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Stereocontrolled Synthesis of (+)-Boronolide

Barry M. Trost* and Vince S. C. Yeh

Department of Chemistry, Stanford University, Stanford, California 94305-5080

bmtrost@stanford.edu

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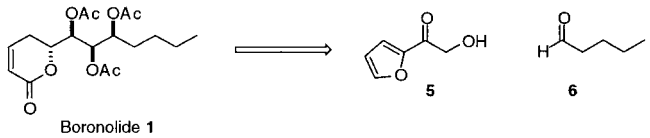
ABSTRACT

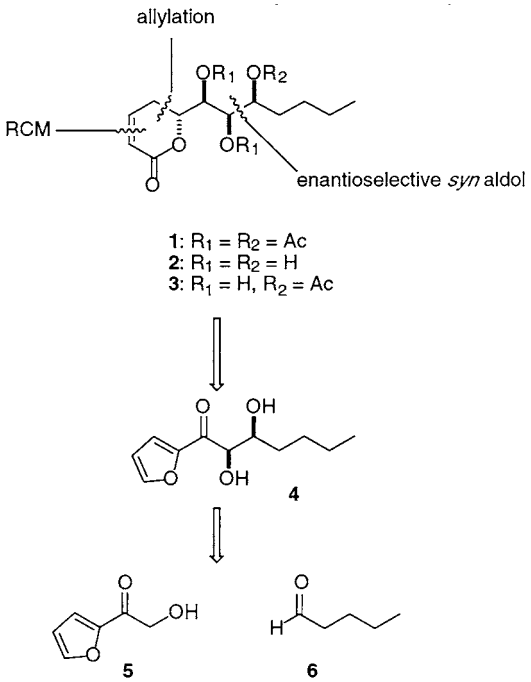


Boronolide was synthesized stereoselectively from hydroxyacetylfuran 5 and valeraldehyde 6 using a novel dizinc aldol catalyst. Ring closing metathesis provides the lactone ring. The synthesis requires 12 steps and proceeds in 26% overall yield.

Polyhydroxylated natural products are abundant in nature. Fascinated by their broad range of biological activities and structural diversity which range from simple carbohydrates to complex alkaloids and polyketides, synthetic chemists continue to pursue their total syntheses and the development of new methodologies.[1] The most direct and atom economical method of assembling polyol functionalities is the aldol reaction.[2] Catalytic enantioselective Mukaiyama type aldol reactions have been the focus of various methodology developments.[3] Despite their tremendous success in obtaining high yields and enantioselectivity, the preconversion of the ketone nucleophile to a more reactive species such as a silyl enol ether is unavoidable in all these catalytic asymmetric aldol reactions. We have recently reported the use of a novel dizinc catalyst in direct aldol reactions[4] which allows an unmodified hydroxy ketone to add to an aldehyde to give a *syn*-diol product in high enantioselectivity and good diastereoselectivity and yield (Scheme 2).[4b] Similar advances have been reported by Shibasaki et al. and List et al. which utilize chiral binol based catalysts or proline to perform direct aldol reactions.[5]

In this paper, we describe an efficient stereoselective synthesis of (+)-boronolide **1** utilizing our aldol methodology. Boronolide is a C12 lactone with a polyhydroxylated side chain isolated from the bark and branches of *Tetradenia*

Scheme 1. Retrosynthetic Analysis



(1) Recent reviews of polyol natural product synthesis, see: (a) Rychnovsky, S. D. *Chem. Rev.* **1995**, *95*, 2012. (b) Schneider, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 1375. See also: Enders, D.; Ince, S. J.; Bonnekessel, M.; Runsink, I.; Raabe, G. *Synlett* **2002**, 962.

(2) For reviews on asymmetric aldol bond constructions using chiral enolates, see: (a) Evans, D. A. *Asymmetric Synth.* **1984**, *3*, 2. (b) Heathcock, C. H. *Asymmetric Synth.* **1984**, *3*, 111. (c) Heathcock, C. H.; Kim, B. M.; Williams, S. F.; Masamune, S.; Paterson, I.; Gennari, C. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford 1991; Vol. 2. (c) Franklin, A. S.; Paterson, I. *Contemp. Org. Synth.* **1994**, *1*, 317.

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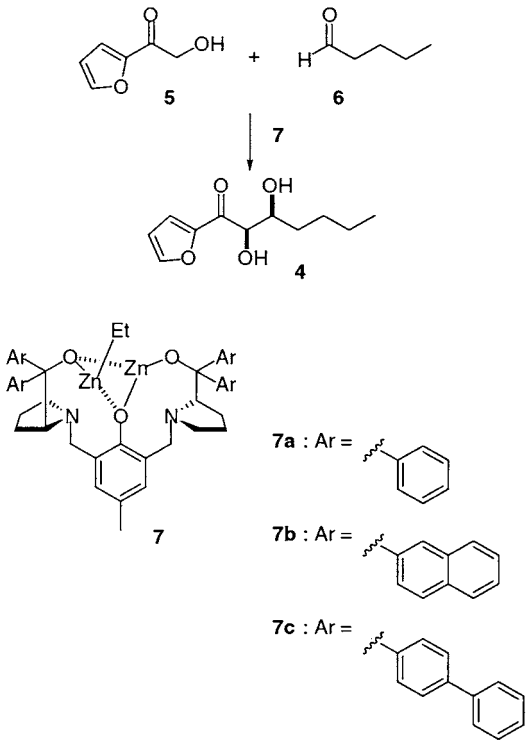
Scheme 2. Asymmetric Aldol



fruticosa and from the leaves of *Tetradenia barberae*[6] which have been used as local folk medicine in Madagasgar and southern Africa.[7] Deacetylated **2** and dideacetylated boronolide **3** have been obtained from *Tetradenia riparia*, a central Africa species typically employed by the Zulu as an emetic, while an infusion of the leaf has been reported to be effective against malaria.[7,8] Previous asymmetric syntheses of **1** were mainly based on chiral pool starting material such as tartrate[9] or glucose,[10] or by Sharpless dihydroxylation.[11] Our synthetic plan relies on the direct aldol reaction between hydroxy acetylfuran **5** and valeraldehyde **6** to give *syn*-diol **4** which contains 8 of the 12 carbons of the natural product (Scheme 1). Appropriate functional group manipulations followed by allylation will install the last stereogenic center, and ring closing metathesis of an acrylic ester followed by global deprotection should afford deacylboronolide **2**, which can be easily converted to boronolide **1** by acylation.

The synthesis began with a detailed study of the key aldol reaction, and the results are summarized in Scheme 2 and Table 1. The reaction required only 1.1 equiv of ketone nucleophile **5** and was complete within 12 h (entry 1 vs 2). In all cases, the enantioselectivity of the major *syn* diol product was above 90% and the % ee of the *anti* product was in the mid-80s. The reported yields were the isolated yield of the respective major *syn* and the minor *anti* product (vide infra for discussion of the minor product). Employment of 5 mol % of catalyst ensured completion of the reaction (entry 2 vs 3). Ligand **7c** gave a superior performance in terms of diastereoselectivity.[4e] The reaction was scaled up to 16 mmol of aldehyde to give multigram quantities of the desired product with consistent dr and ee from run to run (entry 6).

Table 1. Optimization of the Aldol Reaction[a]

entry	ligand	isolated yields *syn*/*anti*	dr[b]	ee *syn*/*anti*[c]
1[d]	**7a**	56/14	4.3:1	97/84
2	**7a**	78/16	4.6:1	97/84
3	**7a**[e]	58/13	3.5:1	95/81
4	**7b**	77/15	4:1	93/83
5	**7c**	78/12	6:1	97/86
6[f]	**7a**	76/17	4.2:1	96/83

[a] All reactions were carried out on 2 mmol scale using 5 mol % catalyst, 1.1 equiv of ketone and 100 mg of 4 Å molecular sieves in 0.33 M of THF solution at −35 °C for 12 h unless noted otherwise. [b] Determined by NMR of the crude reaction isolate. [c] Determined by chiral HPLC using Chirapak AD column; see Experimental Section for details. [d] This reaction was run for 4 h. [e] 2.5 mol % catalyst was used. [f] This reaction was done on a 16 mmol scale of valeraldehyde **6**.

With substantial amounts of **4** in hand, we continued the synthesis of **1** by protection of the diol as its corresponding acetonide **8** (Scheme 3). The reduction of ketone **8** under Felkin−Anh control using L-selectride proceeded with excellent diastereoselectivity (98:2).[12] The secondary alcohol was then protected as a TBS silyl ether **9**. The furan was

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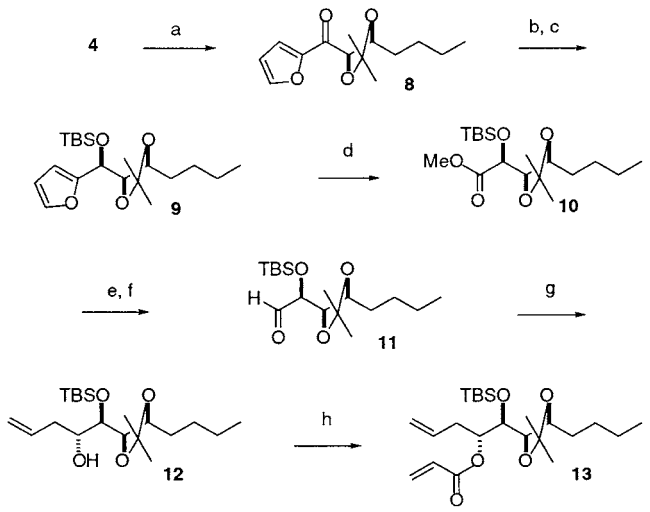
Scheme 3. Propagation of Chirality[a]



[a] (a) DMP, Amberlyst 15, CH_2Cl_2, rt, 98%; (b) L-selectride, THF, −100 °C; H_2O_2, NaOH, 89%, dr 98:2; (c) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 98%; (d) $RuCl_3$ (cat.), $NaIO_4$, CCl_4, CH_3CN, H_2O; CH_2N_2, Et_2O, 70%; (e) $LiBH_4$, Et_2O, MeOH, 0 °C, 98%; (f) Dess−Martin periodinane, CH_2Cl_2, rt, 100%; (g) (+)-$(Ipc)_2$B-allyl, Et_2O, 100 °C; H_2O_2, NaOH, 85%, dr 8:1; (h) acryloyl chloride, *i*-Pr_2NEt, CH_2Cl_2, 0 °C, 89%.

oxidatively cleaved[13] using catalytic amount of $RuCl_3$ and $NaIO_4$ as the stoichiometric oxidant to give the corresponding acid which was directly converted to the methyl ester **10** by treatment of the acid with ethereal diazomethane. Ester **10** was converted via a two-step procedure to give aldehyde **11** quantitatively without epimerization of the α-stereogenic center. Diastereoselective allylation of the aldehyde **11** was more challenging than we anticipated. Using achiral allylmetal reagents, we were met with poor diastereoselectivities: allylation using allyltributyltin and $BF_3{\cdot}Et_2O$[14] in CH_2Cl_2 at −78 °C gave dr of 2:1; reaction with diallyl zinc[15] in THF at −78 °C gave dr of 1:1. Aldehyde **11** decomposed under standard conditions for allylindium (allyl bromide, In powder, THF/H_2O, rt).[16] Obviously, the allylation did not occur under simple Felkin−Anh control, and the influence of the *β*-stereogenic center may also influence the diastereoselectivity. The desired homoallylic alcohol **12** was finally obtained in 85% by using Brown's chiral allylborane[17] which gave a dr of 8:1. The diastereomers could be separated cleanly by silica gel chromatography, and **12** was then treated with acryloyl chloride and DIPEA to give the corresponding acryloyl ester **13** in 89%.

The formation of the α,*β* unsaturated lactone was achieved by ring closing metathesis.[18] Thus, using 2 mol % of Grubbs'

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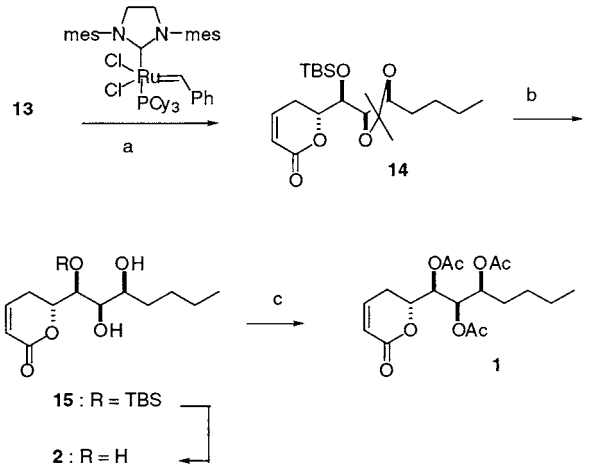
Scheme 4. Endgane[a]



[a] (a) 2 mol % Grubbs' cat., CH_2Cl_2, 40 °C, 92%; (b) aq HF, CH_3CN, 65% **2** and 30% **15**; (c) Ac_2O, DMAP, *i*-Pr_2NEt, CH_2Cl_2, 0 °C, 86%.

N-heterocyclic carbene-containing catalyst[19] in CH_2Cl_2 at 40 °C, lactone **14** was obtained in 92% (Scheme 4). In contrast to the earlier synthesis of Ghosh,[9] the reaction proceeded well without the addition of Ti(O*i*-Pr)$_4$ using the second generation Grubbs' catalyst. Global deprotection of **14** using aqueous HF in CH_3CN occurred slowly. Deacetyboronolide **2** was recovered in 65% after stirring 5 days at room temperature. Silyl ether **15** was also recovered in 30% yield and could be recycled under the same deprotection conditions to give **2,** $[\alpha]^{25}_D$ +75.9 (*c* 2.87, EtOH); lit. $[\alpha]^{22}_D$ +56 (*c* 0.07, EtOH)[6b] in near quantitative yield after 2 days. The spectroscopic data of **2** (^{1}H NMR, ^{13}C NMR, IR) were in

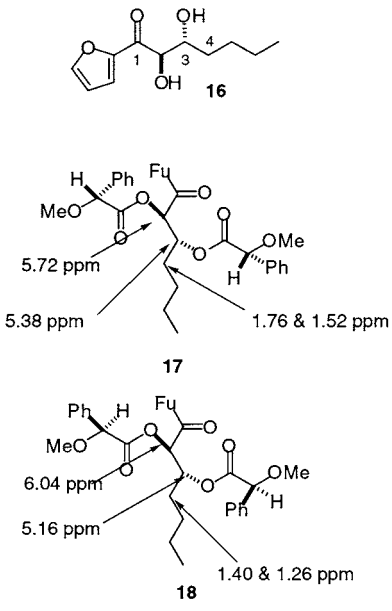


Figure 1. Determination of absolute configuration of **16**.

excellent agreement with the literature.[6b] Finally, peracylation of **2** with acetic anhydride gave (+)-boronolide **1**, $[\alpha]^{25}_{D}$ +29.5 (*c* 1.56, EtOH); lit.[6b] $[\alpha]^{26}_{D}$ +28 (*c* 0.08, EtOH). The spectral data (^{1}H NMR, ^{13}C NMR, IR) were identical to that reported for the natural product itself[6b] as well as a synthetic sample.[9]

The diastereoselectivity of the aldol reaction can derive from either (a) competitive addition to the enantiotopic faces of the enolate and one face of the aldehyde, (b) competitive addition to the enantiotopic faces of the aldehyde and one face of the enolate, (c) indiscriminate addition to both partners, or d) formation of both *E* and *Z* enolates. To determine the source of the diastereoselectivity, the absolute configuration of the minor diastereomer **16** was determined by the *O*-methyl mandelate method[20] and is shown in Figure 1. Thus, the minor diastereomer has the same absolute configuration at C-2 and the epimeric one at C-3 compared to the major diastereomer.

On the basis of our proposed model[4b] as depicted in Figure 2, the enolization of the ketone nucleophile is largely *Z* and it forms a bidentate ligand bridging the two zincs. Coordination of the aldehyde as shown in **19** then delivers the major *syn* product. When the coordination of the aldehyde is as in **20**, then the *anti* product is formed. In line with our previous results,[4e] ligand **7c** exerts greater facial selectivity in the binding of the aldehyde which in this case translates to an increase in the dr of the products.

In summary, a short and efficient stereoselective synthesis of the polyhydroxylated natural product (+)-boronolide **1** has been achieved utilizing our *syn*-selective aldol catalyst. The synthesis consists of 12 steps starting from commercially available valeraldehyde in 24% overall yield. The catalyst exhibits high enantiotopic facial selectivity with respect to the *Z*-enolate and the degree of such selectivity with respect to the aldehyde largely determines the diastereoselectivity.

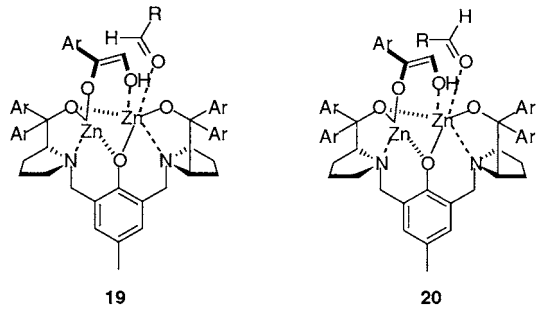


Figure 2. Proposed transition states.

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Supporting Information Available: Experimental procedures and spectroscopic characterization (IR, ^{1}H, ^{13}C NMR, HRMS) of all key compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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