H_2O, 70°C; (d) Ac_2O, Et_3N, DMAP (cat), CH_2Cl_2, 0°C (quant.)

In conclusion, (+)-boronolide has been synthesized in a diastereoselective manner in 19% overall yield from the known isopropylidene derivative **5**.[9] The present synthetic route can easily be amenable to generate the other stereoisomers and structural variants of boronolide. Stereoselective reduction of an α-hydroxy ketone, allylation as well as the efficient construction of unsaturated lactones by olefin metathesis are particularly noteworthy.

Acknowledgements

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15. All new compounds gave satisfactory spectroscopic and analytical data. Compound **14**: $[\alpha]_D^{23}$ +27 *c* 0.15, $CHCl_3$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.90 (1H, ddd, *J*=9.8, 4.3, 4.3 Hz), 6.04 (1H, ddd, *J*=9.8, 1.8, 1.8 Hz), 5.06 (1H, ddd, *J*=8.7, 5.2, 5.0 Hz), 4.42 (1H, ddd, *J*=7.8, 7.2, 7.2 Hz), 4.17 (1H, dd, *J*=6.4, 3.4 Hz), 3.98 (1H, dd, *J*=6.8, 6.7 Hz), 2.12 (3H, s), 2.53 (2H, m), 1.62–1.76 (2H, m), 1.44 (3H, s), 1.40 (3H, s), 1.34–1.38 (4H, m), 0.90 (3H, t, *J*=6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 162.7, 144.5, 121.5, 110.6, 80.0, 78.0, 77.3, 72.5, 30.8, 27.6 (2C), 26.9, 26.0, 22.5, 21.0, 14.0; IR (neat) 2923, 2853, 1738, 1461, 1375, 1236 cm^{-1}.