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TOTAL SYTNHESIS OF RHOIPTELOL B

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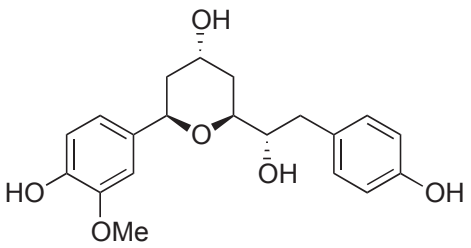
Dedicated to Professor Kiyoshi Tomioka on the occasion of his 70th birthday

Abstract – A stereoselective total synthesis of rhoiptelol B, a diarylheptanoid isolated from the fruits of *Rhoiptelea chiliantha*, is described. The tetrahydropyran ring was constructed via an intramolecular allylation methodology.

Rhoiptelol B (**1**), a diarylheptanoid having a tetrahydropyran (THP) ring, was isolated from the fruits of *Rhoiptelea chiliantha* in 1996.[1] This compound was also isolated from the bark of *Alnus hirsuta* in 2007, and found to show inhibitory activity against lipopolysaccharide (LPS)-induced nuclear factor-*k*B (NF-*k*B) activation, nitric oxide (NO) and tumor necrosis factor-α (TNF-α) production.[2] The unique biological activities and structural features have attracted attention of synthetic chemists. The first total synthesis of **1** was accomplished by Reddy and co-workers in 2010 via the reductive etherification of a hydroxy ketone derivative.[3] Yadav and co-workers reported two different approaches based on $FeCl_3$ catalyzed cyclization[4] and Prins cyclization,[5] respectively.

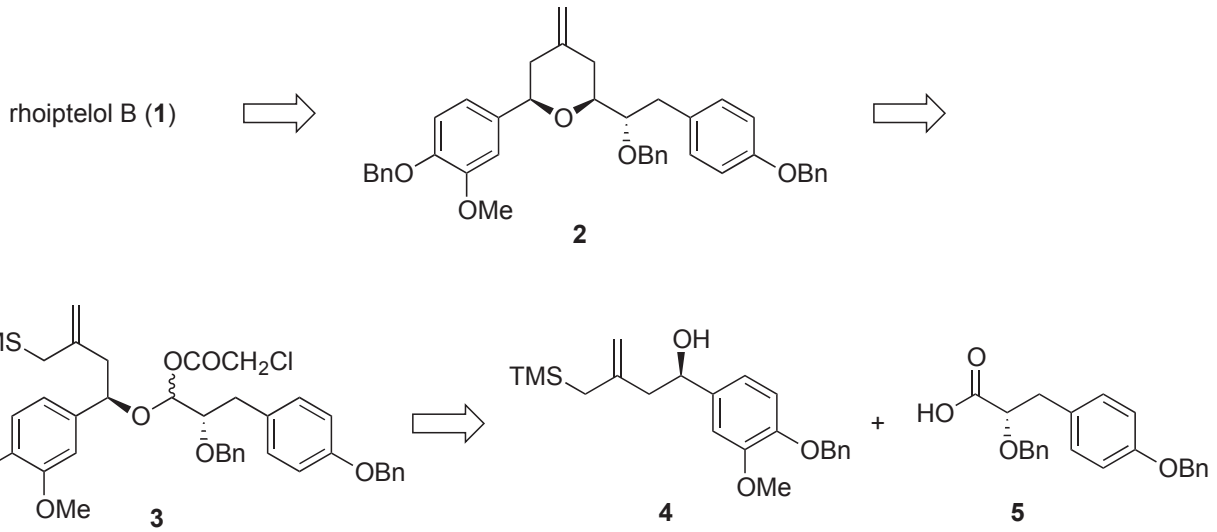
In this paper, we wish to report a stereoselective total synthesis of rhoiptelol B (**1**) via the intramolecular allylation of α-acetoxy ether.



rhoiptelol B (**1**)

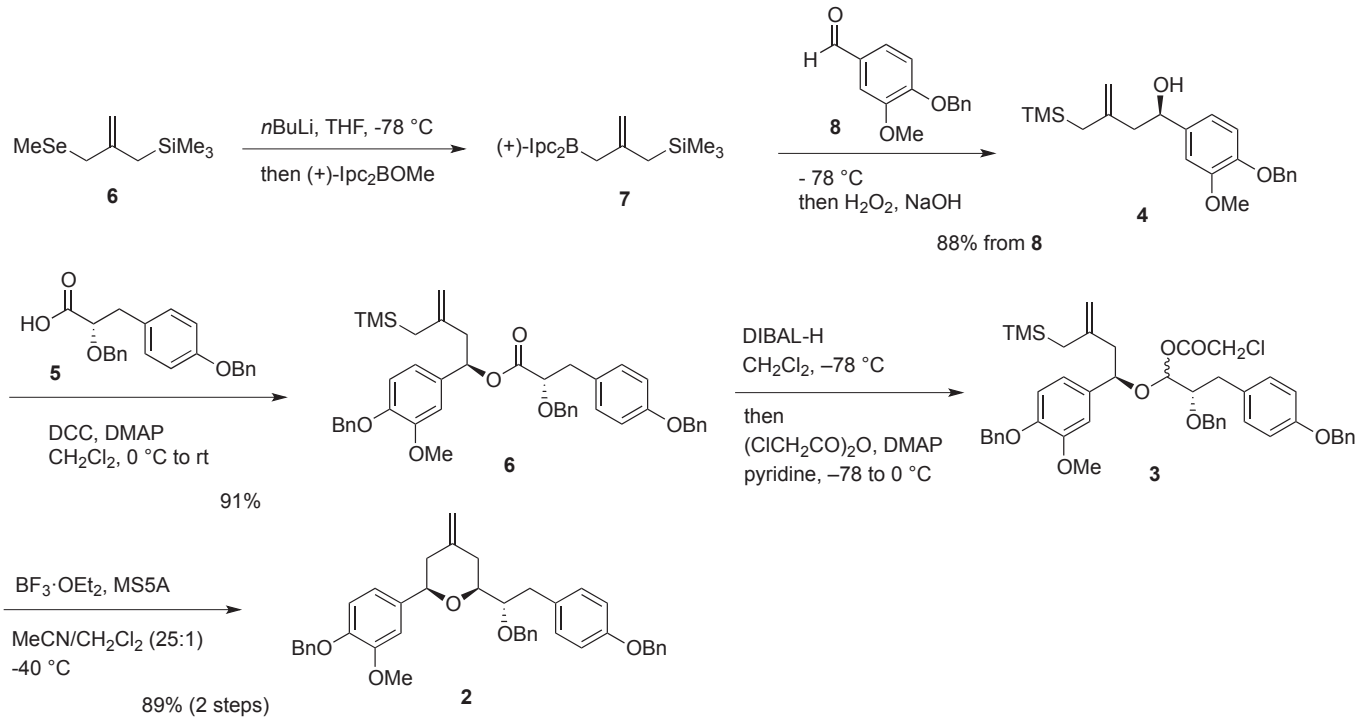
Figure 1. Structure of rhoiptelol B (**1**)

Scheme 1 illustrate our retrosynthetic analysis of **1**. We envisaged that the target molecule **1** could be derived from an *exo*-methylene THP derivative **2**. Recently, we reported a stereoselective synthesis of 2,6-disubstituted THP ring via the intramolecular allylation of α-acetoxy ether and its application to the convergent total synthesis of dactylolide, a marine natural product.[6] According to this methodology, the compound **2** would be synthesized from an α-acetoxy ether **3**. The cyclization precursor **3** could be prepared from alcohol **4** and carboxylic acid **5**.



Scheme 1

Our synthesis of rhoiptelol B (**1**) was started from the preparation of a chiral allylborane **7** (Scheme 1). Thus, treatment of known allylselenide **6**[7] with *n*BuLi followed by the reaction with (+)-Ipc_2BOMe gave **7**.[6] The chiral allylic borane reagent prepared **7** was directly used for the reaction with protected vanillin **8**[8] to afforded **4** in 88% yield with high enantioselectivity (>95% ee). The absolute configuration and optical purity of **4** were confirmed by modified Mosher method as shown in Figure 2.[9] Esterification of **4** with known carboxylic acid **5**[10] was carried out using DCC/DMAP to furnish ester **6** in 91% yield. Partial reduction of **6** with DIBAL-H followed by reaction with $(CH_2ClCO)_2O$/DMAP/pyridine gave α-acetoxy ether **3**.[11,12] The cyclization precursor **3** obtained was subjected to the Lewis acid mediated intramolecular allylation, a key step in the total synthesis. After several experiments, we found that the reaction of **3** proceeded smoothly with $BF_3 \cdot OEt_2$ and MS5A in $MeCN/CH_2Cl_2$ (25:1). The desired *exo*-methylene THP derivative **2** was obtained as a single stereoisomer in 89% overall yield.[13] The stereochemistry of **2** was determined at later stage.



Scheme 2

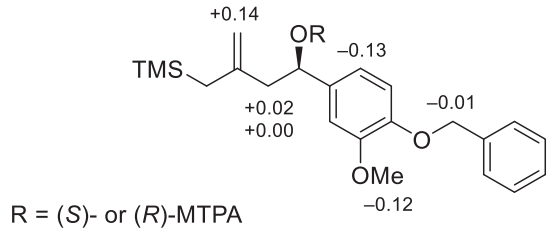


Figure 2. Chemical shift differences ($\Delta\delta = \delta_S - \delta_R$) of MTPA esters derived from **4**

Next task is the conversion of *exo*-methylene moiety of **2** to a hydroxy group. Oxidative cleavage of the C-C double bond with OsO_4/$NaIO_4$/2,6-lutidine gave **7** in 88% yield (Scheme 3).[14] Stereoselective reduction of the ketone **7** was performed with L-Selectride to give desired **8** and its stereoisomer **9** in 69% and 19% yields, respectively. Stereochemistry of **8** was presumed by NOE experiments on the minor product **9** as shown in Figure 3. The undesired stereoisomer **9** was converted to the starting material **2** by Dess-Martin oxidation in 83% yield.[15]

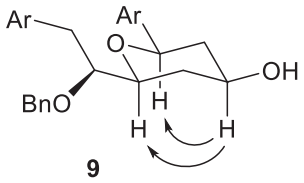
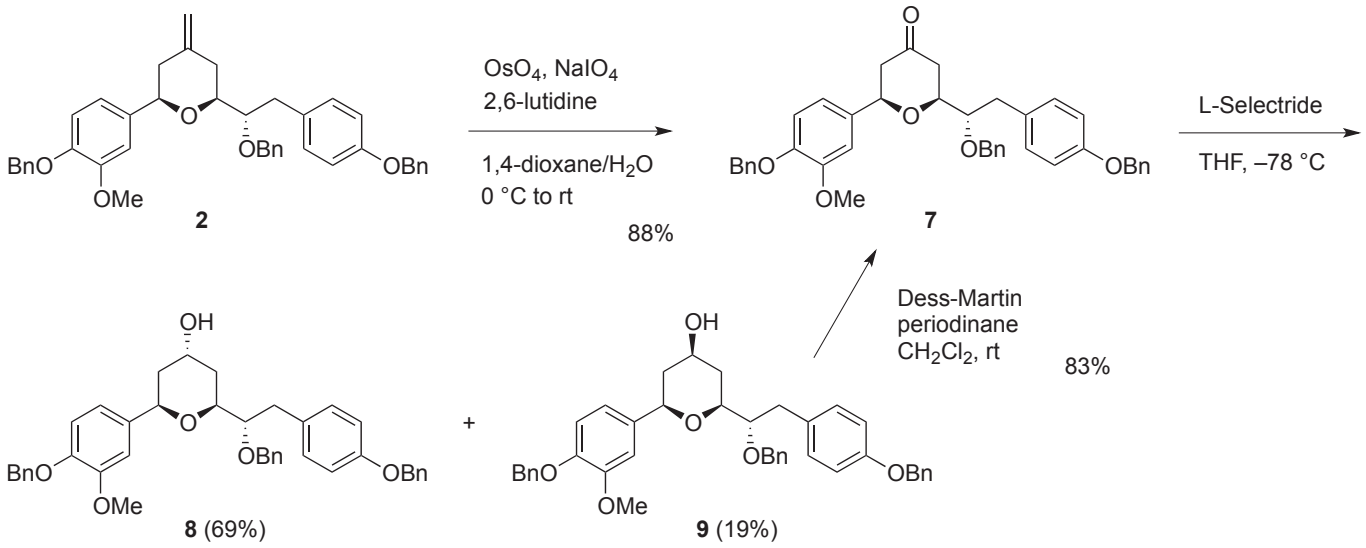
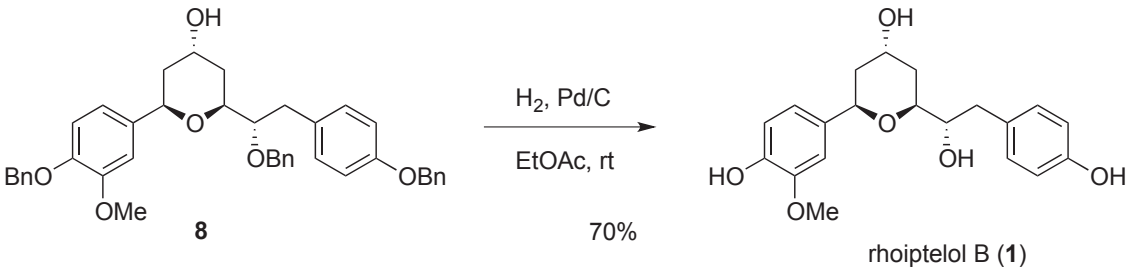


Figure 3. Observed NOEs are shown by arrows



Scheme 3

Finally, removal of the benzyl protecting groups of **8** was carried out with H_2/Pd-C to give rhoiptelol B (**1**) in 70% yield (Scheme 3). The spectroscopic data (^{1}H and ^{13}C NMR) and optical rotation ($[\alpha]_D^{22}$ +106 (*c* 0.25, MeOH) of the synthetic material were identical with those reported previously.[16]



Scheme 4

In conclusion, we have achieved the stereoselective total synthesis of rhoiptelol B (**1**) via the intramolecular allylation methodology. Further application of the present methodology to the total synthesis of natural products is in progress.

EXPERIMENTAL

All reactions involving air- and/or moisture-sensitive materials were carried out under argon with dry solvents purchased from Wako or Kanto chemicals. On workup, extracts were dried over $MgSO_4$. Reactions were monitored by thin-layer chromatography carried out on 0.25 mm Merck silica gel plates (60F-254). Column chromatography was performed with Kanto Chemical silica gel 60N (40-100 mesh, spherical, neutral). Yields refer to chromatographically and spectroscopically homogeneous materials. The NMR spectra were recorded on JEOL JNM-AL400 (^{1}H, ^{13}C NMR). Chemical shifts were reported

in delta units (δ) relative to chloroform (7.24) and methanol (3.30). IR spectra were recorded on a JASCO FT/IR-460 Plus. Optical rotations were measured by a JASCO DIP-1000. Mass spectra were measured by Micromass LCT (ESI TOF-MS).

Alcohol 4. To a solution of **6** (1.44g, 6.51 mmol) in THF (15 mL) at −78 ºC was added *n*BuLi (4.4 mL, 1.48 M in hexane, 6.5 mmol). After stirring for 5 min, a solution of (+)-Ipc$_2$BOMe (2.05g, 6.48 mmol) in THF (4 mL) was add dropwise, and the stirring was continued for 15 min at the same temperature. To the resulting mixture was added a solution of **8** (0.52g, 2.15 mmol) in THF (3 mL), and the mixture was stirred for 1.5 h. The reaction mixture was quenched with MeOH, and 3 M NaOH and 30% H_2O_2 were added at 0 ºC. After stirring for 10 min, the resulting mixture was added aq. Na_2SO_3, and extracted with EtOAc. The organic layer was washed with brine. Concentration and chromatography (CH_2Cl_2/EtOAc, 50:1) gave **4** (699 mg, 88%): solid, R_f = 0.32 (CH_2Cl_2/EtOAc, 50:1); $[\alpha]_D^{21}$ +18.5 (*c* 0.98, $CHCl_3$); IR (neat) 3520, 3067, 3033, 2952, 2912, 1631, 1606, 1593 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44-7.23 (m, 5H), 6.97 (d, *J* = 1.7 Hz, 1H), 6.86-6.80 (m, 2H), 5.15 (s, 2H), 4.78-4.71 (m, 3H), 3.92 (s, 3H), 2.35-2.33 (m, 2H), 2.23 (d, *J* = 2.0 Hz, 1H), 1.63-1.59 (m, 2H), 0.05 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.7, 147.4, 144.4, 137.3, 137.2, 128.4, 127.7, 127.2, 117.9, 114.0, 110.9, 109.6, 71.2, 71.0, 56.0, 49.0, 26.6, −1.2; HRMS (ESI TOF) calcd for $C_{22}H_{30}O_3SiNa$ $(M+Na)^+$ 393.1862, found 393.1861.

Ester 6. To a mixture of **4** (117mg, 317 μmol) and **5** (172 mg, 476 μmol) in CH_2Cl_2 (3.2 mL) at 0 ºC were added DMAP (4.5 mg, 30 μmol) and DCC (201 mg, 951 μmol). After stirring for 10 min at room temperature, the mixture was concentrated. The residue was purified by column chromatography (hexane/EtOAc, 7:1) to give **6** (207 mg, 91%): amorphous solid; R_f = 0.28 (hexane/EtOAc, 7:1); $[\alpha]_D^{21}$ −12.9 (*c* 0.51, $CHCl_3$); IR(neat) 3065, 3034, 2932, 2888, 1736, 1595, 1514, 1193 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44-7.20 (m, 13H), 7.08-7.06 (m, 4H), 6.87-6.81 (m, 5H), 5.96 (dd, *J* = 8.8, 4.9 Hz, 1H), 5.15 (s, 2H), 5.04 (s, 2H), 4.64-4.60 (m, 3H), 4.27 (d, *J* = 11.9 Hz, 1H), 4.04 (dd, *J* = 8.3, 4.6 Hz, 1H), 3.87 (s, 3H), 3.00 (dd, *J* = 14.1, 4.6 Hz, 1H), 2,92 (dd, *J* = 14.1, 8.6 Hz, 1H), 2.58 (dd, *J* = 14.7, 9.3 Hz, 1H), 2.38-2.33 (m, 1H), 1.58-1.48 (m, 2H), 0.02 (s, 9H); ^{13}C NMR (100MHz, $CDCl_3$) δ 171.3, 157.5, 149.5, 149.5, 147.9, 142.5, 137.4, 137.1, 137.0, 133.3, 130.4, 129.5, 128.5, 128.1, 127.8, 127.8, 127.6, 127.5, 127.4, 127.2, 119.1, 114.5, 113.7, 110.8, 110.5, 79.3, 74.5, 72.1, 71.1, 70.0, 56.1, 45.0, 38.5, 26.7, −1.2; HRMS (ESI TOF) calcd for $C_{45}H_{50}O_6SiNa$ $(M+Na)^+$ 737.3275, found 737.3271.

Preparation and Cyclization of 3. To a solution of **6** (52.4 mg, 73.3 μmol) in CH_2Cl_2 (6 mL) at −78 ºC was added DIBAL-H (250 μL, 0.88 M in hexane, 220 μmol). After 3 min, solutions of DMAP (48.8 mg, 399 μmol) and pyridine (120 μL, 1.49 mmol) in CH_2Cl_2 (0.5 mL), and $(ClCH_2CO)_2O$ (133 mg, 778 μmol) in CH_2Cl_2 (0.5 mL) were added successively. The resulting mixture was allowed to warm up to 0 °C,

quenched with aq. Na K tartrate, and extracted with EtOAc. The organic layer was washed with saturated aq. $NaHCO_3$ and brine. Concentration and short column chromatography (hexane/EtOAc, 3:1) gave crude **3** which was used for the next reaction without further purification.

To a mixture of **3** and MS5A (90 mg) in MeCN (7.3 mL) at −40 ºC was added $BF_3{\cdot}OEt_2$ (290 μL, 1 M solution in CH_2Cl_2, 290 μmol). After stirring for 10 min at the same temperature, the reaction mixture was quenched with Et_3N and saturated aq. $NaHCO_3$, and extracted with EtOAc. The organic layer was washed with brine. Concentration and chromatography (hexane/EtOAc, 7:1) gave **2** (41 mg, 89% from **6**): oil; R_f = 0.22 (hexane/EtOAc, 7:1); $[\alpha]_D^{21}$ +14.6 (*c* 0.62, $CHCl_3$); IR (neat) 3893, 3651, 3073, 3033, 2911, 2844, 2576, 1807, 1730, 1651, 1613 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45-7.22 (m, 13H), 7.19-7.12 (m, 4H), 7.00 (s, 1H), 6.89-6.87 (m, 4H), 4.55 (d, *J* = 11.4 Hz, 1H), 4.46 (d, *J* = 11.4 Hz, 1H), 4.24 (dd, *J* = 11.5, 2.2 Hz, 1H), 3.90 (s, 3H), 3.67-3.62 (m, 1H), 3.55-3.51 (m, 1H), 3.01 (dd, *J* = 13.6, 5.4 Hz, 1H), 2.80 (dd, *J* = 13.6, 8.1 Hz, 1H), 2.47-2.21 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.2, 149.5, 147.4, 144.5, 138.5, 137.2, 137.1, 135.8, 131.4, 130.4, 128.5, 128.4, 128.1, 127.9, 127.8, 127.7, 127.4, 127.2, 118.0, 114.6, 113.9, 109.9, 109.2, 82.1, 80.1, 79.1, 72.8, 71.2, 70.1, 56.1, 42.9, 35.7, 35.6; HRMS (ESI TOF) calcd for $C_{42}H_{42}O_5Na$ $(M+Na)^+$ 649.2930, found 649.2927.

Ketone 7. To a solution of **2** (44.5 mg, 71 μmol) in 1,4-dioxane (1 mL) and water (0.3 mL) at 0 ºC were added $NaIO_4$ (84 mg, 395 μmol) and OsO_4 (71 μL, 0.05 M in *i*PrOH, 3.6 μmol). After stirring for 4 h at room temperature, the reaction mixture was quenched with aq. $Na_2S_2O_3$ and extracted with EtOAc. The organic layer was washed with brine. Concentration and chromatography (hexane/EtOAc, 1.5:1) gave **7** (39.4 mg, 88%): oil; R_f = 0.24 (hexane/EtOAc, 2.5:1); $[\alpha]_D^{26}$ +67.9 (*c* 0.67, $CHCl_3$); IR (neat) 3770, 3299, 2986, 2644, 2383, 2192, 1793, 1707 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45-7.21 (m, 15H), 7.11 (d, *J* = 8.6 Hz, 2H), 6.90-6.87 (m, 1H), 5.17 (s, 1H), 5.05 (s, 1H), 4.56 (d, *J* = 11.7 Hz, 1H), 4.51 (d, *J* = 11.7 Hz, 1H), 4.49 (t, *J* = 7.1 Hz, 1H), 3.91 (s, 1H), 3.75-3.71 (m, 1H), 3.63-3.59 (m, 1H), 3.03 (dd, *J* = 13.6, 6.8 Hz, 1H), 2.90 (dd, *J* = 13.6, 7.1 Hz, 1H), 2.75 (dd, *J* = 14.1, 12.2 Hz, 1H), 2.60 (d, *J* = 7.8 Hz, 2H), 2.28 (dd, *J* = 14.4, 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.0, 157.3, 149.7, 147.9, 137.9, 137.1, 137.0, 137.0, 136.7, 133.8, 130.4, 130.3, 128.5, 128.3, 128.0, 127.8, 127.8, 127.7, 127.4, 127.2, 117.9, 114.8, 114.0, 109.8, 81.1, 78.6, 72.8, 71.1, 70.1, 56.1, 49.4, 43.5, 35.4; HRMS (ESI TOF) calcd for $C_{41}H_{40}O_6Na$ $(M+Na)^+$ 651.2723, found 651.2723

Reduction of 7. To a solution of **7** (17 mg, 27 μmol) in THF (0.5 mL) at −78 ºC was added L-Selectride (81 μL, 1 M in THF, 81 μmol). After stirring for 30 min at the same temperature, the reaction mixture was quenched with saturated aq. NH_4Cl and extracted with EtOAc. The organic layer was washed with brine. Concentration and chromatography gave **8** (11.9 mg, 69%) and **9** (3.2 mg, 19%).

8: oil; R_f = 0.21 (hexane/EtOAc, 1.5:1); $[\alpha]_D^{27}$ +38.9 (*c* 0.52, $CHCl_3$), IR (neat) 3450, 3062, 3031, 2925,

2871 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45-7.12 (m, 17H), 6.99 (s, 1H), 6.89-6.87 (m, 4H), 5.15 (s, 2H), 5.05 (s, 2H), 4.78 (dd, J = 11.7, 2.0 Hz, 1H), 4.54 (d, J = 11.7 Hz, 1H), 4.47 (d, J = 11.7 Hz, 1H), 4.39 (s, 1H), 4.10-4.04 (m, 1H), 3.89 (s. 3H), 3.64-3.59 (m, 1H), 3.01 (dd, J = 13.7, 5.1 Hz, 1H), 2.78 (dd, J = 13.7, 8.1 Hz, 1H), 1.93-1.62 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.2, 149.5, 147.4, 138.6, 137.3, 137.2, 136.3, 131.6, 130.4, 128.5, 128.4, 128.1, 127.9, 127.8, 127.7, 127.4, 127.2, 117.9, 114.7, 114.1, 110.1, 82.3, 73.6, 72.7, 72.5, 71.3, 70.1, 65.0, 56.1, 40.6, 35.5, 33.6; HRMS (ESI TOF) calcd for $C_{41}H_{42}O_6Na$ $(M+Na)^+$ 653.2879, found 653.2875

9: oil; R_f = 0.14 (hexane/EtOAc, 1.5:1); $[\alpha]_D^{21}$ +58.1 (c 0.16, $CHCl_3$); IR (neat) 3424, 3031, 2937, 1953, 1879, 1811, 1721, 1609, 1519, 1263, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45-7.12 (m, 17H), 6.98 (s, 1H), 6.90-6.85 (m, 4H), 5.16 (s, 2H), 5.05 (s, 2H), 4.54 (d, J = 11.5 Hz, 1H), 4.45 (d, J = 11.5 Hz, 1H), 4.29 (d, J = 9.8 Hz, 1H), 3.95-3.86 (m, 1H), 3.89 (s, 3H), 3.67-3.62 (m, 1H), 3.58-3.53 (m, 1H), 3.00 (dd, J = 13.7, 4.9 Hz, 1H), 2.79 (dd, J = 13.7, 8.1 Hz, 1H), 2.22-2.18 (m, 1H), 2.01-1.97 (m, 1H), 1.61-1.47 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.2, 149.5, 147.5, 141.1, 138.5, 137.1, 131.4, 130.4, 128.5, 128.4, 128.2, 127.9, 127.9, 127.8, 127.7, 127.4, 127.2, 118.1, 114.7, 113.9, 110.0, 82.0, 73.5, 72.9, 71.2, 70.1, 68.7, 56.1, 43.0, 40.6, 36.2, 35.7, 29.8.

Oxidation of 9. To a solution of **9** (4.0 mg, 6.3 μmol) in CH_2Cl_2 (0.6 mL) at room temperature was added Dess-Martin periodinane (11 mg, 25 μmol). After stirring for 2.5 h, the reaction mixture was filtered through a Celite pad, and the filtrate was concentrated. The residue was purified by column chromatography (hexane/EtOAc, 2.5:1) to give **2** (3.3 mg, 83%).

Rhoiptelol B (1). A mixture of **8** (15.5 mg, 24.6 mmol) and a catalytic amount of Pd-C (5%) in EtOAc (2 mL) was stirred under H_2 atmosphere. After 43 h, the catalyst was filtered off, and the filtrate was concentrated. The residue was purified by column chromatography (hexane/EtoAc, 1:10) to give **1** (6.2 mg, 70%): amorphous solid; R_f = 0.26 (hexane/EtOAc, 1:10); $[\alpha]_D^{22}$ +106 (c 0.25, MeOH); IR (neat) 3348, 2922, 1612, 1516, 1233, 1034 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 7.05-7.02 (m, 3H), 6.84-6.82 (m, 1H), 6.77-6.75 (m, 1H), 6.69-6.67 (m, 2H), 4.71-4.67 (m, 1H), 3.84-3.80 (m, 1H), 3.60 (ddd, J = 10.5, 7.3, 3.4 Hz, 1H), 2.89 (dd, J = 13.2, 6.6 Hz, 1H), 2.70 (dd, J = 13.2, 7.6 Hz, 1H), 1.93-1.72 (m, 3H), 1.59-1.54 (m, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 156.5, 148.7, 146.7, 136.1, 131.3, 131.1, 119.8, 116.0, 115.8, 111.1, 76.4, 75.2, 74.3, 65.7, 56.5, 41.3, 39.7, 35.0; HRMS (ESI TOF) calcd for $C_{20}H_{24}O_6Na$ $(M+Na)^+$ 383.1471, found 383.1470.

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