# Stereoselective synthesis of ophiocerin B

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**Abstract**

A stereoselective total synthesis of ophiocerin B is reported by asymmetric synthesis, starting from L-malic acid. Of the three stereogenic centers, the *vic*-diols C-3, C-4 were obtained by Sharpless asymmetric dihydroxylation.

**Keywords:** Stereoselective, asymmetric synthesis, Sharpless asymmetric dihydroxylation

## Introduction

The tetrahydropyran skeleton features in a variety of biologically active natural products such as polyether antibiotics, marine toxins and pheromones.[1] The substituted tetrahydropyran moiety is a part structure of a wide variety of natural products with diversified biological functions.[2,3] Ophiocerins A-D (**1**-**4**) are a class of natural products isolated from freshwater aquatic fungi by Reategui *et al*.[4] from *Ophioceras venezuelense*[5] (Magnaporthaceae). The structural analysis of ophiocerins A–D was arrived at by Gloer *et a1*. from spectroscopic studies, while the absolute stereochemistry was assigned by CD spectrometry by the use of the excitation chirality method.[6] These new tetrahydropyran derivatives appear to be the first isolated natural products from the above genus.[4] Consequently, compounds **1**–**4** have attracted considerable synthetic attention from various laboratories,[7-11] including our own.[10] So far, two research groups have been reported the total synthesis of Ophiocerin B, the first total synthesis was published by Yadav group,[9] using chiral epoxide as a starting material, in 2008 Lee and Kang reported total synthesis of Ophiocerin B by using α-D-glucopyranoside.[7] Herein, we report the total synthesis of **2** from L-malic acid.

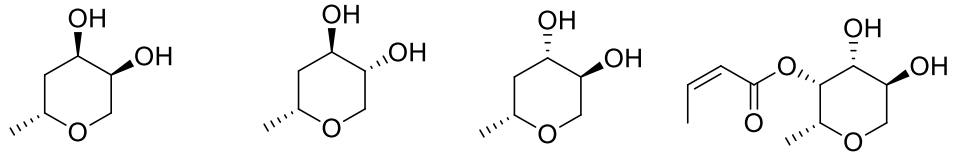
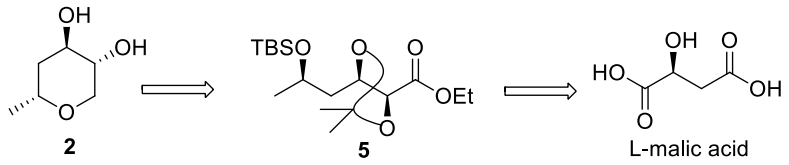


**Figure 1.** Structures of Ophiocerin A-D **1**-**4**.

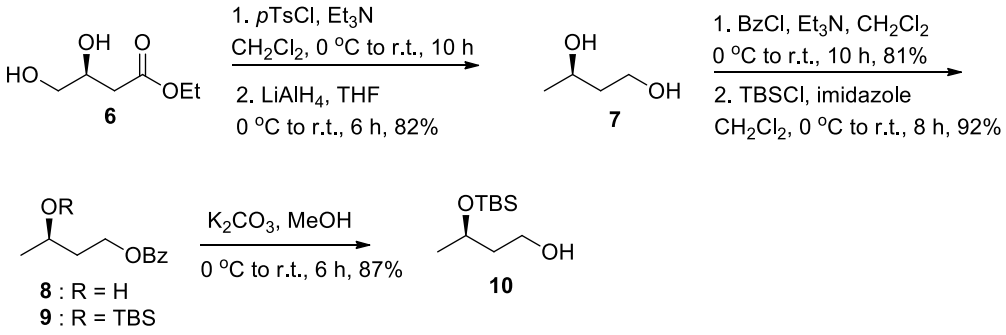
## Results and Discussion

The retrosynthetic analysis is outlined in Scheme 1. Ester **5** was prepared from commercially available L-malic acid, and the target compound **2** was synthesized from ester **5**.




**Scheme1.** Retrosynthetic route to the target molecule **2**.

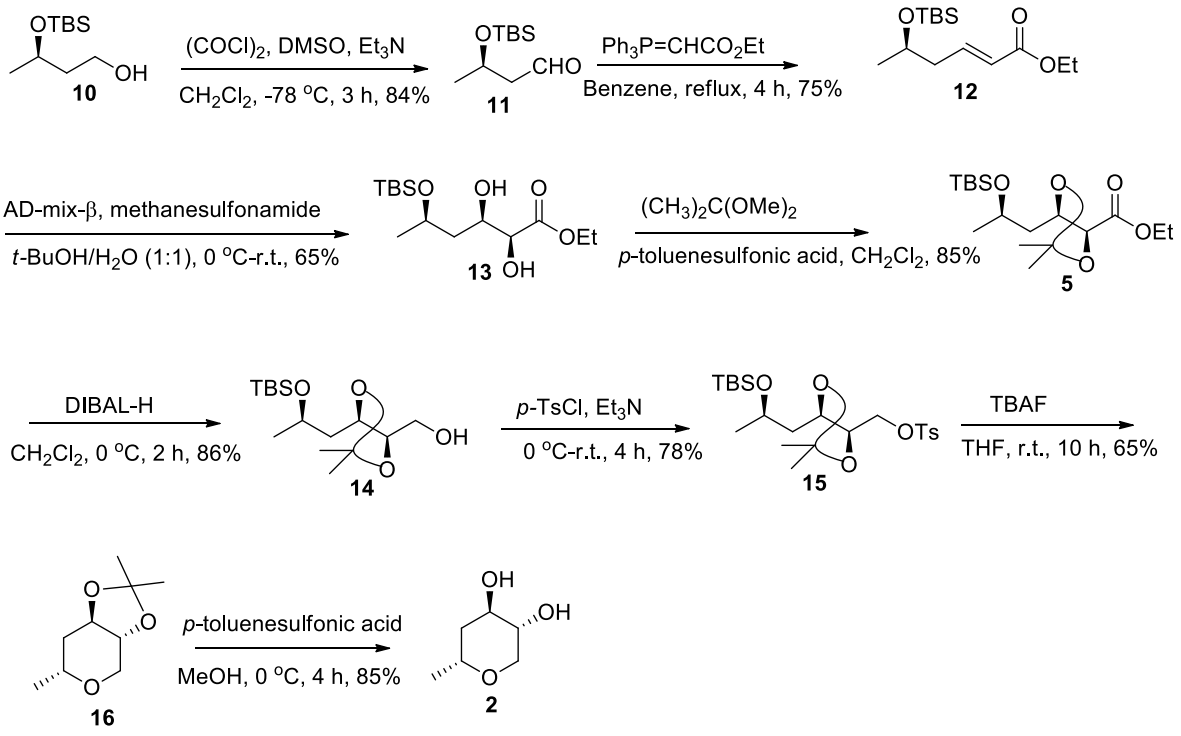
As illustrated in Scheme 2, the synthesis of ophiocerin B **2** started from the commercially available L-malic acid. Accordingly, the known compound **10** (Scheme 2) was initiated from commercially available diol **7**, which was prepared from known ester **6**[12] in two steps. Selective tosylation of **6** and subsequent reduction of the resulting tosylate with $LiAlH_4$ afforded 1,3- diol **7**[13,14] in 82% yield. Reaction of **7** with benzoyl chloride and $Et_3N$ gave benzoate **8** (81%), which upon silylation with TBSCl and imidazole furnished **9** in 92% yield. Base hydrolysis of ester **9** with $K_2CO_3$ and MeOH gave **10** (87%)




**Scheme 2.** Synthesis of compound **10**.

Alcohol **10**[15,16] on oxidation under Swern conditions[17] furnished aldehyde **11** in 84% yield, which was without further purification used for the next step**.** Wittig olefination of aldehyde **11** furnished the ester **12** in 75% yield. Compound **12** was subjected to Sharpless asymmetric dihydroxylation[18] with ADmix-β to afford the compound **13** as pale yellow syrup in 65% yield. The acetonide was prepared under standard conditions using 2,2-dimethoxypropane (2,2-DMP) and catalytic *p*-toluenesulfonic acid (PTSA) in dichloromethane for 30 min at 0 ºC to provide **5** in 85% yield.




**Scheme 3.** Synthesis of target compound **2**.

The ester **5** was then treated with DIBAL-H at 0 ºC to yield alcohol **14** in 86%. Further, tosylation of the resulting alcohol **14** to afford compound **15**. Treatment of compound **15** with tetra-*n*-butylammonium fluoride in THF at room temperature resulted in desilylation and concomitant cyclization[15] in one step to give the cyclized product **16** in 65% yield $[\alpha]_D$ = -11.8 (*c* 0.4, $CHCl_3$). Tetra-*n*-butylammonium fluoride (TBAF) in the present study acted as a desilylating agent, as well as a base to promote a facile cyclization reaction (Scheme 3). Finally, compound **12** on treatment with *p*-toluenesulfonic acid in MeOH gave ophiocerin B **2** in 85% yield, $[\alpha]_D$ = -32.3 (*c* 0.25, $CHCl_3$), matching that of the natural product[4] $[\alpha]_D$ = -34.0 (*c* 0.25, $CHCl_3$).

## Conclusion

In conclusion, we have accomplished total synthesis of ophiocerin B *via* Sharpless asymmetric dihydroxylation and Tetra-*n*-butylammonium fluoride (TBAF) mediated one-pot desilylation/cyclization. Thus, this strategy is adaptable for the generation of a library of stereoisomers. The generality of the method shown has significant potential for further extension to other isomers and related compounds.

## Experimental Section

**General.** All reactions were carried out under argon or nitrogen in oven dried glassware using standard gas-light syringes, cannulas, and septa. Solvents and reagents were purified and dried by standard methods prior to use. IR spectra were recorded on Perkin-Elmer FT-IR 240-c spectrophotometer using KBr optics. $^{1}$H NMR and $^{13}$C NMR spectra were recorded on Gemini-200 spectrometer (200 MHz) and Bruker-300 spectrometer (300 MHz) in $CDCl_3$ using TMS as internal standard. Mass spectra were recorded on Finnigan MAT 1020 mass spectrometer operating at 70 eV. Column chromatography was performed using E. Merck 60-120, mesh silica gel. Optical rotations were measured with JASCO DIP-370 Polarimeter at 25 $^{0}$C.

**(5*R*,*E*)-Ethyl 5-(*t*-butyldimethylsilyloxy)2-hexenoate (12).** To a solution of oxalyl chloride (3.1 mL, 26.47 mmol) in dry $CH_2Cl_2$ (10 mL) at -78 $^{o}$C, dry DMSO (3.7 g, 53.92 mmol) was added drop wise and stirred for 10 min. A solution of **10** (4.5 g, 22.05 mmol) in dry $CH_2Cl_2$ (10 mL) was added and stirred for 3 h at -78 $^{o}$C. $Et_3N$ (6.0 mL, 43.6 mmol) added and diluted with $CH_2Cl_2$ (20 mL). The reaction mixture was washed with water (20 mL), brine (20mL), dried ($Na_2SO_4$) and evaporated to furnish the corresponding aldehyde **11** (3.7 g, 84%).
The aldehyde **11** (3.7 g, 18.31 mmol) was dissolved in benzene and added to a refluxing solution of (ethoxycarbonylmethylene)triphenylphosphorane (9.5 g, 27.4 mmol) in benzene. After 4 h, solvent was evaporated and residue purified by column chromatography (EtOAc:hexane, 1:4) to afford **12** (3.7 g, 75%) as a pale yellow syrup. $[\alpha]_D$ -16.2 (*c* 0.6, $CHCl_3$); IR: 2924, 2854, 1745, 1460, 1376, 1105 cm$^{-1}$; $^{1}$H NMR (300 MHz, $CDCl_3$): $\delta$ 0.04 (s, 6H, 2 × $CH_3$), 0.88 (s, 9H, 3 × $CH_3$), 1.16 (d, 3H, *J* 6.0 Hz, $CH_3$), 1.29 (t, 3H, *J* 7.5 Hz, $CH_3$), 2.34-2.46 (m, 2H, $CH_2$), 3.97-3.85 (m, 1H, CH), 4.21 (q, 2H, *J* 7.5 Hz, $CH_2$), 5.78 (d, 1H, *J* 15.8 Hz, -CH), 6.89 (dt,1H, *J* 7.5, 15.8, Hz, -CH), $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ -4.62, 14.1, 17.9, 23.7, 25.7, 42.3, 59.9, 67.5, 145.8, 123.1, 166.2; HRMS: *m/z* $[M+Na]^+$ calcd 295.1806 found 295.2913 for $C_{14}H_{28}O_3SiNa$.
**(2*R*,3*R*,5*R*)-Ethyl 5-(*t*-butyldimethylsilyloxy)-2,3-dihydroxyhexanoate (13).** A well stirred solution of AD-mix-β (5.7 g, 7.35 mmol) in *t*-BuOH/$H_2O$ (1:1, 30 mL) was treated with methanesulfonamide (0.69 g, 735 mmol) at room temperature. After 30 min, the clear yellow solution was cooled to 0 °C and a solution of ester **12** (2.0 g, 7.35 mmol) in *t*-BuOH (5 mL) was added. The reaction mixture was stirred vigorously at 0 °C for 12 h and then quenched with solid $Na_2SO_4$ (5 g). It was warmed to room temperature and stirred for an additional 1 h. The resultant reaction mixture was extracted with $CH_2Cl_2$ (3 × 100 mL) and the combined extracts were dried ($Na_2SO_4$), filtered and evaporated to give crude residue, which was purified by column chromatography (30:70% EtOAc:hexane) to afford **13** (1.4 g, 65%) as pale yellow syrup. $[\alpha]_D$ -11.1 (*c* = 0.25, $CHCl_3$); IR: 3426, 3019, 2916, 2859, 1760, 1216, 1017 cm$^{-1}$; $^{1}$H NMR (200 MHz, $CDCl_3$): $\delta$ 0.09 (s, 6H, 2 × $CH_3$) 0.90 (s, 9H, 3 × $CH_3$), 1.21 (d, 3H, *J* 5.9 Hz, $CH_3$), 1.33 (t, 3H, *J* 7.4 Hz, $CH_3$), 1.56-1.63 (m, 2H, $CH_2$), 2.80-3.10 (m, 1H, CH), 4.12-3.92 (m, 2H, 2 × CH), 4.36 (q, 2H, *J* 7.4 Hz, $CH_2$); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ -4.12, 14.34, 23.21, 25.81, 30.71, 39.14,

60.56, 64.72, 66.85, 79.51, 169.31; HRMS: *m/z* $[M+Na]^+$ calcd 329.1863 found 329.1842 for $C_{14}H_{30}O_5SiNa$.

**(4*S*,5*R*)-Ethyl 5-[(*R*)-2-(*t*-butyldimethylsilyloxy)propyl]-2,2-dimethyl-1,3-dioxolane-4-carboxylate (5).** To a stirred solution of diol **13** (1.2 g, 3.92 mmol) in $CH_2Cl_2$ (5 mL), 2,2-dimethoxy propane (0.8 mL, 7.84 mmol), cat. *p*-toluenesulfonic acid (PTSA) (67 mg, 0.39) were added and stirred at room temperature for 2 h. Reaction mixture was quenched with $Et_3N$ (0.7 mL) and extracted with $CH_2Cl_2$ (10 mL). Organic layers were washed with water (10 mL), brine (10 mL), dried ($Na_2SO_4$), evaporated under reduced pressure and residue purified the by column chromatography (EtOAc:hexane, 1:10) to afford **5** (1.1 g, 85%) as a colorless oil. $[\alpha]_D$: -3.7 (*c* = 0.4, $CHCl_3$). IR: 2960, 2858, 1741, 1243, 1128 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 0.05 (s, 6H, 2 × $CH_3$), 0.88 (s, 9H, 3 × $CH_3$), 1.18 (d, 3H, *J* 6.2 Hz, -$CH_3$), 1.20 (s, 6H, 2 × $CH_3$), 1.65-1.74 (m, 2H, -$CH_2$) 1.83 (t, 2H, *J* 6.0 Hz, -$CH_3$), 3.94-4.29 (m, 5H), $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ -4.0, -4.9, 13.9, 24.1, 25.6, 42.2, 61.5, 68.0, 71.2, 73.2, 173.1; ESIMS: *m/z* 347 $[M+H]^+$, 369 $[M+Na]^+$. HRMS: *m/z* $[M+Na]^+$ calcd 369.2176 found 369.3142 for $C_{17}H_{34}O_5SiNa$

**[(4*R*,5*R*)-5-[(*R*)-2-(*t*-Butyldimethylsilyloxy)propyl]-2,2-dimethyl-1,3-dioxolan-4-yl]methanol (14).** To a stirred solution of **5** (1.1 g, 3.17 mmol) in dry $CH_2Cl_2$ (10 mL), DIBAL-H (5.4 mL, 3.81 mmol, 10% solution in hexane) was added at 0 ºC and stirred at the same temperature for 2 h. Methanol (0.5 mL) was added to the reaction mixture at 0 ºC and stirred for 10 min. Saturated aq. solution of sodium potassium tartarate (0.5 mL) was added and after 10 min methanol was evaporated. It was diluted with water (10 mL) and extracted with dichloromethane (2 x 10 mL). The combined organic layers were washed with brine (5 mL), dried ($Na_2SO_4$), concentrated and the residue purified by column chromatography (EtOAc: hexane, 1:3) to afford **14** (0.86 g, 86%) as a colorless syrup. $[\alpha]_D$: -12.6 (*c* = 0.4, $CHCl_3$); IR: 3473, 2930, 1112, 1058, 1013 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ $\delta$ 0.06 (s, 6H, 2 × $CH_3$), 0.91 (s, 9H, 3 × $CH_3$), 1.20 (d, 3H, *J* 6.2 Hz, -$CH_3$), 1.41 (s, 6H, 2 × $CH_3$), 1.57-1.74 (m, 2H, $CH_2$), 3.59 (dd, 1H, *J* 3.3, 11.7 Hz, CH) 3.81-3.68 (m, 2H, 2 × CH), 4.13-3.85 (m, 2H, $CH_2$); ESIMS: *m/z* 327 $[M+Na]^+$. HRMS: *m/z* $[M+Na]^+$ calcd 327.2073 found 327.3152 for $C_{15}H_{32}O_4SiNa$

**[(4*R*,5*R*)-5-[(*R*)-2-(*t*-Butyldimethylsilyloxy)propyl]-2,2-dimethyl-1,3-dioxolan-4-yl]methyl 4-methylbenzenesulfonate (15).** To a solution of **14** (1.0 g, 3.08 mmol) in $CH_2Cl_2$ (10 mL) at 0 ºC, $Et_3N$ (0.64 mL, 4.62 mmol) and tosyl chloride (0.73 g, 3.70 mmol) were added sequentially and stirred at room temperature for 4 h. The reaction mixture was washed with water (10 mL), brine (10 mL), dried ($Na_2SO_4$) and evaporated under reduced pressure. The residue was purified by column chromatography (EtOAc:hexane, 1:9) to furnish **15** (1.1 g, 78%) as a pale yellow oil. $[\alpha]_D$: -7.5 (*c* = 0.25, $CHCl_3$); IR: 3473, 2984, 2930, 1345, 1112, 1058, 1013 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 0.05 (s, 6H, 2 × $CH_3$), 0.90 (s, 9H, 3 × $CH_3$), 1.31 (d, 3H, *J* 5.1 Hz, -$CH_3$), 1.39 (s, 3H, $CH_3$), 1.37 (s, 3H, $CH_3$), 1.71-1.64 (m, 2H, $CH_2$), 2.51 (s, 3H, $CH_3$), 4.23-3.41 (m, 5H, -CH), 7.1 (d, 2H, *J* 7.9 Hz, Ar-H), 7.72 (d, 2H, *J* 7.9 Hz, Ar-H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ -4.01, 22.81, 25.51, 30.81, 38.62, 62.21, 67.31, 74.52, 82.63, 117.89; ESIMS: *m/z* 459 $[M+H]^+$.

**(3a*R*,6*R*,7a*R*)-2,2,6-Trimethyltetrahydro-3*H*-[1,3]dioxolo[4,5-*c*]pyran (16).** To a stirred solution of **15** (0.9 g, 1.96 mmol) in dry THF (5 mL) at 0 ºC, *n*-$Bu_4N^+F^-$ in THF (4.3 mL, 4.32

mmol) was added and stirred at room temperature for 10 h. The reaction mixture was evaporated and the residue purified by column chromatography (EtOAc: hexane, 6:4) to afford **16** (0.21 g, 65%) as a pale yellow syrup. $[\alpha]_D$ -11.8 (*c* = 0.4, $CHCl_3$); $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 1.31-1.20 (m, 9H, 3 × $CH_3$), 2.01-1.95 (m, 2H, $CH_2$), 3.38-3.25 (m, 1H, CH), 3.70-3.56 (m, 2H, $CH_2$), 4.02-3.93 (dd, 1H, *J* 4.4, 10.33 Hz, CH), 4.37-4.20 (m, 1H, CH); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 20.98, 24.41, 32.65, 66.68, 73.68, 76.45, 76.98, 117.28; ESIMS: *m/z* 172 $[M+H]^+$, 195 $[M + Na]^+$ ; HRMS: *m/z* $[M+Na]^+$ calcd 195.1099; found 195.2234 for $C_9H_{16}O_3Na$.

**(3*R*,4*R*,6*R*)-6-Methyltetrahydro-2*H*-pyran-3,4-diol (2).** A solution of **16** (0.015g, 0.087 mmol) in MeOH (2 mL) was treated with catalytic *p*-toluenesulfonic acid (1.5 mg, 0.0087) and stirred at room temperature for 4 h. The reaction mixture was quenched with solid $NaHCO_3$ filtered and MeOH was evaporated diluted with EtOAc (10 mL) washed with water (10 mL), brine (10 mL), dried ($Na_2SO_4$), evaporated under reduced pressure and the residue purified by column chromatography (EtOAc:hexane, 3:7) to afford ophiocerin B **2** (94 mg, 85%) as a yellow oil. $[\alpha]_D$ -32.3 (*c* 0.25,$CH_2Cl_2$) [lit.[9] $[\alpha]_D$ -34.0 (*c* 0.25, $CHCl_3$)]; IR: 3388, 1452,1380,1266,1079,1004 $cm^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 1.18 (d, 3H, *J* 6.1 Hz, $CH_3$), 1.64–1.59 (m, 2 H, -$CH_2$), 1.81 (bs, 1H, -OH), 3.45 (s, 1 H, -OH), 3.67 (dd, 1H, *J* 2.1, 12.2 Hz, -CH,), 3.73 (dd, 1H, *J* 2.3, 12.2 Hz, CH), 3.85 (ddq, 1H, *J* 2.6, 6.3,12.0 Hz, CH), 3.97 (dd, 1H, *J* 1.6, 12.4 Hz, CH), 3.91-3.99 (m, 1H, CH); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 21.1, 36.0, 67.2, 67.4, 68.2, 68.4; HRMS: *m/z* $[M+Na]^+$ calcd 155.0684; found 155.0691 for $C_6H_{12}O_3Na$.

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