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Enantio- and Diastereocontrolled Total Synthesis of (+)-Boronolide†

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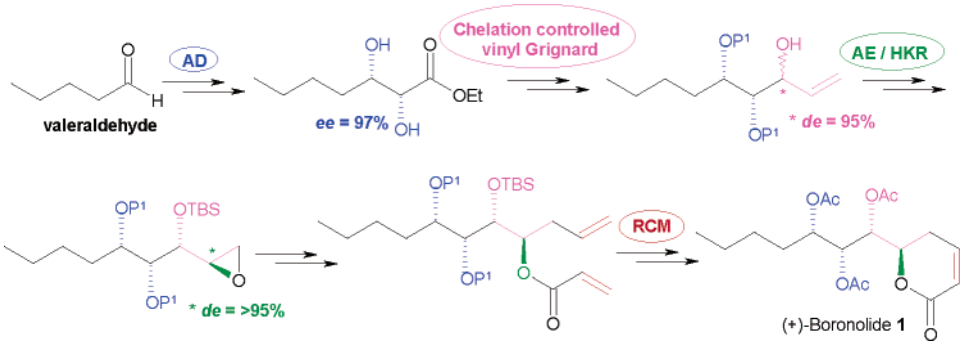
Received February 23, 2006



An efficient stereoselective total synthesis of (+)-boronolide from valeraldehyde is described. The key steps include a Sharpless asymmetric hydroxylation, a chelation-controlled vinyl Grignard reaction followed by a Sharpless asymmetric epoxidation, hydrolytic kinetic resolution, and a ring-closing metathesis.

Introduction

Many natural products with different biological activities, such as insect growth inhibition, antitumor, antibacterial, antifungal, or immunosuppressive properties, possess an α,β-unsaturated δ-lactone moiety as an important structural feature. α,β-Unsaturated δ-lactone[1] functionality is presumed to be responsible for biological activities as a result of its ability to act as a Michael acceptor, enabling these molecules to bind to a target enzyme. The pyrone units are widely distributed in all parts of plants (Lamiaceae, Piperaceae, Lauraceae, and Annonaceae families) including leaves, stems, flowers, and fruits. α-Pyrones possessing polyhydroxy or polyacetoxy side chains have attracted much attention from synthetic and medicinal chemists as a result of their broad range of biological activities. Examples of such compounds include (+)-boronolide **1** and its deacetylated **1a** and dideacetylated derivative **1b** (Figure 1). Boronolide **1** is an α,β-unsaturated C-12 lactone isolated from the leaves and branches of *Tetradenia fruticosa*[2] and from the leaves of *Tetradenia barberae*,[3] which have been used as a local folk medicine in Madagascar and South Africa.[4] Deacetylated **1a** and dideacetylated boronolide **1b** have been obtained from *Tetradenia riparia*,[5] a Central African species typically employed by the Zulu as an emetic, which is an infusion of the leaf that has also been reported to be effective against malaria. The relative stereochemistry of **1** was determined by X-ray analysis.[6] The *R* configuration at the C-6 position was proposed

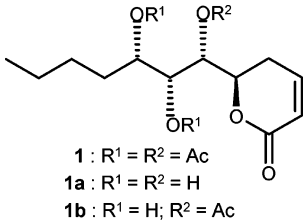


FIGURE 1. Structure of (+)-boronolide (**1**).

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† Dedicated to Professor S. Chandrasekaran on the occasion of his 60th birthday and in recognition of his seminal contributions to so many aspects of organic chemistry.

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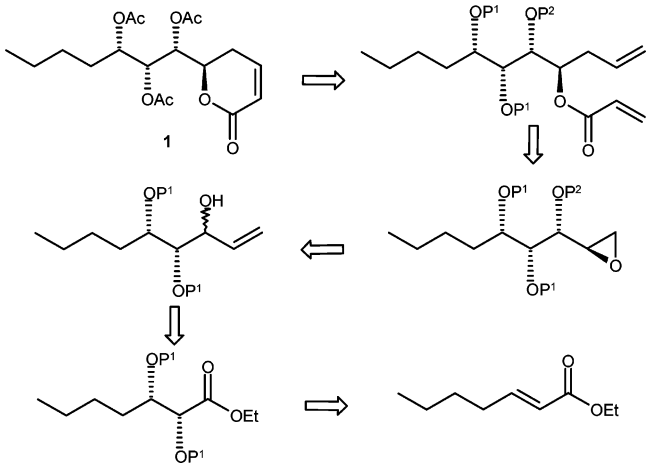
10.1021/jo0603781 CCC: $33.50
Published on Web 04/18/2006

by application of Hudson's lactone rule to the molecular rotation. Later, the stereochemistry at the C-6 position was confirmed by chemical degradation. The first synthesis of **1** was reported from an acrolein derivative[7a] in racemic form. Most of the enantioselective syntheses known for boronolide derive the asymmetry from chiral pool starting materials such as glucose,[7b] mannitol,[7e,i] tartaric acid,[7d,j] D-glucono-δ-lactone[7j] and L-erythrulose,[7f] and so on. However, synthetic approaches involving an achiral substrate as starting material are rather scarce.[7c,h,k−l] As a part of our research program aimed at developing an enantioselective synthesis of naturally occurring lactones[8] and amino alcohols,[9] we now report a detailed description of our study toward the enantio- and diastereocontrolled synthesis of (+)-boronolide. The key steps include a Sharpless asymmetric dihydroxylation, a chelation-controlled Grignard reaction, a hydrolytic kinetic resolution (HKR), a Sharpless asymmetric epoxidation, and a ring-closing metathesis.

SCHEME 1. Retrosynthetic Analysis for (+)-Boronolide



Results and Discussion

Our synthetic strategy for the synthesis of boronolide **1** is outlined in Scheme 1. We envisioned that the lactone ring could be constructed by the ring-closing metathesis of an acrylate ester, which in turn would be obtained from an epoxide. The enantiopure epoxide could be prepared either by the Sharpless asymmetric epoxidation of an allylic alcohol or by the HKR of a racemic epoxide. The chelation-controlled vinylation of an aldehyde would install the third stereogenic center, while the initial two stereocenters could easily be established by the Sharpless asymmetric dihydroxylation of an olefin.

The synthesis of boronolide started from commercially available valeraldehyde **2**, as illustrated in Scheme 2. Thus, valeraldehyde **2** was subjected to Horner−Emmons olefination with triethyl phosphonoacetate to furnish the (*E*)-α,β-unsaturated ester **3** in 89% yield. The ester **3** was treated with osmium tetroxide and potassium ferricyanide as co-oxidant in the presence of the $(DHQ)_2PHAL$ ligand under asymmetric dihydroxylation (AD) conditions[10] to give the diol (2*R*,3*S*)-**4a** in 96% yield with 97% ee.[7k,l,11] Treatment of diol **4a** with 2,2-dimethoxypropane in the presence of *p*-TSA gave the acetonide ester (2*R*,3*S*)-**4b**, which on reduction with DIBAL-H furnished the alcohol (2*S*,3*S*)-**5b** in 91% yield. The resulting alcohol **5b** was subjected to oxidation under Swern conditions[12] to give the aldehyde **6b** in excellent yield. To establish the third stereogenic center with the required stereochemistry, it was thought worthwhile to examine stereoselective vinylation. Thus, treatment of aldehyde **6b** with vinylmagnesium bromide in THF in the presence of $MgBr_2 \cdot Et_2O$[13] at −78 °C furnished the allylic alcohol **7b** in 92% yield with moderate diastereomeric selectivity (dr = 3:1; syn/anti) as an inseparable mixture of diastereomers.

Even after protection of the hydroxy group of **7b** with different protecting groups such as TBS, MOM, Ac, and PMB, we were unable to separate the diastereomers by flash chromatography. To determine the stereochemistry of the newly generated third stereocenter, compound **7b** was subjected to acid treatment, followed by 1,3-dihydroxy protection as the benzylidene derivative. The required major isomer **8** could easily be separated by silica gel column chromatography (Scheme 3). The newly generated stereocenter in **7b** was assigned syn configuration, which was based on the NOE studies, as strong NOE correlations were observed between the 1,3-diaxial protons of the cyclic derivative **8**. (See the Supporting Information).

Subsequently, several attempts were made to achieve better selectivity with the use of additives such as $ZnCl_2$ or $TiCl_4$ and employing the addition of vinyllithium as an alkylating reagent with different solvent systems (CH_2Cl_2 or diethyl ether). However, the required syn selectivity could not be improved. To explore the possibility of achieving a better syn selectivity in the vinylation reaction, it was thought worthwhile to change the protecting group. We assumed that the chelation between MOM and aldehyde would be more effective as compared to other protecting groups. Thus, the diol **4a** was treated with MOMCl in the presence of diisopropylethylamine to afford

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(11) For the measurement of enantiomeric excess, the diol **4a** was converted into its dibenzoate **4d**. The enantiomeric purity of the dibenzoate **4d** was estimated to be >96% by chiral HPLC analysis (Chiral Cel OD, petroleum ether/*i*-PrOH (98:2) 1 mL/min, 240 mm.

(12) For reviews of the Swern oxidation, see: (a) Tidwell, T. T. *Synthesis* **1990**, 857−870. (b) Tidwell, T. T. *Org. React.* **1990**, *39*, 297−572.

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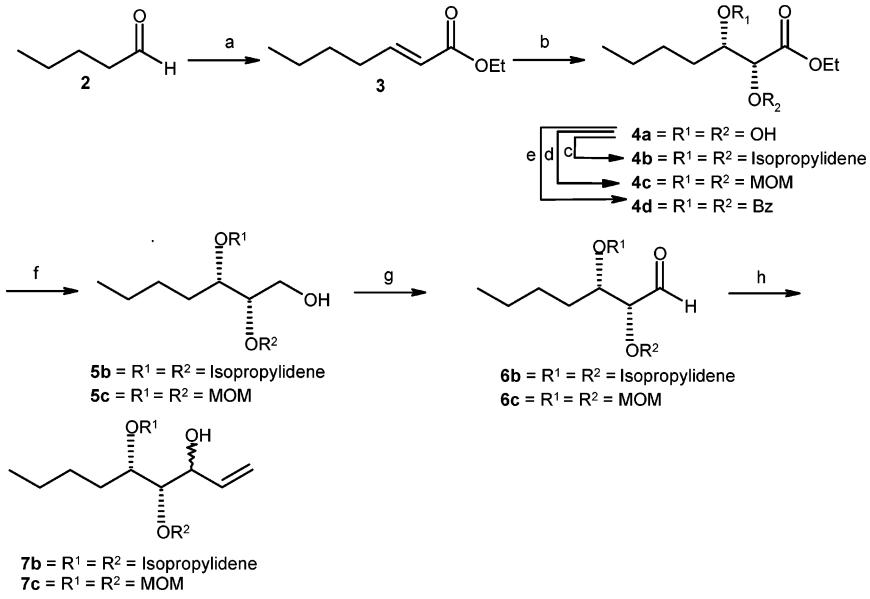
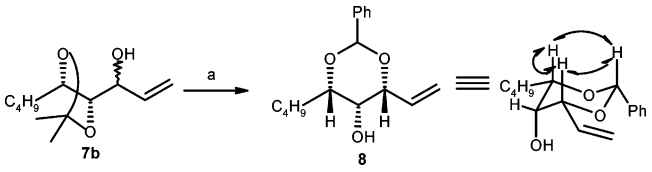
SCHEME 2 [a]



[a] Reagents and conditions: (a) $(EtO)_2P(O)CH_2CO_2Et$, LiBr, Et_3N, THF, rt, overnight, 89%; (b) $(DHQ)_2PHAL$, K_2CO_3, $K_3Fe(CN)_6$, $MeSO_2NH_2$, *t*-BuOH/H_2O (1:1), 0.1 M OsO_4 (0.4 mol %), 0 °C, 24 h, 96%; (c) *p*-TSA, 2,2-DMP, CH_2Cl_2, 95%; (d) MOM chloride, DIPEA, CH_2Cl_2, 0 °C to room temperature, overnight, 91%; (e) BzCl, pyridine, 0 °C to room temperature, overnight, 90%; (f) DIBAL-H, CH_2Cl_2, 0 °C to room temperature, 2 h (91% for **5b**, 89% for **5c**); (g) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C to −60 °C, 95%. (h) CH_2═$CHMgBr$, $MgBr_2{\cdot}Et_2O$, THF or CH_2Cl_2, −78 °C, 6 h, (92% for **7b**, 90% for **7c**).

SCHEME 3 [a]



[a] Reagents and conditions: (a) (i) HCl, MeOH, rt, 12 h; (ii) $PhCH(OMe)_2$, *p*-TSA, CH_2Cl_2, rt, overnight.

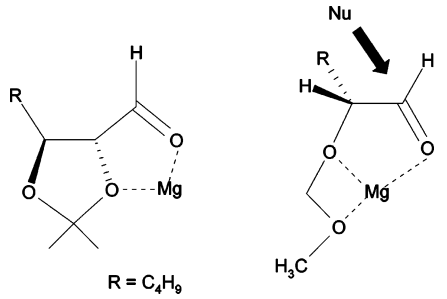


FIGURE 2. Chelation-controlled transition models.

compound (2*R*,3*S*)-**4c** in excellent yield (Scheme 2). A subsequent reduction of the ester with DIBAL-H, followed by Swern oxidation, gave the aldehyde **6c**, which was used immediately in the next reaction without any further purification. Thus, when **6c** was subjected to chelation-controlled vinylation in CH_2Cl_2 at −78 °C with $MgBr_2{\cdot}Et_2O$,[13] it furnished the allylic alcohol **7c** in 90% yield with an excellent diastereoselectivity (dr = 19:1; syn/anti), as determined by ^1H and ^{13}C NMR spectral analysis. The formation of the major syn diastereomer can be explained by the chelated five-membered transition state, as depicted in Figure 2. The improvement in the syn selectivity in the case of **7c** (19:1) as compared to **7b** (3:1) could probably be attributed to the extra chelation by the MOM protecting group with magnesium, as illustrated in Figure 2. After protection of the hydroxyl group in compound **7c** with TBSCl, the required syn diastereomer (3*R*,4*R*,5*S*)-**10** could easily be separated by flash chromatography. To generate the final stereogenic center with an appropriate functionality, a Sharpless asymmetric epoxidation was employed in the next step (Scheme 4). Thus, treatment of allylic alcohol **7c** with titanium tetraisopropoxide and *tert*-butyl hydroperoxide in the presence of (+)-DIPT for 4 days under Sharpless asymmetric epoxidation conditions[14] provided the epoxide **9** albeit in low yield and poor diastereoselectivity. The extra chelation of titanium-tetraisopropoxide with MOM might be the possible cause for retarding the rate of the epoxidation reaction. As a next alternative, it was thought worthwhile to prepare first the diol **11** by the Sharpless asymmetric dihydroxylation of olefin **10**, which could further be converted easily into the required epoxide **12a** by standard transformations. Accordingly, the olefin **10** was treated with osmium tetroxide and potassium ferricyanide as co-oxidant in the presence of the $(DHQ)_2AQN$ ligand under AD conditions[10] to give the diol **11** in 91% yield with moderate diastereomeric selectivity (dr = 5:1; anti/syn) as an inseparable mixture of diastereomers. In another attempt to improve the selectivity and to examine the stereochemical outcome of the epoxidation reaction, we carried out an epoxidation of olefin **10** using *m*-CPBA in various solvent systems in the presence of Na_2HPO_4. The addition of phosphate could be effective in avoiding the unfavorable acid-catalyzed ring opening of epoxide once formed.[15] Thus, compound **10** was treated with *m*-CPBA/Na_2HPO_4 in CH_2Cl_2 to afford the epoxide in 92% yield (dr = 4:1; anti/syn) as a nonseparable mixture of diastereomers. Even with the use of different solvent systems, we could not improve the selectiv-

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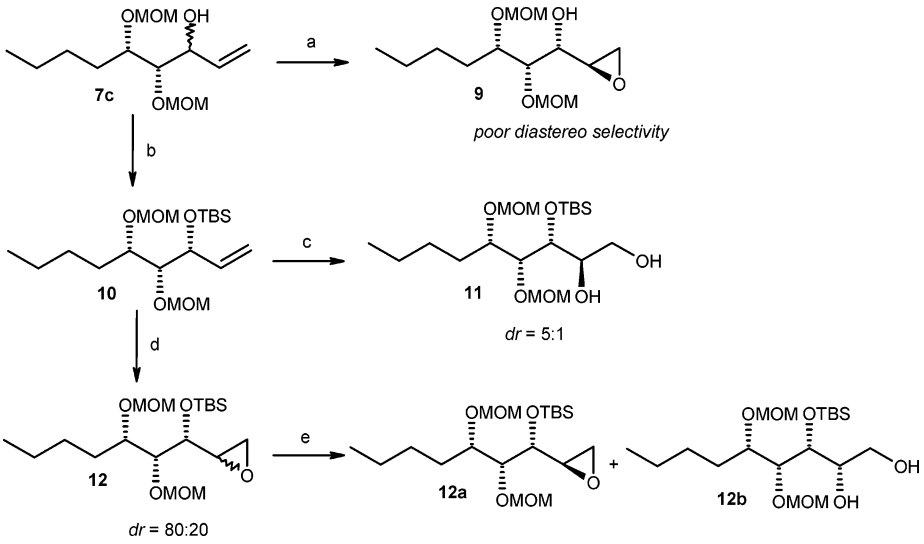
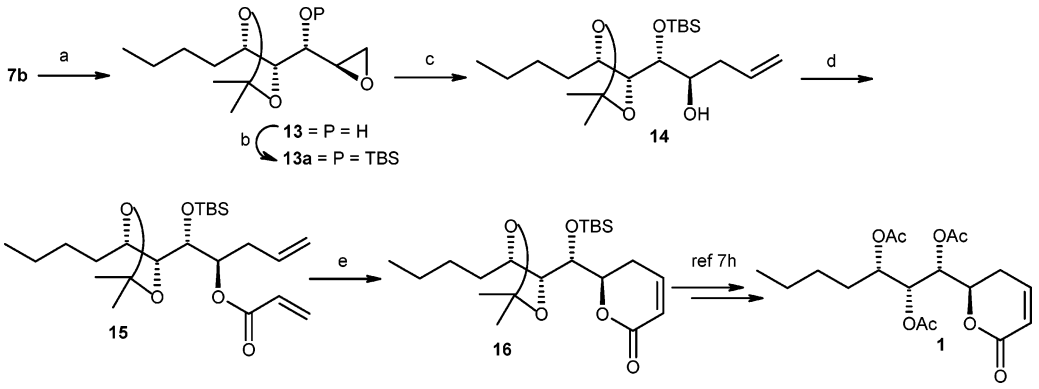
SCHEME 4 [a]



[a] Reagents and conditions: (a) Ti(O-*i*-Pr)$_4$, (+)DIPT, *t*-BuOOH, dry CH_2Cl_2, −20 °C, 4 days, 15%; (b) TBSTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 30 min, 98%; (c) $(DHQ)_2AQN$ (1 mol %), 0.1 M OsO_4 (0.4 mol %), K_2CO_3, $K_3Fe(CN)_6$, *t*-BuOH/H_2O (1:1), 0 °C, 24 h, 91%; (d) *m*-CPBA, Na_2HPO_4, CH_2Cl_2, overnight, 91%; (e) (*R*,*R*)-salen-Co-(OAc) (0.5 mol %), dist. H_2O, 42 h, (94% for **12a**, 90% for **12b**, according to the ratio of the starting material).

SCHEME 5 [a]



[a] Reagents and conditions: (a) Ti(O-*i*-Pr)$_4$, (+)DIPT, *t*-BuOOH, dry CH_2Cl_2, −20 °C, 48 h, 78% (yield based on 75% of syn compound); (b) TBSCl, imidazole, cat. DMAP, CH_2Cl_2, 0 °C to room temperature, 98%; (c) CH_2═CHMgBr, CuI, THF, −30 °C, 90%; (d) acryloyl chloride, Et_3N, cat. DMAP, CH_2Cl_2, 0 °C to room temperature, 88%; (e) 2 mol % $(PCy_3)_2Ru(Cl)_2$═CH−Ph, CH_2Cl_2, reflux, 16 h, 90%.

ity. To get the diastereomerically pure epoxide, we next attempted the HKR method developed by Jacobsen. The HKR method uses readily accessible cobalt-based chiral salen complexes as the catalyst and water as the only reagent to afford the chiral epoxide and diol of high ee in excellent yields. These advantages have made it a very attractive asymmetric synthetic tool. While the HKR was successfully employed for the resolution of simple epoxides of small molecular weight,[16] monofunctional unbranched alkyl-substituted epoxides,[17] and bisepoxides,[18] its application to the multifunctional epoxides has not been fully explored. Therefore, we decided to use this method for the resolution of epoxide **12**, which would further extend the scope of this protocol for the multifunctionalized large molecules having an olefin with a pre-existing adjacent chiral center. Thus, epoxide **12** was resolved with *R*,*R*-salen-Co(OAc) complex (0.5 mol %) and water (0.4 equiv) to yield the epoxide (2*R*,3*R*,3*R*,5*S*)-**12a** in 94% yield (as calculated from 80% epoxide) and diol (2*S*,3*R*,3*R*,5*S*)-**12b** in 90% yield (as calculated from 20% other epoxide). The diol **12b** can be converted into the required epoxide by the conventional method.

It is interesting to note that while asymmetric epoxidation of **7c** gave a rather low yield of the product, the treatment of allylic alcohol **7b** with titanium tetra-isopropoxide and *tert*-butyl hydroperoxide in the presence of (+)-DIPT under the Sharpless asymmetric epoxidation conditions[14] furnished the desired epoxide (2*R*,3*R*,3*R*,5*S*)-**13** in good yield and high diastereomeric excess (de = >95%), as judged by ^{1}H and ^{13}C NMR spectral analysis (Scheme 5). As expected, the Sharpless kinetic resolution in the epoxidation reaction has a pronounced effect in enhancing the diastereomeric purity of the desired product. After the protection of the hydroxyl group as the *tert*-butyldimethylsilyl ether, epoxide **13a** was treated with vinylmagnesium bromide in the presence of a catalytic amount of CuI in THF at

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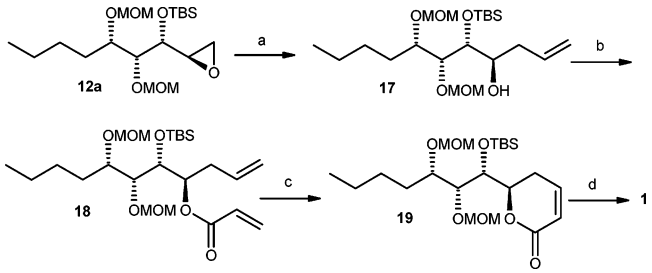
SCHEME 6 [a]



[a] Reagents and conditions: (a) CH_2=$CHMgBr$, CuI, THF, −30 °C, 86%; (b) acryloyl chloride, Et_3N, cat. DMAP, CH_2Cl_2, 0 °C to room temperature, 91%; (c) 2 mol % $(PCy_3)_2Ru(Cl)_2$=CH−Ph, CH_2Cl_2, reflux, 8 h, 89%; (d) BF_3·SMe_2, −30 °C, then aq HF, CH_3CN, rt, then Ac_2O, Et_3N, cat DMAP, CH_2Cl_2, rt, (50% overall).

−20 °C to furnish the homoallylic alcohol **14** in excellent yield. Treatment of **14** with acryloyl chloride and Et_3N in the presence of a catalytic amount of DMAP in CH_2Cl_2 provided the acrylate **15** in 88% yield. Olefin metathesis of **15** with the commercially available first-generation Grubbs catalyst[19] (2 mol %) in the presence of $Ti(OPr\text{-}i)_4$ (0.3 equiv) in refluxing CH_2Cl_2 afforded the α,β-unsaturated δ-lactone **16** in 90% yield. Finally, all protecting groups in compound **16** were deprotected,[7h] and the resulting triol was acetylated with acetic anhydride to give (+)-boronolide **1**.

In the same manner, the ring opening of epoxide **12a** was carried out with vinylmagnesium bromide in the presence of a catalytic amount of CuI in THF at −20 °C to furnish the homoallylic alcohol **17** in excellent yield (Scheme 6). The reaction of **17** with acryloyl chloride and Et_3N in the presence of a catalytic amount of DMAP in CH_2Cl_2 provided the acrylate ester **18** in 91% yield. Olefin metathesis of **18** with commercially available first-generation Grubbs catalyst[19] (2 mol %) in the presence of $Ti(i\text{-}PrO)_4$ (0.3 equiv) in refluxing CH_2Cl_2 afforded the α,β-unsaturated lactone **19** in 89% yield. Finally, all protecting groups in **19** were deprotected, and the resulting triol was acetylated with acetic anhydride to give (+)-boronolide **1**. The physical and spectroscopic data were identical with those reported.[7h]

In conclusion, a practical and stereoselective total synthesis of (+)-boronolide **1** has been achieved in 13 steps from commercially available valeraldehyde **2** in an overall yield of 18% using Sharpless asymmetric dihydroxylation, chelation-controlled addition of vinyl Grignard, epoxidation, Jacobson's HKR, and ring-closing metathesis as the key steps. The HKR on the multifunctional terminal olefin having chiral centers was successfully utilized for the synthesis of boronolide. We believe our new approach is, thus, the most efficient route to (+)-boronolide reported so far and would permit maximum variability in product structure with regard to stereochemical diversity, which is particularly important for making various synthetic analogues required for the screening for biological activity.

Experimental Section

Hept-2-enoic Acid Ethyl Ester (3). IR (neat): ν_{max} 2924, 2856, 1724, 1655, 1466, 1366, 1310, 1178, 1128, 1045, 980, 721 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 6.95 (dt, J = 15.7, 7.1 Hz, 1H), 5.76 (dt, J = 15.7, 1.3 Hz, 1H), 4.18 (q, J = 7.1 Hz, 2H), 2.17 (q, J = 8 Hz, 2H), 1.37−1.40 (m, 4H), 1.27 (t, J = 7.6 Hz, 3H), 0.91 (t, J = 7.1 Hz, 3H). ^{13}C NMR: 165.9, 148.5, 132.0, 59.4, 31.4, 21.7, 13.7.

(2*R*,3*S*)-2,3-Dihydroxyheptanoic Acid Ethyl Ester (4a). $[\alpha]^{25}_D$ −8.8 (*c* 0.9, $CHCl_3$). IR (neat): ν_{max} 3400, 3133, 3018, 2926, 2854, 1732, 1460, 1401, 1215, 760, 667 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 0.88 (t, J = 7.3 Hz, 3H), 1.24−1.37 (m, 6H), 1.59 (t, J = 13.6 Hz, 3H), 3.20 (br s, 2H), 3.85 (dt, J = 6.8, 2.4 Hz, 1H), 4.06 (d, J = 2.4 Hz, 1H), 4.25 (q, J = 7.2 Hz, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.7, 13.81, 22.3, 27.6, 32.9, 61.5, 72.4, 73.2, 173.5.

(2*R*,3*S*)-5-Butyl-2,2-dimethyl-[1,3]dioxolane-4-carboxylic Acid Ethyl Ester (4b). To a solution of the diol **4a** (2.45 g, 12.90 mmol) and *p*-TSA (100 mg) in CH_2Cl_2 (75 mL) was added 2,2-dimethoxypropane (2.02 g, 19.35 mmol), and the mixture was stirred overnight. Solid $NaHCO_3$ (1 g) was added, and the stirring continued for 30 min. The reaction was filtered through a pad of neutral alumina and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (9:1) gave **4b**[7l] (2.52 g, 95%) as a colorless liquid. $[\alpha]^{25}_D$ −13.2 (*c* 3.22, $CHCl_3$). IR (neat): ν_{max} 3400, 3133, 3018, 2926, 2854, 1732, 1460, 1401, 1215, 760, 667 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 4.20 (q, J = 8.0 Hz, 2H), 4.09 (m, 2H), 1.62 (t, J = 8.2 Hz, 3H), 1.44 (s, 3H), 1.42 (s, 3H), 1.27−1.35 (m, 6H), 0.89 (t, J = 7.0 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 170.7, 110.5, 79.1, 60.9, 33.0, 27.0, 25.5, 22.3, 13.9, 13.6.

(2*R*,3*S*)-2,3-Bismethoxymethoxyheptanoic Acid Ethyl Ester (4c). To a solution of the diol **4a** (2.10 g, 11.04 mmol) and diisopropylethylamine (4.99 g, 38.64 mmol) in dry CH_2Cl_2 (50 mL) was added MOMCl (2.13 g, 26.49 mmol) under argon over 5 min at 0 °C, and the mixture was allowed to warm to room temperature overnight. After cooling to 0 °C, the reaction mixture was quenched with water and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were washed with water (3 × 50 mL) and brine, dried (Na_2SO_4), and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (8:2) gave **4c** (2.80 g, 91%) as a colorless liquid. $[\alpha]^{25}_D$ +59.2 (*c* 2.21, $CHCl_3$). IR ($CHCl_3$): ν_{max} 3016, 2955, 2824, 2402, 1726, 1466, 1382, 1215, 1102, 1036 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 4.70 (s, 2H), 4.62 (s, 2H), 4.19 (m, 3H), 3.91 (m, 1H), 3.37 (s, 3H), 3.31 (s, 3H), 1.64 (t, J = 8.2 Hz, 3H), 1.22−1.30 (m, 6H), 0.88 (t, J = 7.1 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.6, 13.8, 22.3, 27.2, 30.2, 55.4, 55.8, 60.5, 76.9, 77.3, 78.1, 96.3, 170.4. Anal. Calcd for $C_{13}H_{26}O_6$ (278.34): C, 56.10; H, 9.42. Found: C, 56.44; H, 9.12.

(2*S*,3*S*)-(5-Butyl-2,2-dimethyl-[1,3]dioxolan-4-yl)-methanol (5b). To a solution of **4b** (2.40 g, 10.42 mmol) in dry CH_2Cl_2 (80 mL) at 0 °C was added dropwise DIBAL-H (25.8 mL, 25.8 mmol, 1 M in toluene) through a syringe. The reaction mixture was allowed to warm to room temperature over 2 h, recooled to 0 °C, and treated with saturated sodium/potassium tartrate. The solid material was filtered through a pad of Celite and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (7:3) as eluent gave **5b** (1.79 g, 91%) as a colorless oil. $[\alpha]^{25}_D$ −21.5 (*c* 1.08, $CHCl_3$). IR (neat): ν_{max} 3440, 2926, 1460, 1361, 1216, 764, 667 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 3.75 (m, 2H), 3.58 (dd, J = 11.3, 3.9 Hz, 2H), 2.17 (s, 1H), 1.44−1.62 (m, 2H), 1.42 (s, 3H), 1.41 (s, 3H), 1.37−1.42 (m, 4H), 0.91 (t, J = 6.7 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.7, 22.5, 26.8, 27.1, 27.9, 32.6, 62.0, 77.00, 81.6, 108.3. Anal. Calcd for $C_{10}H_{20}O_3$ (188.26): C, 63.80; H, 10.71. Found: C, 64.09; H, 10.58.

1-(5-Butyl-2,2-dimethyl-[1,3]-dioxolan-4-yl)-prop-2-en-1-ol (7b). To a solution of oxalyl chloride (1.405 g, 0.966 mL, 11.074 mmol) in dry CH_2Cl_2 (100 mL) at −78 °C was added dropwise dry DMSO (1.730 g, 1.57 mL, 22.15 mmol) in CH_2Cl_2 (20 mL). After 30 min, alcohol **5b** (1.39 g, 7.382 mmol) in CH_2Cl_2 (20 mL) was added over 10 min giving a copious white precipitate. After stirring for 1 h at −78 °C, the reaction mixture was brought to −60 °C, and

(19) For reviews on ring-closing metathesis, see: (a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413−4450. (b) Prunet, J. *Angew. Chem., Int. Ed.* **2003**, *42*, 2826−2830.

Et_3N (2.988 g, 2.169 mL, 29.53 mmol) was added slowly and stirred for 30 min, allowing the reaction mixture to warm to room temperature. The reaction mixture was poured into water (150 mL), and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL), and the combined organic layers were washed with water (3 × 50 mL) and brine (50 mL), dried (Na_2SO_4), and passed through a short pad of silica gel. The filtrate was concentrated to give the aldehyde **6b** (1.31 g) as a pale yellow oil, which was used as such for the next step without purification.

The crude aldehyde **6b** dissolved in CH_2Cl_2 under argon was added via cannula to a stirred suspension of $MgBr_2 \cdot Et_2O$ in a 250-mL round-bottom flask at 0 °C. After stirring for 10 min, the flask was cooled to −78 °C and treated with vinylmagnesium bromide (14.94 mL, 14.94 mmol; purchased from Aldrich as 1.0 M solution in THF); the solvent was removed in vacuo and diluted with CH_2Cl_2 three times over 30 min and allowed to warm to 0 °C. The reaction mixture was diluted with saturated NH_4Cl and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (9:1) as eluent gave the allylic alcohol **7b** as an inseparable mixture of diastereomers (syn/anti = 3:1; 1.39 g, 92%) as a pale yellowish oil. IR (neat): ν_{max} 3358−3250, 2924, 2855, 1466, 1372, 1220, 761, 669 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 5.81−5.91 (m, 1H), 5.34−5.39 (m, 1H), 5.26 (m, 1H), 4.28−4.30 (m, 1H), 3.91−3.96 (m, 1H), 3.69 (dd, J = 7.9, 3.9 Hz, 1H), 3.61 (dd, J = 7.5, 4.5 Hz, 1H, minor diastereomer), 1.49−1.60 (m, 3H), 1.39 (s, 6H), 1.31−1.36 (m, 3H), 0.89 (t, J = 7.1 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 137.1, 136.3, 116.7, 116.3, 108.6, 108.3, 83.51, 83.0, 77.37, 77.2, 72.7, 72.2, 33.7, 33.0, 28.0, 27.3, 26.9, 22.5, 13.7 (mixture of diastereomers). Anal. Calcd for $C_{12}H_{22}O_3$ (214.30): C, 67.26; H, 10.35. Found: C, 67.51; H, 10.11.

4,5-Bismethoxymethoxynon-1-en-3-ol (7c). Compound **7c** was prepared following the procedure as described for compound **7b** in 90% yield as an inseparable mixture of diastereomers (syn/anti = 19:1) as a pale yellowish oil. $[\alpha]^{25}_D$ +26.43 (*c* 0.8, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ 5.87−6.04 (m, 1H), 5.36 (td, J = 23.8, 17.2 Hz, 2H), 4.79 (d, J = 6.7 Hz, 1H), 4.70 (d, J = 6.7 Hz, 1H), 4.68 (s, 2H), 4.32 (tt, J = 5.5, 1.6 Hz, 1H), 3.64−3.73 (m, 1H), 3.44 (s, 3H), 3.39 (s, 3H), 2.97 (br s, 1H), 1.58−1.68 (m, 2H), 1.26−1.35 (m, 4H), 0.88 (t, J = 7 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.8, 22.6, 27.3, 27.7, 30.1, 30.4, 55.7, 56.0, 71.6, 71.9, 78.1, 78.3, 83.0, 83.2, 96.6, 96.9, 97.9, 98.3, 115.9, 116.5, 137.3, 137.7. Anal. Calcd for $C_{13}H_{26}O_5$ (262.34): C, 59.52; H, 9.99. Found: C, 59.86; H, 9.63.

[1-(1,2-Bismethoxymethoxy-hexyl)-allyloxy]-*tert*-butyldimethylsilane (10). To a stirred solution of allylic alcohol **7c** (1.20 g, 4.57 mmol) in CH_2Cl_2 (50 mL) and 2,6-lutidine (2.94 g, 3.175 mL, 27.44 mmol) was added TBSTf (1.33 g, 5.031 mmol) at 0 °C, and the mixture was stirred at the same temperature for 30 min. The reaction mixture was quenched with water and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (3:1) as eluent gave compound **10** (1.69 g, 98%) as a colorless oil. $[\alpha]^{25}_D$ +31.90 (*c* 0.9, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ 5.88−6.04 (m, 1H), 5.16 (dd, J = 27.3, 17.8 Hz, 2H), 4.91 (d, J = 7.04 Hz, 1H), 4.71 (d, J = 7.04 Hz, 2H), 4.63 (s, 2H), 4.37 (t, J = 6.7 Hz, 1H), 3.56−3.64 (m, 1H), 3.40 (s, 3H), 3.38 (s, 3H), 1.51−1.74 (m, 2H), 1.26−1.33 (m, 4H), 0.89 (s, 12H), 0.06 (s, 3H), 0.03 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 138.1, 115.4, 98.3, 96.9, 81.7, 77.6, 74.1, 55.8, 55.7, 30.9, 27.5, 25.7, 22.7, 17.9, 13.9, −4.8, −4.9. Anal. Calcd for $C_{19}H_{40}O_5Si$ (376.60): C, 60.60; H, 10.71; Si, 7.46. Found: C, 60.89; H, 10.42.

(2,3-Bismethoxymethoxy-1-oxiranylheptyloxy)-*tert*-butyldimethylsilane (12). To a stirred solution of olefin **10** (0.940 g, 2.49 mmol) and Na_2HPO_4 (709 mg, 4.99 mmol) in THF (30 mL) was added *m*-CPBA (1.72 g, 4.99 mmol) at 0 °C. The mixture was stirred for 1 h and then overnight at room temperature. The solution was treated with saturated aqueous $NaHCO_3$ and $Na_2S_2O_3$ and extracted with CH_2Cl_2. The organic layer was washed with brine, dried (Na_2SO_4), and concentrated. Silica gel column chromatography using petroleum ether/EtOAc (9:1) as eluent gave the epoxide **12** (0.89 g, 91%) as an inseparable mixture of diastereomers (anti/syn = 4:1) as a colorless syrupy liquid.

Hydrolytic Kinetic Resolution of Epoxide 12. A solution of epoxide **12** (0.574 g, 1.46 mmol) and (*R*,*R*)-salen-Co(III)-OAc (4 mg, 0.007 mmol) in THF (10 μL) was stirred at 0 °C for 5 min, and then distilled water (10 μL, 0.584 mmol) was added. After stirring for 42 h, it was concentrated and purified by silica gel column chromatography using petroleum ether/EtOAc (8:2) to afford **12a** (431 mg, 94%) as a colorless syrupy liquid and as a single isomer (determined by ^1H and ^{13}C NMR analysis). Continued chromatography with petroleum ether/EtOAc (3:2) provided the diol **12b** (103 mg, 90%) as a brown colored liquid and as a single diastereomer.

Data of Compound 12a. $[\alpha]^{25}_D$ −7.1 (*c* 1.28, $CHCl_3$). IR (neat): ν_{max} 2954, 2932, 2893, 2859, 1471, 1376, 1361, 1252, 1215, 1102, 1042, 919, 839, 776, 759 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 4.80 (d, J = 6.1 Hz, 1H), 4.74 (d, J = 6.3 Hz, 2H), 4.65 (d, J = 6.5 Hz, 1H), 3.81 (m, 1H), 3.62 (dd, J = 6.2, 4.0 Hz, 1H), 3.57 (m, 1H), 3.39 (s, 3H), 3.37 (s, 3H), 3.27 (m, 1H), 2.67−2.76 (m, 2H), 1.61−1.66 (m, 2H), 1.25−1.36 (m, 4H), 0.91 (s, 12H), 0.08 (s, 3H), 0.06 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 96.6, 96.3, 83.3, 79.9, 55.6, 55.2, 52.9, 44.2, 28.5, 25.7, 22.9, 17.9, 13.9, −4.86, −5.33. Anal. Calcd for $C_{19}H_{40}O_6Si$ (392.60): C, 58.13; H, 10.27; Si, 7.15. Found: C, 58.51; H, 10.11; Si, 7.54.

Data of Compound 12b. $[\alpha]^{25}_D$ +19.6 (*c* 1.03, $CHCl_3$). IR (neat): ν_{max} 3400, 2933, 2862, 1473, 1367, 1214, 1179, 1027, 929, 874, 638, 758 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 4.79 (d, J = 6.6 Hz, 1H), 4.74 (d, J = 6.3 Hz, 1H), 4.71 (d, J = 6.4 Hz, 2H), 3.91 (m, 2H), 3.86 (m, 2H), 3.63 (m, 2H), 3.44 (s, 3H), 3.42 (s, 3H), 1.73 (br s, 1H), 1.59 (br s, 1H), 1.26−1.39 (m, 6H), 0.91 (t, J = 7.1 Hz, 3H), 0.89 (s, 9H), 0.12 (s, 3H), 0.10 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 97.8, 96.7, 80.5, 77.0, 72.6, 70.6, 63.3, 56.1, 55.8, 30.8, 27.6, 25.7, 22.6, 22.5, 17.8, 13.8, −4.3, −5.0. Anal. Calcd for $C_{19}H_{42}O_7Si$ (410.62): C, 55.58; H, 10.31; Si, 6.84. Found: C, 55.69; H, 10.12; Si, 6.48.

(5-Butyl-2,2-dimethyl-[1,3]-dioxolan-4-yl)-oxiranylmethanol (13). To a solution of titanium(IV) isopropoxide (729 mg, 2.56 mmol) and (−)-diisopropyl-D-tartrate (710 mg, 3.03 mmol) in CH_2Cl_2 (20 mL) at −20 °C was added olefin **7b** (500 mg, 2.33 mmol) in CH_2Cl_2 (4 mL) followed by *tert*-butyl hydroperoxide (420 mg, 0.52 mL, 4.66 mmol). After 48 h at −20 °C, the reaction mixture was diluted with ether and saturated sodium sulfate. The mixture was stirred vigorously for 2 h at room temperature and filtered. The filtrate was concentrated, and the residue was chromatographed over silica gel to give epoxide **13**[7k] (314 mg, 78%; yield based on 75% of syn compound) as a colorless oil. $[\alpha]^{25}_D$ −3.7 (*c* 0.9, $CHCl_3$). IR (neat): ν_{max} 3453, 2956, 2931, 2893, 2859, 1379, 1254, 1192 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 4.02−4.09 (m, 1H), 3.83−3.90 (m, 1H), 3.68 (t, J = 7.13 Hz, 1H), 3.22−3.28 (m, 1H), 2.77−2.89 (m, 2H), 2.09 (s, 1H), 1.46−1.66 (m, 3H), 1.42 (s, 3H), 1.39 (s, 3H), 1.26−1.36 (m, 3H), 0.91 (t, J = 7.1 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 108.9, 81.3, 79.5, 71.5, 52.3, 44.6, 33.8, 28.2, 27.4, 27.0, 22.7, 13.9.

***tert*-Butyl-[(5-butyl-2,2-dimethyl-[1,3]-dioxolan-4-yl)-oxiranylmethoxy]dimethylsilane (13a).** To a stirred solution of epoxy alcohol **13** (0.40 g, 1.737 mmol) and imidazole (260 mg, 3.82 mmol) in CH_2Cl_2 (50 mL) was added TBSCl (0.392 g, 2.61 mmol) at 0 °C, and the reaction mixture was stirred at the same temperature for 30 min. The reaction mixture was quenched with water and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (9:1) as eluent gave compound **13a** (586 mg, 98%) as a colorless oil. $[\alpha]^{25}_D$ −18.1 (*c* 0.8, $CHCl_3$). ^1H NMR (200 MHz,

$CDCl_3$): δ 3.91−4.12 (m, 2H), 3.68 (t, J = 7.2 Hz, 1H), 3.24 (m, 1H), 2.72−2.88 (m, 2H), 1.48−1.66 (m, 2H), 1.43 (s, 3H), 1.39 (s, 3H), 1.24−1.37 (m, 4H), 0.91 (s, 12H), 0.08 (s, 3H), 0.06 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 108.7, 81.4, 78.9, 72.3, 53.4, 43.9, 33.7, 28.3, 27.4, 27.0, 24.5, 22.8, 16.2, 13.86, −4.8, −4.9. Anal. Calcd for $C_{18}H_{36}O_4Si$ (344.56): C, 62.74; H, 10.53; Si, 8.15. Found: C, 62.46; H, 10.87; Si, 8.52.

5-(*tert*-Butyldimethylsilanyloxy)-6,7-bismethoxymethoxy-undec-1-en-4-ol (17). Compound **15** was prepared following the procedure as described for compound **14** in 86% yield as a colorless liquid. $[\alpha]^{25}_D$ +26.3 (*c* 0.9, $CHCl_3$). IR (neat): ν_{max} 3029, 2956, 2931, 2859, 1644, 1464, 1255, 1102, 1036, 918, 873, 837, 776 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.83−6.04 (m, 1H), 5.07−5.17 (m, 2H), 4.78 (d, J = 6.7 Hz, 1H), 4.73 (t, J = 1.96 Hz, 3H), 3.80−3.88 (m, 2H), 3.75 (t, J = 3.52 Hz, 1H), 3.64−3.68 (m, 1H), 3.43 (s, 3H), 3.41 (s, 3H), 2.17−2.25 (m, 2H), 1.60−1.72 (m, 2H), 1.21−1.36 (m, 4H), 0.89 (s, 12H), 0.12 (s, 3H), 0.10 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 136.2, 116.2, 99.1, 96.4, 85.8, 79.3, 73.6, 70.1, 55.7, 37.2, 29.6, 28.6, 25.7, 22.7, 18.0, 13.9, −4.8, −4.9. Anal. Calcd for $C_{21}H_{44}O_6Si$ (420.66): C, 59.96; H, 10.54; Si, 6.68. Found: C, 60.11; H, 10.61; Si, 6.82.

Acrylic Acid 1-[1-(*tert*-Butyldimethylsilanyloxy)-2,3-bismethoxymethoxy-heptyl]-but-3-enyl Ester (18). Compound **18** was prepared following the procedure as described for compound **15** in 91% yield as a yellowish syrupy liquid. $[\alpha]^{25}_D$ −42.14 (*c* 0.84, $CHCl_3$). IR (neat): ν_{max} 2931, 2858, 1726, 1638, 1254, 1256, 1192 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.45 (ddd, J = 17.2, 1.6 Hz, 1H), 6.09 (dd, J = 17.2, 4.3 Hz, 1H), 5.83 (dd, J = 10.2, 1.5 Hz, 1H), 5.75 (dd, J = 11.7, 1.6 Hz, 1H), 5.18 (m, 1H), 5.01 (m, 1H), 4.67 (m, 2H), 4.54 (m, 2H), 3.64−3.66 (m, 1H), 3.92 (dt, J = 8.2, 1.6 Hz, 1H), 3.37−3.42 (m, 2H), 3.33 (s, 3H), 3.30 (s, 3H), 2.24−2.48 (m, 2H), 1.27−1.34 (m, 6H), 0.81 (s, 12H), −0.04 (s, 3H), −0.05 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 165.7, 134.6, 131.7, 128.2, 117.1, 98.8, 96.9, 80.8, 79.4, 75.82, 74.4, 74.0, 56.1, 56.0, 32.8, 29.6, 29.4, 28.5, 22.7, 18.2, 14.1, −4.1, −4.7. Anal. Calcd for $C_{24}H_{46}O_7Si$ (474.70): C, 60.72; H, 9.77; Si, 5.92. Found: C, 61.09; H, 9.62; Si, 6.21.

6-[1-(*tert*-Butyldimethylsilanyloxy)-2,3-bismethoxymethoxy-heptyl]-5,6-dihydropyran-2-one (19). Compound **19** was prepared following the procedure as described for compound **16** in 89% yield as a colorless syrupy liquid. $[\alpha]^{25}_D$ +51.4 (*c* 1.18, $CHCl_3$). IR (neat): ν_{max} 2954, 2934, 2856, 1712, 1469, 1386, 1252, 1149, 1123, 1102, 1018, 923, 838, 779 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.92 (ddd, J = 8.2, 6.3, 2.0 Hz, 1H), 5.99 (dd, J = 9.7, 2.3 Hz, 1H), 4.58−4.82 (m, 4H), 4.21 (dd, J = 8.2, 1.7 Hz, 1H), 3.62−3.70 (m, 1H), 3.46−3.49 (m, 2H), 3.39 (s, 6H), 2.77 (m, 1H), 2.17 (ddd, J = 19.9, 5.9, 3.9 Hz, 1H), 1.31−1.42 (m, 6H), 0.88 (s, 12H), 0.16 (s, 3H), 0.11 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 164.0, 145.6, 120.7, 98.9, 96.4, 79.2, 78.28, 78.21, 73.8, 56.1, 55.9, 29.6, 28.3, 25.9, 22.9, 22.7, 18.2, 14.0, −4.2, −4.3. Anal. Calcd for $C_{22}H_{42}O_7Si$ (446.65): C, 59.16; H, 9.48; Si, 6.29. Found: C, 59.45; H, 9.34; Si, 6.19.

Deacetylated Boronolide (1a). Lactone **19** (182 mg, 0.41 mmol) was dissolved in dimethyl sulfide (3 mL) and cooled to −10 °C. Then $BF_3{\cdot}Et_2O$ (1.02 mL, 8.15 mmol) was added to the solution, which was stirred at the room temperature for 30 min. The reaction mixture was quenched with water and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated to give an oily material that was dissolved in MeCN (5 mL) and treated with 45% aq HF (172 mg, 0.15 mL, 4.1 mmol) at room temperature. After stirring at room temperature overnight, the reaction mixture was quenched with $NaHCO_3$ (1 g). The aqueous layer was extracted with CH_2Cl_2, and the organic layer was washed with brine, dried (Na_2SO_4), and concentrated. Silica gel column chromatography of the crude product using EtOAc as eluent gave deacetylated boronolide **1a** (106 mg, 86%) as a white solid: mp 101 °C (lit.[7h] 99−100 °C); $[\alpha]^{25}_D$ +57.4 (*c* 0.71, EtOH) (lit.[7h] $[\alpha]^{25}_D$ +56 (*c* 0.07, EtOH)). ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.95 (ddd, J = 9.6, 6.1 Hz, 1H), 6.02 (dd, J = 10.1, 2.6 Hz, 1H), 4.52 (ddd, J = 11.5, 7.3, 4.1 Hz, 1H), 3.85 (d, J = 7.1 Hz, 1H), 3.64 (br s, 2H), 3.01 (br s, 3H), 2.64 (ddd, J = 18.7, 5.2, 4.2 Hz, 1H), 2.51 (ddd, J = 18.8, 11.5, 2.5 Hz, 1H), 1.46−1.66 (m, 2H), 1.26−1.34 (m, 4H), 0.89 (t, J = 7.1 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 163.9, 145.9, 120.9, 77.1, 76.7, 74.3, 70.1, 33.4, 27.7, 25.8, 22.6, 14.0.

Boronolide (1). Acetic anhydride (0.18 mL, 1.96 mmol) was added dropwise to a stirred and cooled (0 °C) solution of **1a** (48 mg, 0.196 mmol), *i*-Pr_2EtN (0.5 mL, 2.94 mmol), and DMAP (catalytic amount) in CH_2Cl_2 (5 mL). The resulting mixture was allowed to stir for 6 h at room temperature. The resulting mixture was diluted with Et_2O (40 mL). The organic phase was washed with saturated NH_4Cl, water, and brine, dried (Na_2SO_4), and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (7:3) as eluent gave compound **1** (62 mg, 85%) as a clear oil that solidified on standing: mp 88−90 °C (lit.[7] 90 °C); $[\alpha]^{25}_D$ +26.4 (*c* 0.7, EtOH) (lit.[7h] $[\alpha]_D^{25}$ +25 (*c* 0.2, EtOH)). ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.89 (ddd, J = 9.7, 6.2, 2.7 Hz, 1H), 6.01 (dd, J = 9.8, 2.4 Hz, 1H), 5.33−5.38 (m, 2H), 5.01 (q, J = 6.1 Hz, 1H), 4.55 (dt, J = 12.1, 4.5 Hz, 1H), 2.51 (dddd, J = 18.1, 11.8, 2.6, 2.5 Hz, 1H), 2.31 (m, 1H), 2.11 (s, 3H), 2.05 (s, 3H), 2.03 (s, 3H), 1.54 (m, 2H), 1.17−1.30 (m, 4H), 0.89 (t, J = 6.7 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 170.5, 169.8, 169.5, 162.5, 144.0, 121.2, 75.1, 71.6, 70.6, 70.5, 30.1, 27.1, 25.2, 22.3, 21.1, 20.6, 13.8.

Acknowledgment. S.V.N. thanks CSIR New Delhi for financial assistance. P.K. is thankful to Department of Science and Technology, New Delhi, for generous funding of the project (Grant No. SR/S1/OC-40/2003). We are grateful to Dr. M. K. Gurjar for his support and encouragement. This is NCL communication No. 79.

Supporting Information Available: Experimental procedures and spectroscopic data of compounds **3**, **4a**, **4d**, **5c**, **9**, **11**, **14**−**16**; ^{1}H and ^{13}C NMR spectra of compounds **1a**, **3**, **4a**−**4d**, **5b**, **5c**, **7b**, **7c**, **8**, **10**, **12a**, **12b**, **13**, **16**−**19**, and (+)-boronolide **1**, NOE of **8**, and HPLC of **4d**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0603781