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Stereoselective synthesis of (+)-boronolide and (−)-5-*epi*-boronolide

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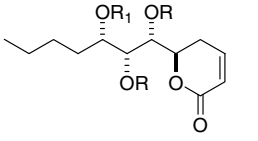
Received 23 March 2006; accepted 27 March 2006
Available online 27 April 2006

Abstract—Stereoselective synthesis of boronolide and 5-*epi*-boronolide was achieved from D-(−)-tartaric acid. The key step involves the reduction of a keto Weinreb amide for the synthesis of boronolide, and a single pot construction of a diketone from the bis-Weinreb amide of tartaric acid and subsequent reduction with L-Selectride for 5-*epi*-boronolide.

1. Introduction

Polyhydroxylated δ-lactones are ubiquitous natural products possessing a variety of medicinal applications. Boronolide **1** and its derivatives, 1,2-dideacetylboronolide **2**, deacetylboronolide **3**, having such δ-lactone functionality were isolated from the bark and branches of *Tetradenia fruticosa* and from the leaves of *Tetradenia barberae* and *Tetradenia riparia*, which have been widely utilized as local folk medicine in Madagascar and in southern Africa.[1,2] The root extract of these plants is traditionally used by the Zulu as an emetic agent, while an infusion of the leaves has been reported to be effective against malaria. The high activity associated with these compounds has resulted in considerable synthetic efforts. Many of these originate from the chiral pool, such as carbohydrates[3] and tartaric acid,[4] while an asymmetric hydroxylation[5] or direct aldol reaction[6] was employed in other syntheses.[7] Herein, we report a convenient and concise formal approach for the synthesis of boronolide **1** and a concise approach to the synthesis of 5-*epi*-boronolide **4**, starting from D-(−)-tartaric acid.



1 R = R_1 = Ac = boronolide
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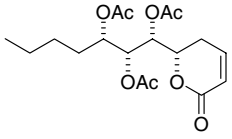

4

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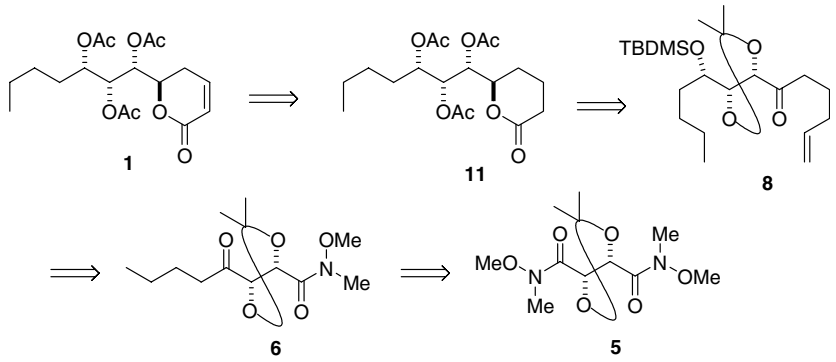
doi:10.1016/j.tetasy.2006.03.028

2. Results and discussion

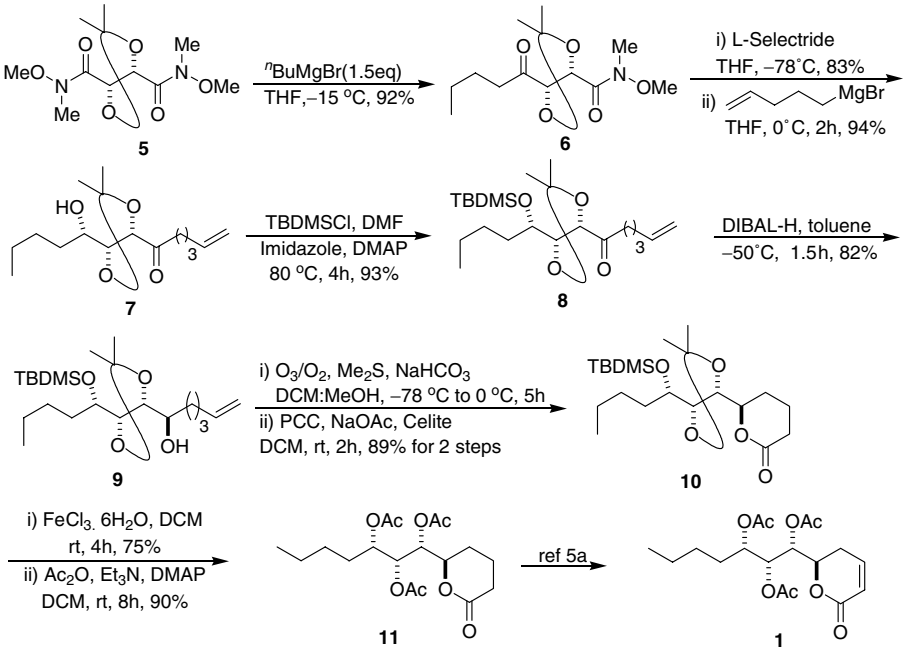
Recently, we have shown that a series of symmetrical 1,4-diaryl diketones derived from tartaric acid can be reduced to the corresponding C_2-symmetric diols with good selectivity.[8] Over the course of this investigation, we found that the controlled addition of a Grignard reagent to the bis-Weinreb amide **5** derived from tartaric acid leads to the keto Weinreb-amide **6**, which can be further elaborated.[9] We envisaged that the known precursor **11** for the synthesis of boronolide can be assembled from silyloxy ketone **8**. Ketone **8** can be obtained through the stepwise addition of Grignard reagents and the reduction of the corresponding ketones (Scheme 1).

The controlled addition of butylmagnesium bromide to the bis-Weinreb amide **5**[10] resulted in the formation of mono keto Weinreb-amide **6** in 92% yield. Stereoselective reduction of the keto group in **6** was achieved with L-Selectride yielding a single diastereomer of the alcohol, which on reaction with 4-pentenylmagensium bromide afforded hydroxy ketone **7** in 78% overall yield for two steps. The alcohol group in **7** was protected as its silyl ether under standard conditions. Stereoselective reduction of silyloxy ketone **8** was carried out with a number of reducing agents. Of the several reducing agents examined, DIBAL-H was found to be selective, affording the required alcohol **9** in 83% yield along with 13% of the other isomer, which was separable by column chromatography (Scheme 2).

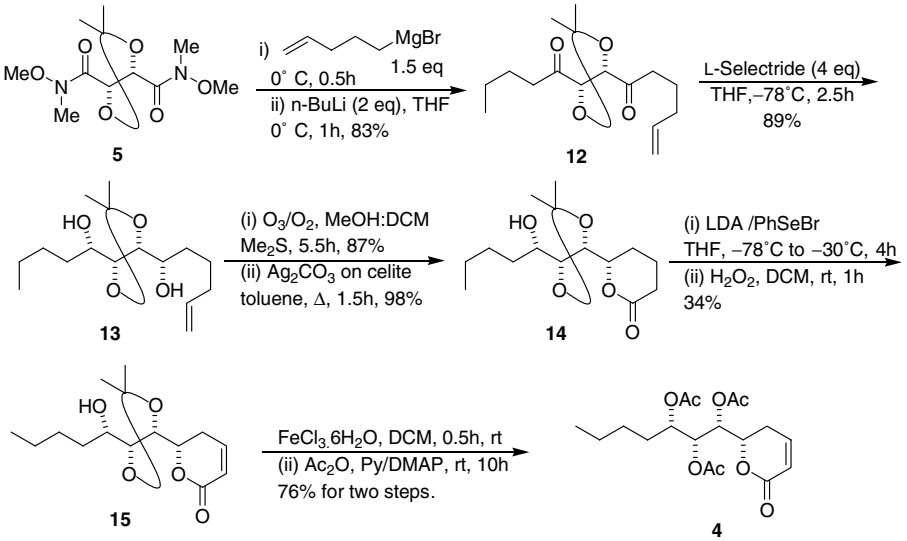
Ozonolysis of alcohol **9**, followed by oxidation of the resultant lactol with PCC, afforded the lactone **10** in 89% yield.[11] Deprotection of the TBDMS group and the



Scheme 1. Retrosynthesis for boronolide.



Scheme 2. Synthesis of (+)-boronolide.



Scheme 3. Synthesis of 5-*epi*-boronolide.

acetonide was achieved with $FeCl_3$ yielding the triol in 75% yield, which was acetylated with Ac_2O in the presence of Et_3N/DMAP to yield triacetate **11** in 90% yield. Triacetate **11**, $[\alpha]_D = -21$ (*c* 3, EtOH); {lit.[5a] $[\alpha]_D = -19.5$ (*c* 0.36, EtOH)} exhibited spectral data identical to that reported in the literature.[5a] Since conversion of triacetate **11** to boronolide **1** has already been reported in the literature, the present sequence constitutes a formal synthesis of boronolide.

We turned our attention to the synthesis of 5-*epi*-boronolide, which was achieved as follows. Reaction of the bis-Weinreb amide **5** successively with 4-pentenylmagnesium bromide (1.5 equiv) and with *n*-butyllithium (2 equiv) in one-pot afforded diketone **12** in 83% yield. We anticipated that the steric differentiation between the two alkyl groups viz. 4-pentenyl and *n*-butyl in diketone **12** would be minimal and that the diketone could be reduced with good selectivity under the conditions that were employed for the C_2-symmetric diketones. In fact, reduction of diketone **12** with L-Selectride produced diol **13** as a single diastereomer in 89% yield. Ozonolysis of diol **13** afforded the lactol in 87% yield. Oxidation of the lactol with silver carbonate[12] cleanly produced the corresponding lactone **14**. Phenylselenation of the unprotected hydroxy lactone **14**, followed by the elimination of the phenylselenyl group, afforded α,β-unsaturated lactone **15**, albeit in 34% yield. Facile deprotection of the acetonide was performed with ferric chloride,[13] which on acylation with acetic anhydride afforded 5-*epi*-boronolide **4** (Scheme 3).

3. Conclusion

In conclusion, an expeditious formal approach for the enantiospecific synthesis of boronolide was achieved from the bis-Weinreb amide of tartaric acid. The methodology was applied to the synthesis of 5-*epi*-boronolide. Construction of the key tetrol unit in boronolide was achieved by a stepwise stereoselective reduction of ketones derived from the bis-Weinreb amide with L-Selectride and DIBAL-H.

4. Experimental

4.1. Preparation of (4*S*,5*S*)-*N*-methoxy-*N*,2,2-trimethyl-5-pentanoyl-1,3-dioxolane-4-carboxamide 6

In an oven dried two neck 50 mL round-bottom flask equipped with a magnetic stir bar and argon inlet was placed the bis-Weinreb amide **5** (0.5 g, 1.8 mmol) dissolved in 6 mL of THF. This was cooled to −15 °C after which a THF solution of *n*-butylmagnesium bromide (3 mL of 1 M solution in THF, 3 mmol) was added dropwise under an argon atmosphere. The reaction mixture was stirred for 0.5 h at the same temperature. After the reaction was complete (TLC), it was quenched with satd NH_4Cl (10 mL) and extracted with ether (3 × 10 mL). The combined ether extracts were washed with brine and dried over Na_2SO_4. The residue obtained after the evaporation of solvent was purified by column chromatography to afford **6** in 92% yield (0.45 g) as a colorless oil. $[\alpha]_D = -7$ (*c* 1, $CHCl_3$); IR (neat): 2987, 2874, 1718, 1672, 1463, 1380, 1257, 1181, 1080, 987, 857, 749 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.04 (d, *J* = 5.7 Hz, 1H), 4.82 (d, *J* = 5.7 Hz, 1H), 3.72 (s, 3H), 3.24 (s, 3H), 2.87–2.52 (m, 2H), 1.66–1.52 (m, 2H), 1.50 (s, 3H), 1.44 (s, 3H), 1.40–1.29 (m, 2H), 0.92 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.4, 169.8, 112.7, 82.2, 73.9, 61.6, 38.9, 32.4, 26.6, 26.2, 25.1, 22.2, 13.8; HRMS for $C_{13}H_{23}NO_5$+Na calcd 296.1474; found 296.1474.

4.2. Preparation of (4*S*,5*R*)-5-((*S*)-1-hydroxypentyl)-*N*-methoxy-*N*,2,2-trimethyl-1,3-dioxolane-4-carboxamide

To a solution of **6** (0.4 g, 1.5 mmol) in 5 mL of THF at −78 °C L-Selectride (3 mL of 1 M solution in THF, 3 mmol) was added dropwise over 10 min, under an argon atmosphere. The reaction mixture was stirred for 2.5 h, quenched with water (5 mL) and extracted with ether (3 × 10 mL). The combined ethereal extracts were washed with brine and dried over Na_2SO_4. The residue obtained after evaporation of solvent was purified by column chromatography to yield (4*S*,5*R*)-5-((*S*)-1-hydroxypentyl)-*N*-methoxy-*N*,2,2-trimethyl-1,3-dioxolane-4-carboxamide as a colorless oil in 89% yield (0.41 g). $[\alpha]_D = +6.1$ (*c* 1.2, $CHCl_3$); IR (neat): 3478, 2933, 2861, 1670, 1450, 1380, 1213, 1070 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.76 (br s, 1H), 4.39 (br s, 1H), 3.75 (s, 3H), 3.61 (br s, 1H), 3.24 (s, 3H), 1.60–1.32 (m, 6H), 1.48 (s, 3H), 1.46 (s, 3H), 0.90 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 110.9, 80.8, 73.7, 70.2, 61.6, 34.2, 27.9, 26.9, 26.0, 22.5, 13.9; HRMS for $C_{13}H_{25}NO_5$+Na calcd 298.1630; found 298.1638.

4.3. Preparation of (4*S*,5*R*)-4-(hex-5-enoyl)-5-((*S*)-1-hydroxypentyl)-2,2-dimethyl-1,3-dioxolane 7

To a solution of alcohol prepared above (0.35 g, 1.3 mmol) in 4 mL of THF was added 4-pentenylmagnesium bromide (3.9 mL, 1 M solution in THF, 3.9 mmol) at 0 °C under an argon atmosphere. The reaction mixture was stirred for 2 h at the same temperature, quenched with saturated NH_4Cl (8 mL), and extracted with ether (3 × 10 mL). The combined ether extracts were washed with brine and dried over Na_2SO_4. The residue obtained after the evaporation of solvent was purified by column chromatography to yield **7** in 94% (0.34 g) as a colorless oil. $[\alpha]_D = -28$ (*c* 1, $CHCl_3$); IR (neat): 3502, 2935, 2861, 1716, 1457, 1380, 1213, 1164, 1081, 914, 877 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.77 (ddt, *J* = 17.1, 10.2, 6.6 Hz, 1H), 5.07–4.93 (m, 2H), 4.33 (d, *J* = 7.2 Hz, 1H), 3.98 (dd, *J* = 7.2, 3.0 Hz, 1H), 3.68–3.57 (m, 1H), 2.77–2.55 (m, 2H), 2.12–2.02 (m, 2H), 1.76–1.63 (m, 2H), 1.59–1.29 (m, 6H), 1.47 (s, 3H), 1.39 (s, 3H), 0.91 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.8, 137.8, 115.2, 110.5, 81.5, 80.3, 70.5, 38.0, 34.1, 32.9, 27.8, 26.7, 26.1, 22.5, 21.8, 13.9; HRMS for $C_{16}H_{28}O_4$+Na calcd 307.1885; found 307.1876.

4.4. Preparation of (4*S*,5*S*)-5-((*S*)-1-*tert*-butyldimethylsilyl-oxypentyl)-4-(hex-5-enoyl)-2,2-dimethyl-1,3-dioxolane 8

To a solution of **7** (0.3 g, 1.05 mmol) in 3 mL of DMF was added imidazole (0.18 g, 2.6 mmol), DMAP (0.025 g,

0.2 mmol), and TBDMSCl (0.3 g, 2 mmol). The reaction mixture was kept at 80 °C and stirred at the same temperature for 2 h. It was cooled to room temperature and poured into water (10 mL) and extracted with ether (3 × 10 mL). The combined ethereal extracts were washed with brine and dried over Na_2SO_4. The residue obtained after evaporation of solvent was purified by column chromatography to yield **8** as a colorless oil in 93% (0.39 g). $[\alpha]_D = -9.7$ (*c* 1.6, $CHCl_3$); IR (neat): 2956, 2857, 1718, 1457, 1380, 1255, 1213, 1143, 1087, 1004, 914, 875, 808, 775 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.76 (ddt, $J = 16.8$, 10.2, 6.6 Hz, 1H); 5.05–4.93 (m, 2H), 4.27 (d, $J = 7.2$ Hz, 1H), 4.04 (dd, $J = 7.2$, 3.6 Hz, 1H), 3.74 (td, $J = 6.3$, 3.6 Hz, 1H), 2.76–2.54 (m, 2H), 2.10–2.01 (m, 2H), 1.75–1.26 (m, 8H), 1.43 (s, 3H), 1.36 (s, 3H), 0.88 (s, 12H), 0.07 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.5, 137.9, 115.2, 110.3, 80.9, 79.9, 71.7, 38.0, 33.3, 33.0, 27.7, 26.7, 26.4, 25.9, 22.7, 21.9, 18.2, 14.0, −4.4; HRMS for $C_{22}H_{42}O_4Si$+Na calcd 421.2750; found 421.2765.

4.5. Preparation of (4*R*,5*S*)-5-((*S*)-1-*tert*-butyldimethylsilyloxypentyl)-4-((*R*)-1-hydoxyhex-5-enyl)-2,2-methyl-1,3-dioxolane 9

To a solution of **8** (0.15 g, 0.5 mmol) in 3 mL of toluene DIBAL-H (0.8 mL, 1 M solution in toluene, 0.8 mmol) was added dropwise for 5 min at −50 °C under an argon atmosphere. The reaction mixture was stirred for 1.5 h at the same temperature, quenched with water and filtered through Celite. The Celite pad was washed with ether (20 mL) and dried over Na_2SO_4. Evaporation of solvent yielded a mixture of diastereomers, which were separated by column chromatography to obtain the major diastereomer **9** as a colorless oil in 83% (0.12 g) yield. $[\alpha]_D = -13.1$ (*c* 1.3, $CHCl_3$); IR (neat): 3453, 2931, 2859, 1463, 1378, 1253, 1168, 1073, 912, 836, 775 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.81 (ddt, $J = 17.1$, 10.2, 6.6 Hz, 1H), 5.04–4.89 (m, 2H), 3.92–3.85 (m, 1H), 3.79–3.70 (m, 2H), 3.60–3.50 (m, 2H), 2.10–2.04 (m, 2H), 1.82–1.24 (m, 10H), 1.36 (s, 3H), 1.35 (s, 3H), 0.90 (s, 12H), 0.11 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.9, 114.3, 107.9, 82.6, 78.8, 71.9, 71.6, 33.8, 32.8, 32.2, 28.6, 27.0, 26.8, 25.8, 24.5, 22.7, 18.0, 13.9, −4.4, −4.6; HRMS for $C_{22}H_{44}O_4Si$+Na calcd 423.2907; found 423.2908.

4.6. Preparation of (6*S*)-6-((4*S*,5*R*)-5-((*R*)-1-*tert*-butyldimethylsilyloxypentyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-tetrahydro-2*H*-pyran-2-one 10

Ozone was bubbled through a pre-cooled (−78 °C) solution of **9** (0.1 g, 0.25 mmol) in 4:1 DCM/MeOH (10 mL) containing solid $NaHCO_3$ (10 mg) until the pale blue color persisted. Excess ozone was flushed off with oxygen, and Me_2S (0.5 mL) was added and stirred for 5 h at 0 °C. The reaction mixture was concentrated under reduced pressure, filtered through a short pad of Celite, and the Celite pad washed with ether (15 mL). The ether layers were combined, and evaporation of the solvent yielded the crude lactol, which was subjected to oxidation without further purification.

To a solution of crude lactol (obtained above) in 3 mL of DCM was added a pinch of Celite and NaOAc (60 mg, 0.75 mmol) at room temperature and stirred for 5 min. PCC (0.16 g, 0.75 mmol) was introduced into the reaction mixture at the same temperature. It was stirred at rt for 2 h and after the reaction was complete (TLC), it was filtered through a short pad of Celite and the Celite pad was washed with ether (15 mL). The ether layers were combined and the residue obtained after evaporation of solvent was purified by column chromatography to yield **10** as a colorless oil in 89% (0.09 g). $[\alpha]_D = +3.5$ (*c* 4.6, $CHCl_3$); IR (neat): 2956, 2857, 1747, 1463, 1378, 1251, 1162, 1051, 1006, 932, 877, 775 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.38–4.29 (m, 1H), 4.08 (dd, $J = 7.5$, 6.3 Hz, 1H), 3.90 (dd, $J = 7.5$, 3.0 Hz, 1H), 3.79 (td, $J = 6.6$, 3.0 Hz, 1H), 2.63–2.35 (m, 2H), 2.06–1.27 (m, 10H), 1.38 (s, 3H), 1.35 (s, 3H), 0.86 (s, 12H), 0.05 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3, 109.4, 81.0, 80.9, 77.3, 71.7, 33.4, 29.7, 27.8, 27.2, 26.9, 25.8, 23.8, 22.8, 18.1, 18.0, 13.9, −4.4; HRMS for $C_{21}H_{40}O_5Si$+Na calcd 423.2543; found 423.2541.

4.7. Preparation of (6*R*)-6-((1*R*,2*R*,3*S*)-1,2,3-triacetoxyhept-1-yl)-tetrahydro-2*H*-pyran-2-one 11

To a solution of **10** (65 mg, 0.16 mmol) in 2 mL of DCM was added $FeCl_3{\cdot}6H_2O$ at room temperature. The reaction mixture was stirred for 4 h, filtered through a short pad of Celite. The Celite pad was washed with ether (10 mL). Solid Na_2CO_3 was added to the ether layer with few drops of water and stirred for 5 min. The residue obtained after evaporation of solvent was purified by column chromatography to yield triol (6*R*)-6-(1*S*,2*R*,3*S*)-1,2,3-(trihydroxyhept-1-yl)-tetrahydro-2*H*-pyran-2-one in 75% (0.03 g) as a colorless oil. $[\alpha]_D = -25.4$ (*c* 2.4, $CHCl_3$); IR (neat): 3401, 2938, 1718, 1444, 1243, 1209, 1049, 929 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.46–4.38 (m, 1H), 4.16–3.20 (m, 6H), 2.68–2.36 (m, 2H), 2.22–2.13 (m, 1H), 2.04–1.77 (m, 2H), 1.74–1.22 (m, 7H), 0.91 (t, $J = 6.3$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.0, 79.8, 74.7, 74.0, 70.5, 33.3, 29.7, 27.7, 23.9, 22.6, 18.0, 13.9; HRMS for $C_{12}H_{22}O_5$+Na calcd 269.1365; found 269.1358.

To a solution of the triol obtained above (20 mg, 0.08 mmol) in 2 mL of DCM was added DMAP (5 mg, 0.04 mmol), Et_3N (0.4 mL), and Ac_2O (0.05 mL, 0.5 mmol) at room temperature. The reaction mixture was stirred for 8 h at the same temperature, during which the reaction was complete (TLC). The reaction mixture was poured into water (8 mL) and extracted with ether (3 × 5 mL). The combined ether extracts were washed with dil. HCl (2 × 10 mL), brine and dried over Na_2SO_4. The residue obtained after evaporation solvent was purified by column chromatography to yield **11** in 90% (0.027 g) as a colorless oil. $[\alpha]_D = -21$ (*c* 3, EtOH); {lit.[5a] $[\alpha]_D = -19.5$ (*c* 0.36, EtOH)}; IR (neat): 2958, 2863, 1749, 1457, 1373, 1222, 1168, 1025, 960, 933, 852 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.35 (dd, $J = 6.0$, 4.2 Hz, 1H), 5.20 (dd, $J = 6.0$, 4.2 Hz, 1H), 5.01 (td, $J = 6.3$, 6.0 Hz, 1H), 4.47–4.36 (m, 1H), 2.66–2.38 (m, 2H), 2.13 (s, 3H), 2.10 (s, 3H), 2.07 (s, 3H), 2.02–1.65 (m, 4H), 1.60–1.49

(m, 2H), 1.36–1.25 (m, 4H), 0.88 (t, $J = 6.6$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 169.9, 169.7, 77.7, 71.7, 71.3, 70.6, 30.2, 29.5, 26.9, 23.4, 22.3, 20.8, 20.7, 20.6, 18.1, 13.8.

4.8. Preparation of 1-((4*S*,5*S*)-2,2-dimethyl-5-pentanoyl-1,3-dioxolan-4-yl)-hex-5-en-1-one 12

In an oven dried two neck 50 mL round-bottom flask equipped with a magnetic stirrer bar and argon inlet was placed the bis-Weinreb amide **5** (0.5 g, 1.8 mmol) dissolved in 6 mL of THF. The reaction mixture was cooled to −15 °C and a THF solution of 4-pentenylmagnesium bromide (3 mL of 1 M solution in THF, 3 mmol) was added drop wise under an argon atmosphere. The reaction mixture was stirred for 0.5 h and a hexane solution of ^{n}BuLi (2.2 mL of 1.6 M, 3.6 mmol) was added dropwise at the same temperature. The reaction mixture was warmed up to 0 °C over a period of 1 h, quenched with saturated NH_4Cl (3 mL), and extracted with ether (2 × 15 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The residue obtained after the evaporation of solvent was purified by column chromatography to yield **12** as a colorless oil in 83% (0.41 g). $[\alpha]_D = -14.3$ (*c* 1.2, $CHCl_3$); IR (neat): 2959, 2873, 1724, 1456, 1382, 1259, 1153, 993, 967, 914, 860 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.77 (ddt, $J = 16.8$, 10.2, 6.6 Hz, 1H), 5.06–4.94 (m, 2H), 4.55 (s, 2H), 2.69–2.61 (m, 4H), 2.12–2.04 (m, 2H), 1.77–1.67 (m, 2H), 1.64–1.56 (m, 2H), 1.42 (s, 6H), 1.37–1.27 (m, 2H), 0.91 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.7, 208.4, 137.7, 115.3, 112.3, 81.4, 38.7, 38.1, 32.9, 26.1, 25.1, 22.2, 22.0, 13.8; HRMS for $C_{16}H_{26}O_4$+Na calcd 305.1729; found 305.1709.

4.9. Preparation of (1*S*)-1-((4*S*,5*R*)-5-((*S*)-1-hydroxypentyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-hex-5-en-1-ol 13

To a solution of **12** (0.40 g, 1.4 mmol) in 4 mL of THF at −78 °C L-Selectride (2.8 mL of 1 M solution in THF, 2.8 mmol) was added dropwise over 10 min, under an argon atmosphere. The reaction mixture was stirred for 2.5 h. After the reaction was complete (TLC), it was quenched with 2 M NaOH (3 mL) followed by 30% w/v hydrogen peroxide in water (1.5 mL) was added at the same temperature and stirred for 3 h at room temperature. (H_2O_2 treatment is necessary to remove residual borane impurities resulting from the Selectride.) The reaction mixture was filtered through a short pad of Celite, and the Celite pad was washed with ether (20 mL). The combined ether layers were washed with brine and dried over Na_2SO_4. The residue obtained after evaporation of solvent was purified by column chromatography to yield **13** in 89% (0.36 g) as a colorless oil. $[\alpha]_D = +8.3$ (*c* 1.2, $CHCl_3$); IR (neat): 3447, 2985, 2861, 1458, 1378, 1240, 1166, 1071, 996, 910, 881, 824 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.80 (ddt, $J = 16.8$, 10.2, 6.6 Hz, 1H), 5.05–4.94 (m, 2H), 3.90 (s, 2H), 3.50 (br s, 2H), 2.17–2.01 (m, 4H), 1.68–1.21 (m, 14H), 0.91 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.5, 114.8, 109.3, 80.0, 70.1, 70.0, 34.6, 34.3, 33.5, 27.9, 27.3, 25.0, 22.6, 14.0; HRMS for $C_{16}H_{30}O_4$+Na calcd 309.2042; found 309.2035.

4.10. Preparation of (6*S*)-6-((4*R*,5*R*)-5-((*S*)-1-hydroxypentyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-tetrahydro-2*H*-pyran-2-one 14

Ozone was bubbled through a pre-cooled (−78 °C) solution of **13** (0.3 g, 1.05 mmol) in 4:1 DCM/MeOH (15 mL) containing solid $NaHCO_3$ (20 mg) till the pale blue color persisted. Excess ozone was flushed off with oxygen and Me_2S (1 mL) was added and stirred for 5 h at 0 °C. The reaction mixture was concentrated under reduced pressure and filtered through a short pad of Celite. The Celite pad was washed with ether (15 mL). Evaporation of the solvent yielded the crude lactol, which was subjected to the next reaction without purification.

To a solution of crude lactol (obtained above) in 6 mL of toluene was added Ag_2CO_3 impregnated on Celite (33% impregnation, 1.3 g) under an argon atmosphere. The reaction mixture was kept at 110 °C and stirred at the same temperature for 1 h 15 m. It was then cooled to room temperature, filtered through a pad of Celite, and the Celite pad was washed with ether (15 mL). The residue obtained after evaporation of solvent was purified by column chromatography to yield **14** as a colorless oil in 86% (0.26 g). $[\alpha]_D = +28$ (*c* 3.4, $CHCl_3$); IR (neat): 3460, 2985, 2872, 1731, 1461, 1379, 1244, 1165, 1048, 991, 887, 752 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.34 (dt, $J = 6.7$, 1.5 Hz, 1H), 4.18 (dd, $J = 8.1$, 2.4 Hz, 1H), 4.04 (dd, $J = 8.1$, 1.5 Hz, 1H), 3.49 (br s, 1H), 2.69–2.43 (m, 2H), 2.09–1.76 (m, 4H), 1.60–1.33 (m, 12H), 0.91 (t, $J = 6.9$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 109.8, 78.5, 78.3, 76.8, 69.5, 34.6, 29.9, 27.9, 27.3, 26.7, 25.3, 22.5, 18.4, 13.9; HRMS for $C_{15}H_{26}O_5$+Na calcd 309.1678; found 309.1664.

4.11. Preparation of (6*S*)-6-((4*R*,5*R*)-5-((*S*)-1-hydroxypentyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-5,6-dihydro-2*H*-pyran-2-one 15

To a solution of LDA [prepared from diisopropyl amine (0.3 mL, 2.1 mmol) and ^{n}BuLi (1.2 mL, 1.6 M solution in hexane, 2 mmol) at −78 °C] was added a THF solution of **14** (0.075 g, 0.26 mmol) dropwise, under an argon atmosphere at −78 °C. The reaction mixture was slowly warmed up to −30 °C and stirred for 1.5 h. It was then cooled to −78 °C and a THF solution of PhSeBr (0.4 g, 1.7 mmol) was introduced into the flask. It was stirred for 2 h at −30 °C and after the reaction was complete (TLC), it was quenched with satd NH_4Cl (5 mL) and extracted with ether (3 × 5 mL). Combined ether extracts were washed with brine and dried over Na_2SO_4. Evaporation of solvent under reduced pressure at room temperature yielded the crude seleno lactone, which was used as such in the next step.

To a solution of crude seleno lactone (obtained above) in 3 mL of DCM was added H_2O_2 (4 mL of 30% w/v in water) and stirred for 1 h at room temperature. The reaction mixture was poured to water (10 mL) and extracted with DCM (3 × 5 mL). The combined DCM extracts were washed with satd sodium thiosulfate, brine and dried over Na_2SO_4. Evaporation of the solvent, followed by column

chromatography of the resulting residue, yielded **15** as a colorless oil in 34% (0.026 g). $[\alpha]_D = -27.1$ (*c* 1.6, $CHCl_3$); IR (neat): 3425, 2933, 2866, 1725, 1598, 1456, 1380, 1246, 1157, 1068, 882, 753 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.90 (ddd, $J = 9.9$, 5.7, 2.1 Hz, 1H), 6.03 (dd, $J = 9.9$, 1.8 Hz, 1H), 4.45 (dddd, $J = 11.7$, 5.7, 3.9, 2.1 Hz, 1H), 4.24 (dd, $J = 8.1$, 2.1 Hz, 1H), 4.10 (dd, $J = 8.1$, 2.1 Hz, 1H), 3.51 (br s, 1H), 2.82–2.67 (m, 1H), 2.41–2.26 (m, 1H), 1.59–1.33 (m, 12H), 0.91 (t, $J = 6.9$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.6, 145.1, 121.1, 109.9, 77.9, 77.5, 74.6, 69.5, 34.6, 27.9, 27.2, 26.7, 26.5, 22.5, 13.9; HRMS for $C_{15}H_{24}O_5$+Na calcd 307.1521; found 307.1520.

4.12. Preparation of 5-*epi*-boronolide 4

To a solution of **15** (0.025 g, 0.09 mmol) in 2 mL of DCM was added $FeCl_3 \cdot 6H_2O$ (0.073 g, 0.27 mmol) at room temperature. The reaction mixture was stirred for 0.5 h, filtered through a short pad Celite, and the Celite pad washed with ether (10 mL). Solid Na_2CO_3 was added to the ether layer with a few drops of water and stirred for 5 min. The residue obtained after evaporation of solvent was purified by column chromatography to yield (6*S*)-6-((1*R*,2*R*,3*S*)-1,2,3-trihydroxyhept-1-yl)-5,6-dihydro-2*H*-pyran-2-one in 85% (0.014 g) as a colorless oil. $[\alpha]_D = -45$ (*c* 0.2, EtOH); IR (neat): 3402, 2928, 1705, 1465, 1385, 1260, 1189, 1052, 900, 818 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.92–6.99 (m, 1H), 6.03 (dd, $J = 9.9$, 2.4 Hz, 1H), 4.67–4.60 (m, 1H), 3.83–3.58 (m, 3H), 3.21–3.05 (m, 2H), 2.65–2.46 (m, 2H), 1.57–1.25 (m, 6H), 0.91 (t, $J = 6.6$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.7, 145.6, 120.8, 79.3, 74.5, 72.9, 71.6, 33.1, 27.7, 25.4, 22.6, 14.0.

To a solution of the triol prepared above (12 mg, 0.05 mmol) in pyridine (2 mL) was added DMAP (5 mg, 0.04 mmol) and Ac_2O (0.05 mL, 0.5 mmol) at room temperature. The reaction mixture was stirred for 10 h at the same temperature, poured into water (6 mL), and extracted with ether (2×5 mL). The combined ethereal extracts were washed with dil. HCl, brine and dried over Na_2SO_4. The residue obtained after evaporation solvent was purified by column chromatography to yield **4** in 89% (0.015 g) as a colorless oil. $[\alpha]_D = -66$ (*c* 0.7, $CHCl_3$), IR (neat): 2926, 2854, 1746, 1557, 1398, 1312, 1225, 1159, 1028, 997, 955, 831, 759 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.85 (ddd, $J = 9.0$, 5.7, 3.3, Hz, 1H), 6.05–6.01 (m, 1H), 5.51 (dd, $J = 7.5$, 3.6 Hz, 1H), 5.18–5.11 (m, 2H), 4.75–4.69 (m, 1H), 2.55–2.32 (m, 2H), 2.12 (s, 3H), 2.11 (s, 3H), 2.10 (s, 3H), 1.62–1.54 (m, 2H), 1.29–1.25 (m, 4H), 0.88 (t, $J = 6.6$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 170.2, 169.8, 162.5, 144.1, 121.3, 75.2, 71.5, 71.4, 71.3, 30.6, 27.1, 25.7, 22.3, 20.9, 20.6, 20.5, 13.8; HRMS for $C_{18}H_{26}O_8$+Na calcd 393.1525; found 393.1524.

Acknowledgments

We thank the Department of Science and Technology for funding of this project. One of us (P.A.) is thankful to CSIR, New Delhi, for research fellowship.

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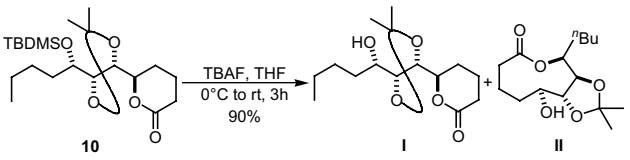
11. Deprotection of TBDMS group in **10** leads to a 4:5 mixture of lactones **I** and **II**. Conversion of lactone **I** $[\alpha]_D^{25} = -13.0$ (*c* 1, $CHCl_3$) lit.[3b] $[\alpha]_D^{25} = -12.6$ (*c* 1.98, $CHCl_3$) to boronolide is known in the literature.[3b]



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