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Stereoselective synthesis of (+)-boronolide and its 8-epimer

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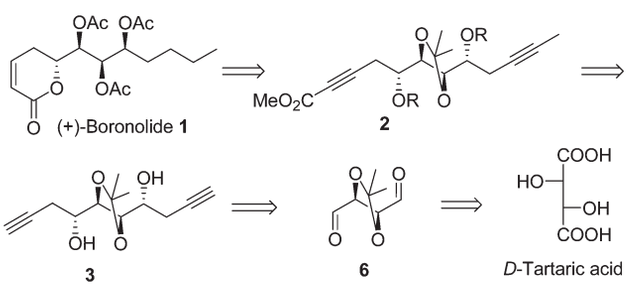
Starting from readily available carbohydrates the synthesis of 8-epi-(+)-boronolide **19** and (+)-boronolide **1** was achieved with diastereoselective propargylation of α-oxygenated aldehyde as a key step.

(+)-Boronolide (**1**) (Scheme 1) and its deacetylated products are polyhydroxylated natural compounds isolated from *Tetradenia fruticosa*, *T. barberae* and *T. riparia* and these plants have long been used for various medicinal purposes in Madagascar and Southern Africa.[1,2] A wide variety of biological properties of **1** and its derivatives as well as their structural complexities attracted significant interest in their synthesis.[3–10] All reports, except the first one, concerned asymmetric synthesis of target molecules, and Sharpless dihydroxylation,[5] asymmetric aldol reaction[8–10] or the chiron approach[4,6,7] have been employed to construct the four contiguous oxygenated stereogenic centers, while the introduction of α,β-unsaturated δ-lactone relied mainly on dehydrogenation of δ-lactone by using benzeneseleninic anhydride,[3–6] or ring-closing olefin metathesis (RCM).[7–10] In this paper, we describe the synthesis of (+)-boronolide (**1**) and its 8-epimer utilizing diastereoselective propargylation of α-hydroxy aldehyde. Propargylation was extensively investigated by us,[11] and the alkyne group thus introduced were potential for further synthetic manipulations,[12] therefore this methodology has found its use in the synthesis of structurally diverse natural products.[13]



Scheme 1 Retrosynthetic analysis of **1**.

As shown in Scheme 1, our synthetic plan relies on two-direction propargylation of aldehyde **6** with propargylzinc bromide, manipulations of the two incoming alkyne groups will lead to the unsaturated lactone moiety and the alkyl tail, respectively, while one of the two newly formed stereogenic centers should be inverted at a later stage.

The synthesis began with D-tartaric acid (Scheme 2), which was converted to diethyl (2*S*,3*S*)-2,3-*O*-isopropylidenetartrate **4** according to known procedures.[14] We initially attempted to prepare aldehyde **6** from **4** by a two-step procedure, that is, reduction of **4** with LAH to diol **5** followed by oxidation. However, aldehyde **6** couldn't be obtained from diol **5**, though several oxidation methods were examined. A possible reason was the formation of intramolecular semiacetal **7** during the oxidation process, which would not give the desired product. Thus, a well established method with DIBAL-H as the reducing agent at −78 °C was employed to reduce ester **4** directly to aldehyde **6**. The latter was then treated with propargyl bromide and active zinc powder in DMF/diethyl ether (v/v, 1 : 1) to give a diastereomeric mixture of **8**. The mixture was protected as TBS ethers, and the desired diyne **9** was separated from its diastereomers, the ratio of **9** to the other diastereomers was 5.2 : 1. Subsequent methylation followed by methoxycarbonylation resulted in desymmetrization of dialkyne **9** to afford intermediate **11**. Partial hydrogenation of **11** in the presence of Lindlar catalyst afforded *cis*,*cis*-diene **12** in excellent yield.

With *cis*,*cis*-diene **12** in hand we set out to elaborate α,β-unsaturated δ-lactone (Scheme 3). Treatment of **12** with TBAF (tetrabutylammonium fluoride) in THF, however, didn't give desired deprotection product **15** but acid **13**; presumably lactone **14** was an intermediate for this conversion, which rapidly decomposed to **13** by elimination under the conditions. A better result was obtained when aqueous HF was used, and diol **15** as well as the spontaneous ring-closing product **14** and tetraol **16** was produced. Finally, NH_4F proved to be the choice for this deprotection. Thus **12** was treated with NH_4F in methanol to give lactone **14** in 70% yield along with **15** in 24% yield, the latter could be easily converted to lactone **14** in acidic conditions. After regioselective hydrogenation of **14** in the presence of Wilkinson's catalyst in benzene/ethanol, alcohol **17** was subjected to Mitsunobu reaction in the hope of inversion of configuration at C8. Unfortunately, all the screened reaction conditions could not effect this conversion. Nevertheless, removal of the acetonide group in **14** with $CuCl_2{\cdot}2H_2O$ followed by global acetylation furnished the synthesis of 8-epi-(+)-boronolide **19**.

Failure to reach the target molecule by the above approach prompted us to complete the synthesis of **1** *via* an alternative route. As shown in Scheme 4, three of the four sterogenic centers of **1** would be correlated to D-glucono-δ-lactone while the left one could be constructed by diastereoselective propargylation of an aldehyde. Similar to the former route, manipulation of the alkyne group finally would lead to the unsaturated lactone moiety.

Thus D-glucono-δ-lactone derived **22**[15] was protected as TBS ether **23**, which was reduced with DIBAL-H at −78 °C to give aldehyde **24** (Scheme 5). Subsequent three-carbon elongation of **24** *via* Wittig reaction followed by hydrogenation afforded compound **25**. Selective removal of the 1,2-acetonide group in **25** and *in situ* oxidative cleavage of the resulting glycol were effected smoothly with periodic acid hydrate (H_5IO_6)[16] to give aldehyde **26**, which then reacted with propargyl bromide and active zinc powder in 1 : 1 of DMF/diethyl ether. Homopropargyl alcohol **27** was obtained along with its diastereomer in 4.5 : 1 ratio favoring **27**; the two diastereomers were separable by silica gel chromatography. The hydroxy group of compound **27** was protected with *tert*-butyldimethylsilyl chloride to afford alkyne **28**. After treatment with n-butyllithium, the resulting lithium acetylide reacted with methyl chloroformate to furnish alkyne **29**. Subsequent hydrogenation in the presence of Lindlar catalyst produced alkene **30**. Treatment of **30** with a solution of HCl in aqueous THF removed all the protecting groups and concomitant ring cyclization took place to afford lactone **31**. Finally, full acetylation of triol **31** provided (+)-boronolide uneventfully and the physical data of the synthetic compound were well in accord with those of the natural compound

In conclusion, we describe the synthesis of (+)-boronolide and 8-epi-(+)-boronolide from readily available carbohydrates as the start-

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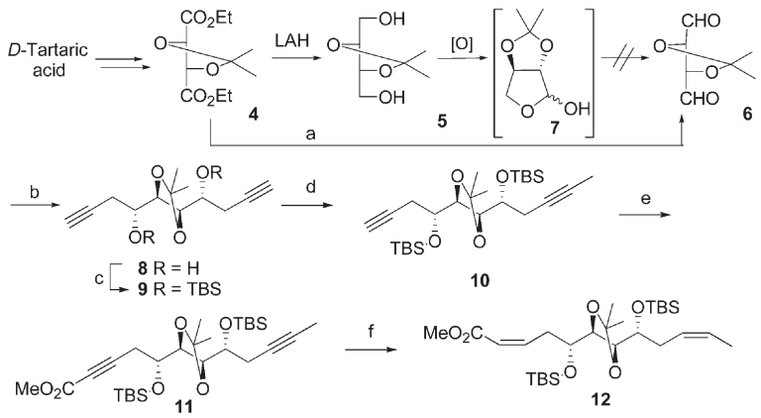
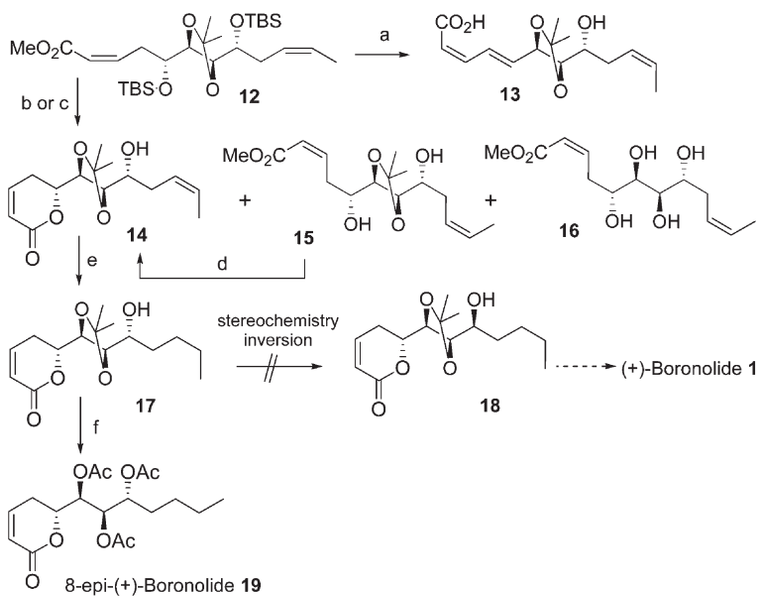
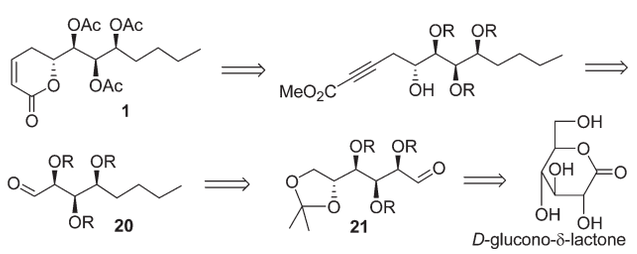


Scheme 2 Reagents and conditions: (a) DIBAL-H (2.4 eq), toluene, −78 °C. (b) Propargyl bromide, Zn powder, DMF–Et_2O. (c) TBSCl, DMF, imidazole., DMAP, rt, 44% for three steps. (d) BuLi (1.15 eq, 1.6 M in hexane), CH_3I, THF, −78 °C to rt, 83%. (e) BuLi (1.5 eq, 1.6 M in hexane), $ClCO_2Me$, THF, −78 °C to rt, 81.3%. (f) H_2, Lindlar cat., quinoline, ethyl acetate, 50–60 °C, 91%.



Scheme 3 Reagents and conditions: (a) TBAF, THF, 72%. (b) HF (40%)–acetonitrile (16 : 1), **14**: 21%, **15**: 37%, **16**: 32%. (c) NH_4F, MeOH, 60 °C, 2 days, **14**: 70%; **15**: 24%. (d) PPTS (cat.) or *p*-TSOH (cat.), toluene, 50–60 °C, 88%. (e) H_2, $(Ph_3P)RhCl$, benzene–EtOH (6 : 1), rt, 86%, (f) (i) $CuCl_2{\cdot}2H_2O$, MeCN–MeOH (6 : 1), rt to 50 °C. (ii) Ac_2O, Py, DMAP, CH_2Cl_2, 77% for two steps.



Scheme 4 Retrosynthesis analysis of **1**, the second route.

ing materials and (+)-boronolide was obtained in about 14% overall yield starting from D-glucono-δ-lactone derivative **22**. Noteworthy is the key step, diastereoselective propargylation, which proved again its versatility for use in the synthesis of structurally diverse compounds.

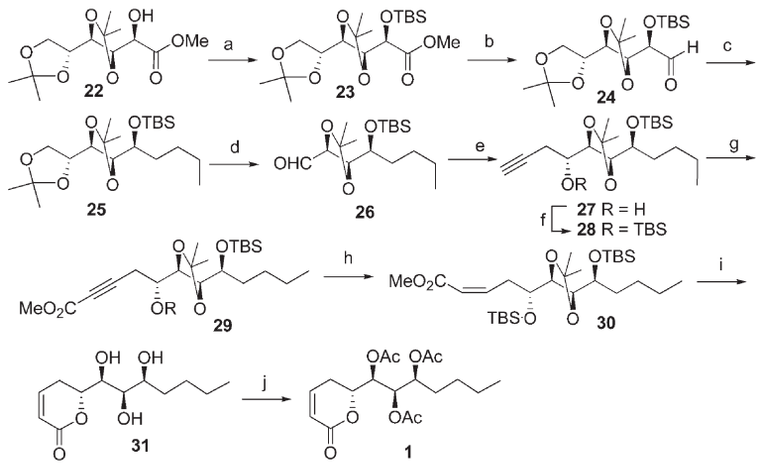
Experimental

General

IR spectra were recorded on Bio-Rad FTS-185 spectrometers. ^1H NMR spectra were measured in $CDCl_3$ on Mercury-300 or Gemini-2000 spectrometers with TMS as the internal standard. Mass spectra were taken on a HP5973N or HP5989A instrument. HRMS (EI) and (ESI) spectra were obtained on an APEXIII 7.0 Tesla FTMS mass spectrometer. Optical rotations were measured on a Perkin-Elmer 241 MC polarimeter. Elemental analyses were carried out at the Microanalytic Laboratory of Shanghai Institute of Organic Chemistry. Flash column chromatography was performed on silica gel H (10–40 μm) with petroleum ether–ethyl acetate or ethyl acetate–ethanol system as eluent.

4,5-Bis-[1-(*tert*-butyldimethylsilanyloxy)-but-3-ynyl]-2,2-dimethyl-[1,3]dioxolane (9). To a stirred solution of compound **4** (13.50 g, 58.2 mmol) in dry toluene (250 mL) was added dropwise DIBAL-H (144 mL, 144 mmol, 1.0 M solution in toluene) over 1.5 hours at −78 °C under nitrogen. The reaction mixture was stirred for another 1.5 hour and then methanol (80 mL) was slowly added at the same temperature. After warming to room temperature, the reaction mixture was diluted with diethyl ether, and filtered. The filtrate was concentrated to give a clear liquid, which was used without further purification in the next reaction.

To a stirred mixture of the aldehyde obtained above and prop-2-ynyl bromide (20.825 g, 175 mmol) in DMF–Et_2O (1 : 1, 5 mL) was slowly added zinc dust (15.145 g, 233 mmol). An exothermic reaction started within a few minutes and the mixture came to reflux automatically. After starting material was consumed, the reaction mixture was poured into aqueous saturated NH_4Cl solution and filtered. The separated aqueous layer was extracted with ether, and the combined organic layers were successively washed with water and brine, and dried over anhydrous Na_2SO_4. Filtration and concentration gave a residue, which was purified by flash column chromatography using petroleum ether : ethyl acetate (8 : 1) as eluent to afford a mixture (8.69 g, 63.0%). ^1H NMR (300 MHz,



Scheme 5 Reagents and conditions: (a) TBSCl, Im, DMAP(cat.), CH_2Cl_2, 94%. (b) DIBAL-H (1 M solution in toluene), toluene, −78 °C. (c) (i) $Ph_3PC_3H_7Br$, n-BuLi (1.6 M solution in hexanes), −40 to 0 °C; (ii) Pd/C, H_2, 35 atm, EtOAc–CH_3OH (5 : 1), 58% for three steps. (d) H_5IO_6, ether, rt. (e) Propargyl bromide, DMF–Et_2O, Zn powder, total yield 59% for two steps. (f) TBSCl, DMF, Im., DMAP, rt, 92%. (g) BuLi (1.2 eq, 1.6 M in hexanes), $ClCO_2Me$, THF, −78 °C to rt, 87%. (h) Lindlar cat., quinoline, ethyl acetate, 91.2%. (i) 6 M HCl–THF (1 : 2), rt. (j) Ac_2O, Py, DMAP, CH_2Cl_2, 73% for two steps.

$CDCl_3$): δ 4.13 (2H, m), 3.95 (2H, m), 3.50 (2H, d, J = 3.5 Hz), 2.74 (2H, dt, J = 2.9, 16.9 Hz), 2.48 (2H, ddd, J = 2.6, 7.5, 16.9 Hz), 2.1 (2H, t, J = 2.7 Hz), 1.37 (3H, s), 1.34 (3H, s); IR (film): 3402, 3294, 2121, 1957, 1741 cm^{-1}; EIMS m/z (%): 223($M^+ - CH_3$, 19), 213(4), 199(1), 169(6), 123(4.46), 111(14), 59(100).

To a solution of the above mixture (3.84 g, 16.1 mmol) in DMF (10 mL) was added imidazole (10.9 g, 161 mmol), DMAP (cat.) and TBDMSCl (12.07 g, 80.5 mmol), and the reaction mixture was kept for 24 hours at room temperature. The reaction solution was diluted with diethyl ether, and washed with water and brine. The organic layer was dried over anhydrous Na_2SO_4 and evaporated to dryness. The residue was purified by flash chromatography using petroleum ether/ethyl acetate (200 : 1) as eluent to give the title compound **9** (5.19 g, 69%) as a clear liquid and its diastereomers (0.982 g). $[\alpha]_D^{20}$ −26.5 (c 0.76, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.23 (2H, m), 3.87 (2H, ddd, J = 1.2, 4.8, 10.2 Hz), 2.56 (2H, ddd, J = 2.5, 4.6, 16.9 Hz), 2.46 (2H, ddd, J = 2.9, 5.3, 16.9 Hz), 1.99 (2H, t, J = 2.7 Hz), 1.39 (6H, s), 0.92 (18H, s), 0.14 (12H, s); IR (film): 3316, 2124 cm^{-1}; EIMS m/z (%): 451($M^+ - CH_3$, 1), 351 (12), 283 (11), 215 (19), 183 (51), 73 (100); Anal. Calc. for $C_{25}H_{46}O_4Si_2$: C, 64.32; H, 9.93. Found: C, 64.08; H, 9.93%.

4-[1-(*tert*-Butyldimethylsilanyloxy)-but-3-ynyl]-5-[1-(*tert*-butyldimethylsilanyloxy)-pent-3-ynyl]-2,2-dimethyl-[1,3]dioxolane (10). To a solution of compound **9** (232 mg, 0.53 mmol) in dry THF (20 mL) at −78 °C was dropwise added n-BuLi (0.4 mL of 1.6 M solution in hexanes, 0.64 mmol) over 10 minutes under nitrogen. The reaction mixture was allowed to warm to 0 °C over 2 hours, and then cooled to −78 °C again, and then methyl iodide (0.165 mL, 2.65 mmol) was added dropwise. The mixture was slowly warmed to room temperature, and stirred for another 10 hours. The reaction was then quenched with aqueous saturated NH_4Cl at 0 °C, and extracted with diethyl ether. The combined organic layers were successively washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash chromatography using petroleum ether/ethyl acetate (200 : 1) as eluent to give the title compound **10** (197 mg, 82.8%) as a yellowish liquid. $[\alpha]_D^{20}$ −27.4 (c 1.15, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.25–4.18 (2H, m), 3.91–3.81 (2H, m), 2.56–2.49 (2H, m), 2.47–2.42 (2H, m), 1.97 (1H, dd, J = 2.6, 4.5 Hz), 1.77 (3H, t, J = 2.5 Hz), 1.38 (3H, s), 1.37 (3H, s), 0.93, 0.92, 0.91 (18H, 3s′), 0.14, 0.13, 0.12, 0.11 (12H, 4s′); IR (film): 3316, 2124 cm^{-1}; HRMS Calc. for $C_{26}H_{48}O_4NaSi_2$ (M + Na^+) 503.2989, Found 503.2983.

5-(*tert*-Butyldimethylsilanyloxy)-5-{5-[1-(*tert*-butyldimethylsilanyloxy)-pent-3-ynyl]-2,2-dimethyl-[1,3]dioxolan-4-yl}-pent-2-ynoic acid methyl ester (11). To a solution of compound **10** (81 mg, 0.169 mmol) in dry THF (12 mL) was dropwise added n-BuLi (0.12 mL, 0.186 mmol, 1.6 M solution in hexanes) at −78 °C under nitrogen. The reaction mixture was stirred for 1 hour at −78 °C, and then methyl chloroformate (65 μL, 0.845 mmol) was added dropwise. The mixture was slowly warmed to room temperature, and stirred for another 10 hours. The reaction was then quenched with aqueous saturated NH_4Cl at 0 °C, and extracted with diethyl ether. The combined organic layers were successively washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash chromatography using petroleum ether/ethyl acetate (80 : 1) as eluent to give the title compound **11** (74 mg, 81.3%). $[\alpha]_D^{20}$ −25.5 (c 0.92, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.17 (2H, dt, J = 4.1, 6.1 Hz), 3.95–3.81 (2H, m), 3.76 (3H, s), 2.73 (1H, dd, J = 5.2, 17.3 Hz), 2.64 (1H, dd, J = 4.5, 17.3 Hz), 2.50 (1H, m), 2.39 (1H, m), 1.78 (3H, t, J = 2.4 Hz), 1.38 (6H, s), 0.93 (9H, s), 0.91 (9H, s), 0.15 (6H, s), 0.12 (6H, s); IR (film): 2243, 1720 cm^{-1}. EIMS (m/z, %): 523($M^+ - CH_3$, 1), 481($M^+ - C_4H_9$, 9), 423(5), 341(11), 291(10), 241(15), 197(24), 73(100). HRMS m/z Calc. for $C_{24}H_{41}O_6Si_2$ ($M^+ - C_4H_9$): 481.2442, Found: 481.2459.

5-(*tert*-Butyldimethylsilanyloxy)-5-{5-[1-(*tert*-butyldimethylsilanyloxy)-pent-3-enyl]-2,2-dimethyl-[1,3]dioxolan-4-yl}-pent-2-enoic acid methyl ester (12). To a solution of compound **11** (80 mg, 0.152 mmol) in ethyl acetate (3 mL) was added Lindlar catalyst (40 mg) and quinoline (2 μL). The mixture was stirred under a hydrogen atmosphere at 50 °C for 2 hours. The reaction mixture was worked up by filtering and concentrating *in vacuo*. The residue was purified by flash chromatography (petroleum ether/ethyl acetate, 30 : 1) to give **12** (74 mg, 91%). $[\alpha]_D^{20}$ −3.0 (c 0.89, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.46 (1H, dt, J = 7.0, 11.6 Hz), 5.87 (1H, dt, J = 1.9, 11.6 Hz), 5.56–5.46 (2H, m), 4.06 (1H, t, J = 5.4 Hz), 3.96 (1H, t, J = 5.5 Hz), 3.91 (1H, dd, J = 5.2, 10.7 Hz), 3.84 (1H, dd, J = 5.3, 10.7 Hz), 3.70 (3H, s), 3.04–2.98 (2H, m), 2.50–2.19 (2H, m), 1.63–1.59 (3H, m), 1.38 (6H, s), 0.90 (9H, s), 0.88 (9H, s), 0.10, 0.09, 0.08, 0.07 (12H, 4s′); IR (film): 3024, 1727, 1647 cm^{-1}; ESIMS m/z: 543 (M + H^+), 560 (M + NH_4^+), 565 (M + Na^+), 561 (M + H_3O^+); HRMS(ESI) m/z: Calc. for $C_{28}H_{54}O_6Si_2Na$ (M + Na^+): 565.3351, Found: 565.3357.

5-[5-(1-Hydroxy-pent-3-enyl)-2,2-dimethyl-[1,3]dioxolan-4-yl]-penta-2,4-dienoic acid (13). To a solution of compound **12** (325 mg, 0.60 mmol) in dry THF (5 mL) was added tetrabutylammonium fluoride (1.8 mL, 1.8 mmol, 1 M solution in THF). The reaction mixture was stirred for 5 hours at room temperature, and another 10 hours at 40 °C. The solvent was removed *in vacuo*, and the residue was purified by flash chromatography over silica gel (petroleum ether : ethyl acetate, 2 : 1) to give **13** as a yellowish oil (122 mg, 72%). $[\alpha]_D^{20}$ +10.9 (c 0.61, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.67 (1H, dd, J = 11.5, 15.3 Hz), 6.67 (1H, t, J = 11.5 Hz), 6.07 (1H, dd, J = 7.3, 15.3 Hz), 5.74 (1H, d, J = 11.5), 5.69–5.64

(1H, m), 5.44–5.40 (1H, m), 4.64 (1H, t, J = 7.4 Hz), 3.86 (1H, dt, J = 5.0, 7.8 Hz), 3.79 (1H, dd, J = 4.8, 7.6 Hz), 2.33–2.27 (2H, m), 1.62 (3H, dd, J = 1.0, 6.8 Hz), 1.46 (3H, s), 1.45 (3H, s); IR (film): 3431(br), 1694, 1642, 1604 cm^{-1}; EIMS m/z (%): 300 ($M + NH_4^+$), 305 ($M + Na^+$), 321 ($M + K^+$); HRMS(ESI) m/z: Calc. for $C_{15}H_{22}O_5Na$ ($M + Na^+$): 305.1359, Found: 305.1366.

6-[5-(1-Hydroxy-pent-3-enyl)-2,2-dimethyl-[1,3]dioxolan-4-yl]-5,6-dihydro-pyran-2-one (14).

Method A. To a solution of compound **12** (27 mg, 0.05 mmol) in acetonitrile (1.6 mL) was added hydrofluoric acid (0.1 mL, 40%) at 0 °C. After being stirred for 2 hours at 0 °C, the reaction mixture was carefully neutralized with aqueous saturated $NaHCO_3$ and then concentrated *in vacuo*. The residue was purified by flash chromatography to give compounds **14** (4 mg, 21%), **15** (8 mg, 37%) and **16** (6 mg, 32%).

Method B. To a solution of compound **12** (22 mg, 0.04 mmol) in dry methanol (6 mL) was added ammonium fluoride (78 mg, 2.11 mmol). The reaction mixture was stirred for 2 days at 60 °C, and concentrated *in vacuo*. The residue was purified by flash chromatography to give compounds **14** (8 mg, 70%) and **15** (3 mg, 24%).

*Conversion of **15** to **14***. To a solution of compound **15** (18 mg, 0.06 mmol) in toluene (4 mL) was added PPTS or *p*-TsOH (cat.), and the reaction mixture was stirred for 18 hours at 60 °C until most of the starting material had been consumed. The solvent was removed *in vacuo*, and the residue was purified by flash chromatography over silica gel (petroleum ether :ethyl acetate, 2 : 1) to give **14** as a clear liquid (14 mg, 88%).

14. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.95 (1H, ddd, J = 2.7, 6.0, 9.7 Hz), 6.05 (1H, ddd, J = 1.1, 1.6, 9.7 Hz), 5.73 (1H, m), 5.50 (1H, m), 4.58 (1H, ddd, J = 4.7, 6.1, 10.7 Hz), 4.25 (1H, t, J = 6.4 Hz), 3.90 (1H, t, J = 6.7 Hz), 3.77–3.72 (1H, m), 2.66–2.53 (2H, m), 2.49–2.32 (2H, m), 1.67 (3H, dd, J = 0.7, 6.8 Hz), 1.43 (3H, s), 1.42 (3H, s); ESI-MS m/z: 283 ($M + H^+$), 300 ($M + NH_4^+$), 305 ($M + Na^+$); HRMS(ESI) m/z: Calc. for $C_{15}H_{22}O_5Na$ ($M + Na^+$): 305.1359, Found: 305.1356.

16. $[\alpha]_D^{20}$ +1.52 (c 0.79, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.46 (1H, dt, J = 8.3, 11.4 Hz), 6.01 (1H, dt, J = 1.2, 11.4 Hz), 5.71–5.65 (1H, m), 5.48–5.44 (1H, m), 4.02–3.75 (5H, m), 3.74(3H, s), 3.52–3.46 (1H, m), 3.36–3.32 (1H, m), 3.01–2.91 (2H, m), 2.79–2.71 (1H, m), 2.40 (2H, t, J = 6.8 Hz), 1.65 (3H, t, J = 0.8 Hz); IR (film): 3324 (br), 3022, 1729, 1650 cm^{-1}; ESI-MS m/z: 275 ($M + H^+$), 297 ($M + Na^+$); HRMS(ESI) m/z: Calc. for $C_{13}H_{22}O_6Na$ ($M + Na^+$): 297.1309, Found: 297.1305.

6-[5-(1-Hydroxy-pentyl)-2,2-dimethyl-[1,3]dioxolan-4-yl]-5,6-dihydro-pyran-2-one (17). To a solution of compound **14** (7 mg, 0.025 mmol) in benzene/ethanol (6 : 1, 0.7 mL) was added $RhCl(PPh_3)_3$ (3 mg). The mixture was stirred under a H_2 atmosphere for 28 hours. The reaction mixture was worked up by filtering and concentrating *in vacuo*. The residue was purified by flash chromatography (petroleum ether/ethyl acetate, 6 : 1) to give **17** (6 mg, 86%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.91 (1H, ddd, J = 3.1, 5.6, 9.6 Hz), 6.02 (1H, ddd, J = 1.3, 2.3, 9.8 Hz), 4.49 (1H, ddd, J = 1.6, 5.1, 10.5 Hz), 4.20 (1H, t, J = 6.6 Hz), 3.90 (1H, t, J = 6.3 Hz), 3.74–3.67 (2H, m), 2.62–2.51 (2H, m), 1.71–1.52 (2H, m), 1.43–1.32 (4H, m), 1.41 (3H, s), 1.38 (3H, s), 0.91 (3H, t, J = 7.2 Hz); ESI-MS m/z: 285 ($M + H^+$), 302 ($M + NH_4^+$), 307 ($M + Na^+$); HRMS(ESI) m/z: Calc. for $C_{15}H_{24}O_5Na$ ($M + Na^+$): 307.1516, Found: 307.1518.

8-epi-(+)-Boronolide (19). To a solution of compound **17** (6 mg, 0.021 mmol) in acetonitrile/ethanol (6 : 1, 2.8 mL) was added $CuCl_2 \cdot 2H_2O$ (15 mg, 0.088 mmol). The reaction mixture was stirred for 24 hours at room temperature, and then another 2 hours at 50 °C. The solvent was removed *in vacuo*, and the residue was purified by flash chromatography over silica gel (petroleum ether : ethyl acetate, 1 : 8).

To a solution of the product triol obtained above in dry CH_2Cl_2 (1.5 mL) was added pyridine (0.2 mL), 4-dimethylaminopyridine (DMAP, cat.) and acetic anhydride (0.1 mL) at room temperature. After 24 hours the solvent was removed *in vacuo*, and the residue was purified by flash chromatography over silica gel (petroleum ether : ethyl acetate, 3 : 1) to give compound **19** (6 mg, two steps 77%). $[\alpha]_D^{20}$ +14.06 (c 0.36, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.89 (1H, ddd, J = 2.6, 6.0, 9.8 Hz), 6.03 (1H, ddd, J = 1.0, 2.6, 9.8 Hz), 5.42 (1H, dd, J = 3.5, 6.6 Hz), 5.35 (1H, dd, J = 3.5, 6.6 Hz), 5.00 (1H, m), 4.48 (1H, ddd, J = 4.1, 6.8, 11.6 Hz), 2.40–2.31 (1H, m), 2.58–2.42 (1H, m), 2.13 (3H, s), 2.12 (3H, s), 2.04 (3H, s), 1.72–1.18 (6H, m), 0.89 (3H, t, J = 6.8 Hz); IR (film): 1747 (br) cm^{-1}; ESI-MS m/z: 371 ($M + H^+$), 388 ($M + NH_4^+$), 389 ($M + H_3O^+$), 393 ($M + Na^+$); HRMS(ESI) m/z: Calc. for $C_{18}H_{26}O_8Na$ ($M + Na^+$): 393.1520, Found: 393.1517.

(*tert*-Butyldimethylsilanyloxy)-(2,2,2′,2′-tetramethyl-[4,4′]bi-[[1,3]dioxolanyl]-5-yl)-acetic acid methyl ester (23). To a solution of compound **22** (6.46 g, 22.3 mmol) in DMF (4 mL) was added imidazole (4.55 g, 66.9 mmol), DMAP (cat.) and TBDMSCl (5.04 g, 33.45 mmol), and the reaction mixture was kept at room temperature for 24 hours. The solution was diluted with diethyl ether, and washed with water and brine. The organic layer was dried over anhydrous Na_2SO_4 and evaporated to dryness. The residue was purified by flash chromatography using petroleum ether : ethyl acetate (40 : 1) as eluent to give the title compound **23** (8.5 g, 94%) as a clear liquid. $[\alpha]_D^{20}$ +49.7 (c 0.91, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.37–4.34 (2H, m), 4.17 (1H, dd, J = 5.9, 8.1 Hz), 4.08–4.03 (2H, m), 3.85 (1H, dd, J = 6.0, 8.1 Hz), 3.77 (3H, s), 1.41 (3H, s), 1.40 (3H, s), 1.36 (3H, s), 1.35 (3H, s), 0.94 (9H, s), 0.12 (3H, s), 0.07 (3H, s); IR (film):1770 cm^{-1}; ESI-MS m/z: 427 ($M + Na^+$); HRMS(ESI) m/z: Calc. for $C_{19}H_{36}O_7SiNa$ ($M + Na^+$): 427.2123, Found: 427.2121.

***tert*-Butyl-dimethyl-[1-(2,2,2′,2′-tetramethyl-[4,4′]bi[[1,3]dioxolanyl]-5-yl)-pentyloxy]-silane (25).** To a solution of compound **23** (844 mg, 2.09 mmol) in dry toluene (20 mL) was added dropwise DIBAL-H (2.61 mL, 2.61 mmol, 1.0 M solution in toluene) at −78 °C under nitrogen, and the reaction mixture was stirred for 1 hour at the same temperature. Methanol (2 mL) was slowly added at −78 °C. Then the reaction mixture was slowly warmed to room temperature. The mixture was diluted with diethyl ether and filtered. The filtrate was concentrated to give a clear liquid. It was used in the next reaction without further purification.

To the suspension of n-propyltriphenylphosphonium bromide (1.61 g, 4.18 mmol) in THF (20 mL) was added n-BuLi (2.6 mL, 4.18 mmol, 1.6 M solution in hexanes) at −40 °C under nitrogen, and the mixture was stirred for one hour between −30 and −20 °C. To the reaction mixture was dropwise added the solution of the aldehyde obtained above in THF (10 mL) at −40 °C, and then the mixture was warmed to room temperature, and stirred overnight. It was then quenched with aqueous saturated NH_4Cl, and extracted with diethyl ether. The organic phases were washed with water and brine, dried over anhydrous Na_2SO_4, and then evaporated under reduced pressure to afford a clear liquid. Without further purification, it was directly used in the next hydrogenation.

To the solution of the crude product obtained above in ethyl acetate–methanol (5 : 1, 30 mL) was added Pd/C (10%, 100 mg). The mixture was stirred overnight under 35 atm H_2 at room temperature, and then worked up by filtering and concentrating *in vacuo*. The residue was purified by flash chromatography with petroleum ether/ethyl acetate (40 : 1) as eluent to give **25** (487 mg, 58% for three steps) as a pale yellow oil. $[\alpha]_D^{20}$ +31.7 (c 0.85, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.15–4.06 (2H, m), 4.02–3.97 (1H, m), 3.91–3.88 (2H, m), 3.73 (1H, dt, J = 3.1, 6.4 Hz), 1.72–1.30 (6H, m), 1.41 (6H, s,), 1.37 (3H, s), 1.35 (3H,s), 0.94 (3H, t, J = 7.0 Hz), 0.90 (s, 9H), 0.08 (s, 6H); EIMS m/z (%): 387 ($M^+ - CH_3$, 11.16), 287 (60.63), 201 (97.13), 143 (69.79),

101 (100); HRMS(ESI) *m/z* Calcd for $C_{21}H_{42}O_5SiNa$ (M + Na^+): 425.2694, Found: 425.2699.

1-{5-[1-(*tert*-Butyldimethylsilanyloxy)-pentyl]-2,2-dimethyl-[1,3]dioxolan-4-yl}-but-3-yn-1-ol (27). A suspension of $HIO_4{\cdot}2H_2O$ (171 mg, 0.75 mmol) in anhydrous diethyl ether (5 mL) was stirred for 10 minutes at room temperature. Then a solution of compound **25** (202 mg, 0.5 mmol) in anhydrous diethyl ether (6 mL) was added into the above suspension. The reaction mixture was stirred for 10 hours, then filtered through a celite pad, and washed with diethyl ether. The combined organic layers were successively washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to give a colorless liquid. It was directly used in the next reaction without further purification.

To the stirred mixture of the aldehyde obtained above and prop-2-ynyl bromide (89 mg, 0.75 mmol) in DMF–Et_2O (1 : 1, 5 mL) was slowlyadded zinc dust (65 mg, 1 mmol). An exothermic reaction started within a few minutes and brought the mixture to slowly reflux; this was allowed to continue until most of the aldehyde had been consumed. The reaction mixture was then poured into aqueous saturated NH_4Cl, filtrated, and the combined organic layers were successively washed with water and brine, dried over anhydrous Na_2SO_4. The clear solution obtained was evaporated to dryness and the residue was purified by flash chromatography using petroleum ether : ethyl acetate (80 : 1) as eluent to afford the title compound **27** (89 mg) and the corresponding *threo* product (20 mg) with the total yield of 59%. $[\alpha]_D^{20}$ −10.5 (*c* 0.71, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.96–3.90 (2H, m), 3.82 (1H, dd, *J* = 2.9, 8.3 Hz), 3.72–3.65 (2H, m), 2.66 (1H, ddd, *J* = 2.6, 3.6, 17.0 Hz), 2.51 (1H, ddd, *J* = 2.7, 7.2, 17.0 Hz), 2.05 (1H, t, *J* = 2.7 Hz), 1.78–1.30 (6H, m), 1.41 (3H, s), 1.38 (3H, s), 0.92 (9H, s), 0.91 (3H, t, *J* = 6.6 Hz), 0.14 (s, 3H), 0.13 (s, 3H); IR (film): 3480, 3315, 1958 cm^{-1}; ESI-MS *m/z*: 393 (M + Na^+); HRMS(ESI) *m/z*: Calc. for $C_{20}H_{38}O_4SiNa$ (M + Na^+): 393.2432, Found: 393.2435.

5-(*tert*-Butyldimethylsilanyloxy)-5-{5-[1-(*tert*-butyldimethylsilanyloxy)-pentyl]-2,2-dimethyl-[1,3]dioxolan-4-yl}-pent-2-ynoic acid methyl ester (29). To a solution of compound **27** (69 mg, 0.186 mmol) in DMF (1.3 mL) was added imidazole (38 mg, 0.558 mmol), DMAP (cat.) and TBDMSCl (42 mg, 0.28 mmol), and the reaction mixture was kept for 36 hours at room temperature. The solution was diluted with diethyl ether, and then washed with water and brine. The organic layer was dried over anhydrous Na_2SO_4 and evaporated to dryness. The residue was purified by flash chromatography using petroleum ether : ethyl acetate (80 : 1) as eluent to give compound **28** (83 mg, 92%) as a clear liquid.

To a solution of compound **28** (105 mg, 0.22 mmol) in dry THF (12 mL) was dropwise added n-BuLi (0.17 mL, 0.26 mmol, 1.6 M solution in hexanes) at −78 °C under nitrogen. The reaction mixture was stirred for 1 hour at −78 °C, and then methyl chloroformate (0.1 mL, 1.30 mmol) was added dropwise. The mixture was slowly warmed to room temperature, and stirred for another 10 hours. The reaction was then quenched with aqueous saturated NH_4Cl at 0 °C, and the reaction mixture was extracted with diethyl ether. The combined organic layers were successively washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash chromatography using petroleum ether : ethyl acetate (80 : 1) as eluent to give the title compound **29** (102 mg, 87%) as a colorless liquid. $[\alpha]_D^{20}$ −5.5 (*c* 0.88, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.11–4.07 (1H, m), 3.95 (1H, dd, *J* = 2.3, 6.7 Hz), 3.88 (1H, dt, *J* = 4.7, 6.6 Hz), 3.76 (3H, s), 3.71 (1H, dt, *J* = 2.5, 6.4 Hz), 2.74–2.71(2H, m), 1.32–1.70 (6H, m), 1.43 (3H, s), 1.37 (3H, s), 0.93 (9H, s), 0.92 (9H, s), 0.16 (3H, s), 0.12 (3H, s), 0.11 (3H, s), 0.09 (3H, s); ^{13}C NMR (75 MHz; $CDCl_3$): 0.06, 0.10, 18.3, 22.4, 22.5, 27.3, 29.0, 30.2, 30.3, 31.5, 32.2, 32.5, 38.4, 56.7, 76.4, 76.8, 79.1, 82.5, 85.8, 90.8, 113.6, 158.3; IR (film): 2243, 1721 cm^{-1}; ESI-MS *m/z*: 543(M + H^+), 560 (M + NH_4^+), 561 (M + H_3O^+); HRMS(ESI) *m/z*: Calc. for $C_{28}H_{54}O_6Si_2Na$ (M + Na^+): 565.3351, Found: 565.3341.

5-(*tert*-Butyldimethylsilanyloxy)-5-{5-[1-(*tert*-butyldimethylsilanyloxy)-pentyl]-2,2-dimethyl-[1,3]dioxolan-4-yl}-pent-2-enoic acid methyl ester (30). To a solution of compound **29** (34 mg, 0.063 mmol) in ethyl acetate (1 mL) was added Lindlar catalyst (20 mg) and quinoline (1 μL). The mixture was stirred under a H_2 atmosphere at room temperature for 1 hour. The reaction mixture was worked up by filtering and concentrating *in vacuo*. The residue was purified by flash chromatography (petroleum ether/ethyl acetate, 100 : 1) to give **30** (31 mg, 91%). $[\alpha]_D^{20}$ +3.76 (*c* 0.43, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.46 (1H, dt, *J* = 7.0, 11.7 Hz), 5.87 (1H, dt, *J* = 2.0, 11.7 Hz), 4.02–3.97 (1H, m), 3.93–3.87 (2H, m), 3.72–3.66 (1H, m), 3.70 (3H, s), 3.13 (1H, dddd, *J* = 1.7, 4.5, 7.3, 16.5 Hz), 2.93 (1H, dddd, *J* = 2.1, 5.1, 6.5, 16.5 Hz), 1.31–1.73 (6H, m), 1.38 (3H, s), 1.37 (3H, s), 0.89 (9H, s), 0.88 (9H, s), 0.08 (6H, s), 0.07 (6H, s); IR (film):1727, 1647 cm^{-1}; ESI-MS *m/z*: 545 (M + H^+), 562 (M + NH_4^+), 563 (M + H_3O^+); HRMS(ESI) *m/z*: Calc. for $C_{28}H_{56}O_6Si_2Na$ (M + Na^+): 567.3508, Found: 567.3508.

6-(1,2,3-Trihydroxy-heptyl)-5,6-dihydro-pyran-2-one (31). To a stirred solution of compound **30** (16 mg, 0.029 mmol) in THF (0.8 mL) was dropwise added 6 M HCl (0.4 mL). After being stirred for 17 hours at room temperature, the reaction mixture was carefully neutralized with aqueous saturated $NaHCO_3$ at 0 °C, and then concentrated *in vacuo*. The residue was used without further purification for the next step. For analysis, the sample was purified by flash chromatography (petroleum ether/ethyl acetate, 1 : 2). White solid. mp 80–82 °C [Lit.[2] 99–100 °C]; $[\alpha]_D^{20}$ +73.0 (*c* 0.39, $CHCl_3$) [Lit.[17] $[\alpha]_D^{25}$ +59 (*c* 0.2, $CHCl_3$)]; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.97 (1H, ddd, *J* = 2.5, 5.9, 9.8 Hz), 6.04 (1H, ddd, *J* = 0.7, 2.6, 9.8 Hz), 4.55 (1H, ddd, *J* = 4.3, 7.4, 11.4 Hz), 3.87 (1H, m), 3.82–3.65 (2H, m), 3.49–3.37 (1H, m), 2.83–2.72 (1H, m), 2.73–2.62 (1H, m), 2.56–2.45 (1H, m), 2.41–2.28 (1H, m), 1.72–1.32 (6H, m), 0.92 (1H, t, *J* = 7.0 Hz).

(+)-Boronolide (1). To a solution of the above crude product in dry CH_2Cl_2 (1.5 mL) were added pyridine (0.3 mL), 4-dimethylaminopyridine (DMAP, cat.) and acetic anhydride (0.2 mL) at room temperature. After 24 hours the solvent was removed *in vacuo*, and the residue was purified by flash chromatography over silica gel (petroleum ether : ethyl acetate, 2 : 1) to give (+)-boronolide **1** as a colorless solid (8 mg, two steps 73%). mp 89–92 °C [Lit.[2] 89–90 °C]; $[\alpha]_D^{20}$ +24.7 (*c* 0.34, EtOH) [Lit.[2] $[\alpha]_D$ +28 (*c* 0.08, EtOH)]; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.89 (1H, ddd, *J* = 2.1, 5.8, 9.6 Hz), 6.04 (1H, ddd, *J* = 0.9, 2.7, 9.6 Hz), 5.36 (1H, dd, *J* = 4.5, 7.5 Hz), 5.34 (1H, dd, *J* = 4.5, 7.5 Hz), 5.03 (1H, q, *J* = 6.0 Hz), 4.54 (1H, ddd, *J* = 4.2, 5.9, 11.8 Hz), 2.54 (1H, ddt, *J* = 2.7, 11.7, 18.0 Hz), 2.36–2.26 (1H, m), 2.15 (3H, s), 2.11 (3H, s), 2.09 (3H, s), 1.65–1.51 (2H, m), 1.35–1.21 (m, 4H), 0.89 (3H, t, *J* = 6.7 Hz); IR (film):1744 (br) cm^{-1}; ESI-MS *m/z*: 388 (M + NH_4^+), 393 (M + Na^+); HRMS(ESI) *m/z*: Calc. for $C_{18}H_{26}O_8Na$ (M + Na^+): 393.1520, Found: 393.1530.

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