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TOTAL SYNTHESIS OF RHOIPTOLOL B

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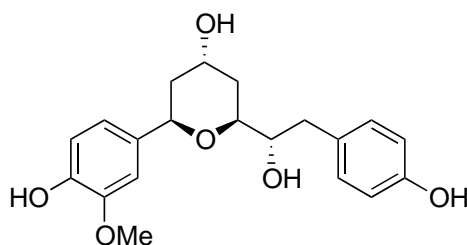
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Dedicated to Professor Kiyoshi Tomioka on the occasion of his 70th birthday

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- κ B (NF- κ 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 FeCl₃ catalyzed cyclization⁴ and Prins cyclization,⁵ respectively.

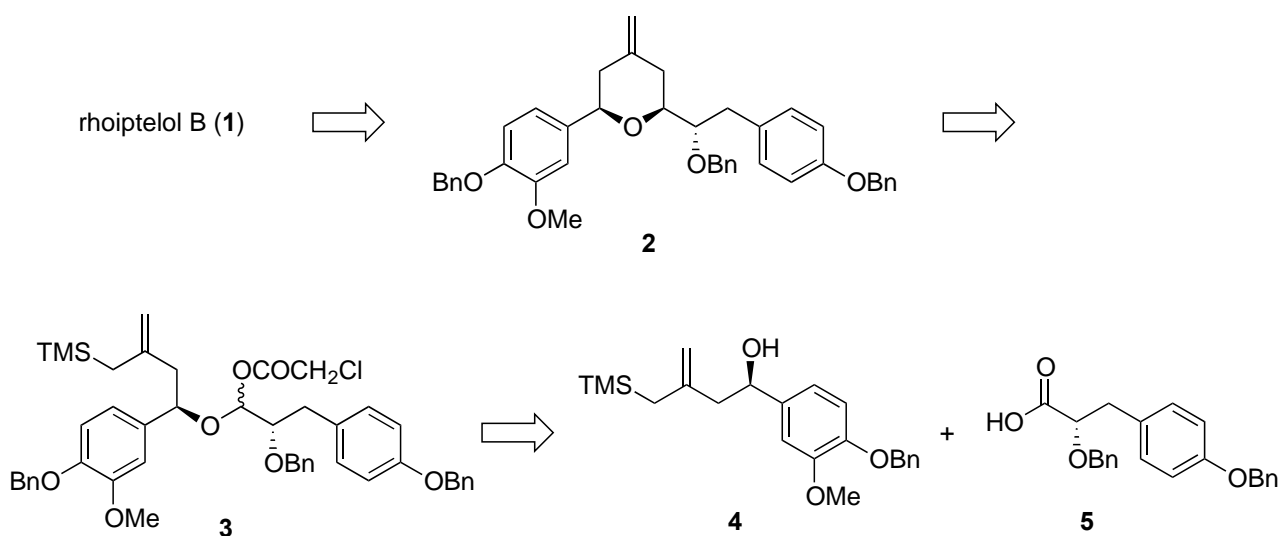
In this paper, we wish to report a stereoselective total synthesis of rhoiptelol B (**1**) via the intramolecular allylation of α -acetoxy ether.



rhoiptelol B (**1**)

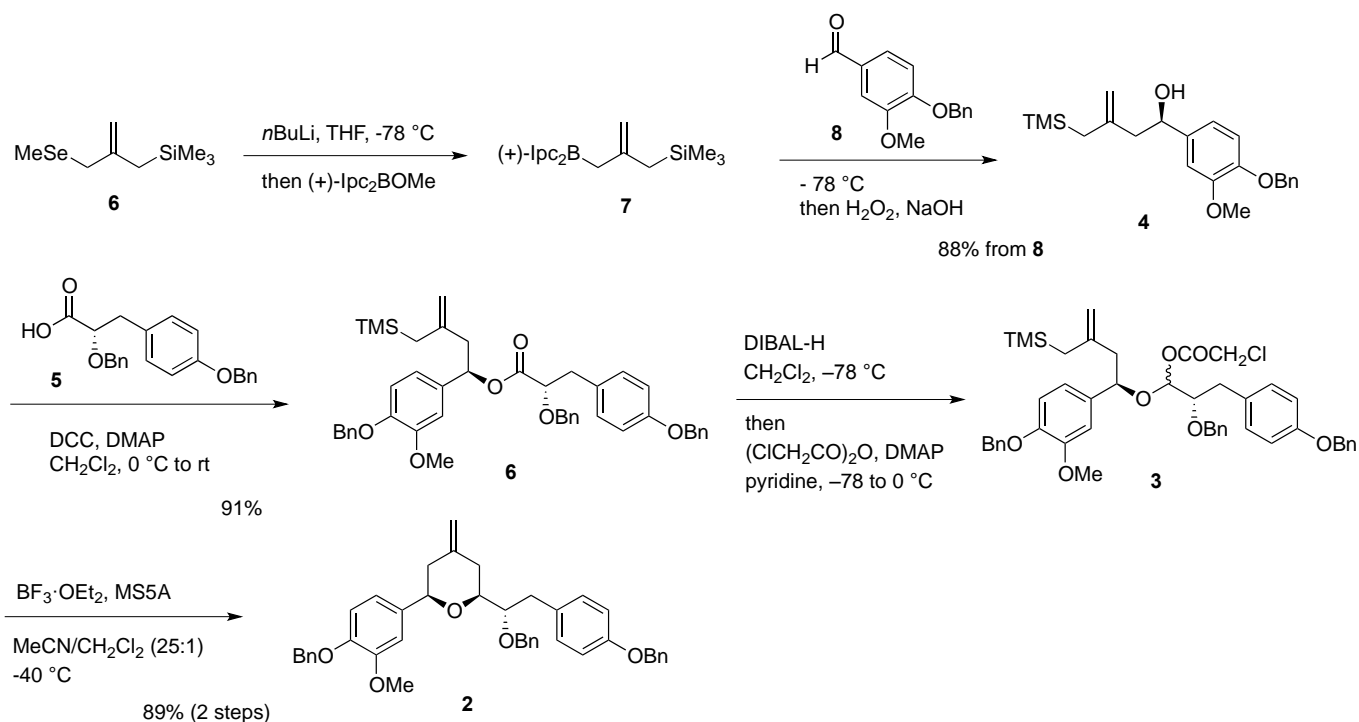
Figure 1. Structure of rhoiptelol B (**1**)

Scheme 1 illustrates 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 dactyloide, 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**.

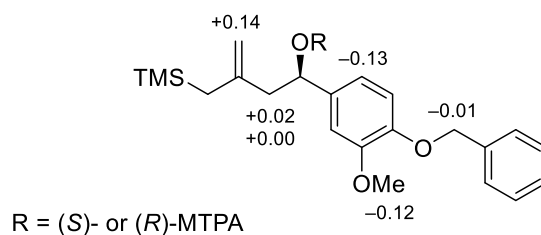


Scheme 1

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 (+)-Ipc₂BOMe gave **7**.⁶ The chiral allylic borane reagent prepared **7** was directly used for the reaction with protected vanillin **8**⁸ to afford **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 (CH₂ClCO)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 BF₃·OEt₂ and MS5A in MeCN/CH₂Cl₂ (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 $\text{OsO}_4/\text{NaIO}_4/2,6\text{-lutidine}$ 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

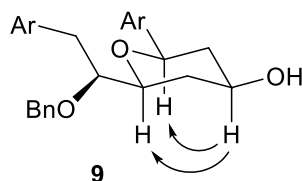
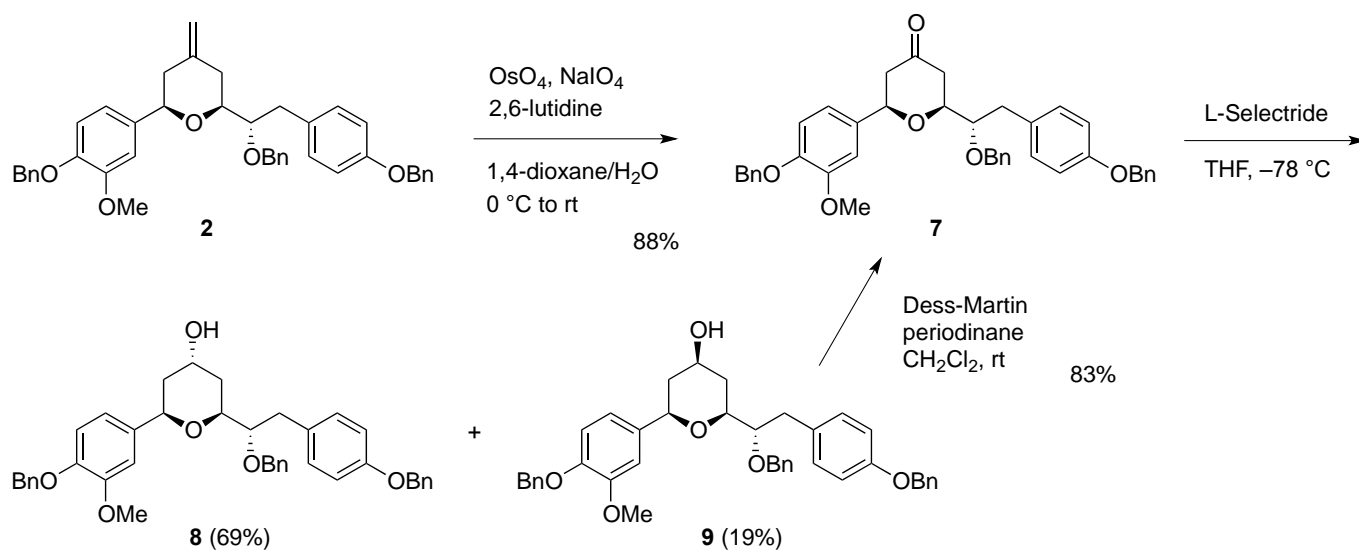
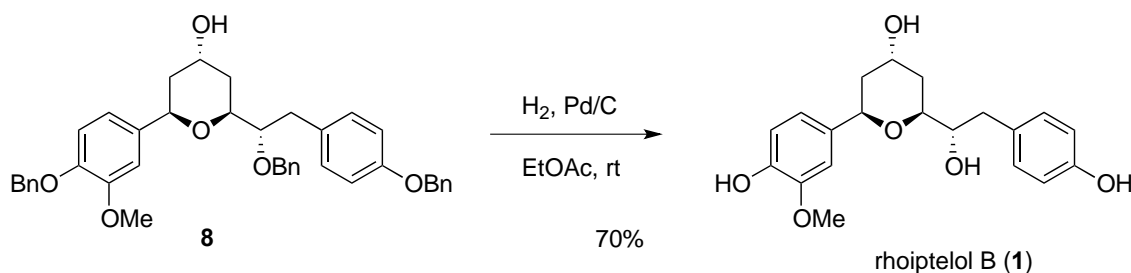


Figure 3. Observed NOEs are shown by arrows



Scheme 3

Finally, removal of the benzyl protecting groups of **8** was carried out with $\text{H}_2/\text{Pd-C}$ to give rhoiptelol B (**1**) in 70% yield (Scheme 3). The spectroscopic data (^1H and ^{13}C NMR) and optical rotation ($[\alpha]_{\text{D}}^{22} +106$ (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 (^1H , ^{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 °C was added *n*BuLi (4.4 mL, 1.48 M in hexane, 6.5 mmol). After stirring for 5 min, a solution of (+)-Ipc₂BOMe (2.05g, 6.48 mmol) in THF (4 mL) was added 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% H₂O₂ were added at 0 °C. After stirring for 10 min, the resulting mixture was added aq. Na₂SO₃, and extracted with EtOAc. The organic layer was washed with brine. Concentration and chromatography (CH₂Cl₂/EtOAc, 50:1) gave **4** (699 mg, 88%): solid, $R_f = 0.32$ (CH₂Cl₂/EtOAc, 50:1); $[\alpha]_D^{21} +18.5$ (c 0.98, CHCl₃); IR (neat) 3520, 3067, 3033, 2952, 2912, 1631, 1606, 1593 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 C₂₂H₃₀O₃SiNa (M+Na)⁺ 393.1862, found 393.1861.

Ester 6. To a mixture of **4** (117mg, 317 μ mol) and **5** (172 mg, 476 μ mol) in CH₂Cl₂ (3.2 mL) at 0 °C were added DMAP (4.5 mg, 30 μ mol) and DCC (201 mg, 951 μ mol). 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, CHCl₃); IR(neat) 3065, 3034, 2932, 2888, 1736, 1595, 1514, 1193 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100MHz, CDCl₃) 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 C₄₅H₅₀O₆SiNa (M+Na)⁺ 737.3275, found 737.3271.

Preparation and Cyclization of 3. To a solution of **6** (52.4 mg, 73.3 μ mol) in CH₂Cl₂ (6 mL) at -78 °C was added DIBAL-H (250 μ L, 0.88 M in hexane, 220 μ mol). After 3 min, solutions of DMAP (48.8 mg, 399 μ mol) and pyridine (120 μ L, 1.49 mmol) in CH₂Cl₂ (0.5 mL), and (ClCH₂CO)₂O (133 mg, 778 μ mol) in CH₂Cl₂ (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. NaHCO₃ 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 °C was added BF₃·OEt₂ (290 μL, 1 M solution in CH₂Cl₂, 290 μmol). After stirring for 10 min at the same temperature, the reaction mixture was quenched with Et₃N and saturated aq. NaHCO₃, 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); [α]_D²¹ +14.6 (*c* 0.62, CHCl₃); IR (neat) 3893, 3651, 3073, 3033, 2911, 2844, 2576, 1807, 1730, 1651, 1613 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 C₄₂H₄₂O₅Na (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 °C were added NaIO₄ (84 mg, 395 μmol) and OsO₄ (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. Na₂S₂O₃ 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); [α]_D²⁶ +67.9 (*c* 0.67, CHCl₃); IR (neat) 3770, 3299, 2986, 2644, 2383, 2192, 1793, 1707 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 C₄₁H₄₀O₆Na (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 °C 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. NH₄Cl 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); [α]_D²⁷ +38.9 (*c* 0.52, CHCl₃), 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 $\text{C}_{41}\text{H}_{42}\text{O}_6\text{Na}$ ($\text{M}+\text{Na}$) $^+$ 653.2879, found 653.2875

9: oil; $R_f = 0.14$ (hexane/EtOAc, 1.5:1); $[\alpha]_{\text{D}}^{21} +58.1$ (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 μmol) 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); $[\alpha]_{\text{D}}^{22} +106$ (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 $\text{C}_{20}\text{H}_{24}\text{O}_6\text{Na}$ ($\text{M}+\text{Na}$) $^+$ 383.1471, found 383.1470.

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