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Stereoselective synthesis of ophiocerins A and C

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ABSTRACT

An efficient synthesis of ophiocerins A and C has been achieved via a common intermediate. The stereogenic centers were generated by means of Jacobsen's hydrolytic kinetic resolution and Sharpless kinetic resolution.

1. Introduction

During the search for new bioactive metabolites from freshwater fungi, Shearer et al. isolated ophiocerins A–C **1**–**3** (three diastereomeric tetrahydropyran derivatives) and ophiocerin D **4**, an isocrotonyl derivative of tetrahydropyran from the freshwater aquatic fungi *Ophioceras venezuelense* (Magnaporthaceae).[1,2] The absolute stereochemistry of **1**–**4** (Fig. 1) was assigned through circular dichroism spectroscopy by the exciton chirality method.[3,4] The substituted tetrahydropyran moiety[5] is found in a number of natural products that show excellent biological activities.[6] Due to the interesting array of substituents on the tetrahydropyran ring, the ophiocerins have attracted considerable amount of interest from synthetic organic chemists worldwide.[7,8]

Kang and co-workers described the synthesis of ophiocerins A–C from chiral pool starting materials such as carbohydrate and (*R*)-(−)-4-penten-2-ol,[8] while Yadav et al. reported the synthesis of ophiocerins A and B using tartaric acid[7c] and chiral epoxides[7a] as the starting materials.

As part of our ongoing research program aimed at developing enantioselective syntheses of naturally occurring bioactive compounds,[9] we became interested in developing a new route to ophiocerins A and C. Herein we report a new and highly enantioselective total synthesis of ophiocerin A and C via a common intermediate, starting from an achiral starting material using Jacobsen hydrolytic kinetic resolution[10,11] and Sharpless kinetic resolution[12] as the key steps.

2. Results and discussion

Our synthetic approach for the synthesis of ophiocerins A and C was envisioned via the retrosynthetic route as shown in Scheme 1. The allylic alcohol **10** was visualized as a common intermediate for the synthesis of both ophiocerins A and C. Ophiocerin A **1** would be obtained by base induced cyclization of tosylate **16** which in turn could be obtained from epoxide **11** via epoxide opening, acetonide protection followed by olefinic oxidation, subsequent reduction, and tosylation. Epoxide **11** could be obtained via Sharpless kinetic resolution of racemic allylic alcohol **10**, which in turn could be obtained from propylene oxide **5**. Similarly, ophiocerin C could be synthesized from epoxide **17** using a similar sequence of reactions. Epoxide **17** could be obtained from allylic alcohol **12** via a Sharpless epoxidation which in turn could be obtained from allylic alcohol **10** by Sharpless kinetic resolution.

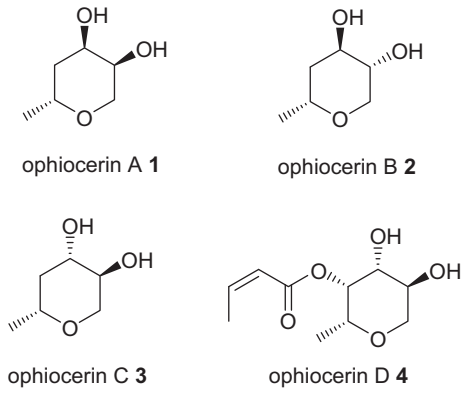

Figure 1. Structures of ophiocerins A-D **1–4**.

As illustrated in Scheme 2, the synthesis of ophiocerins A and C started from the commercially available propylene oxide **5**, which was subjected to Jacobsen's hydrolytic kinetic resolution using an (*R*,*R*)-salen-Co(III)-OAc catalyst to give (*R*)-propylene oxide (*R*)-**5** as a single isomer,[10a] which was easily isolated from the more polar diol **6** by distillation. (*R*)-Propylene oxide (*R*)-**5** was treated with vinylmagnesium bromide in the presence of CuI to give the homoallylic alcohol **7** in good yield.

Compound **7** was subjected to epoxidation with *m*-CPBA followed by TBS protection to afford diastereomeric epoxide **9** in 95% yield. Epoxide **9** was then treated with an excess of

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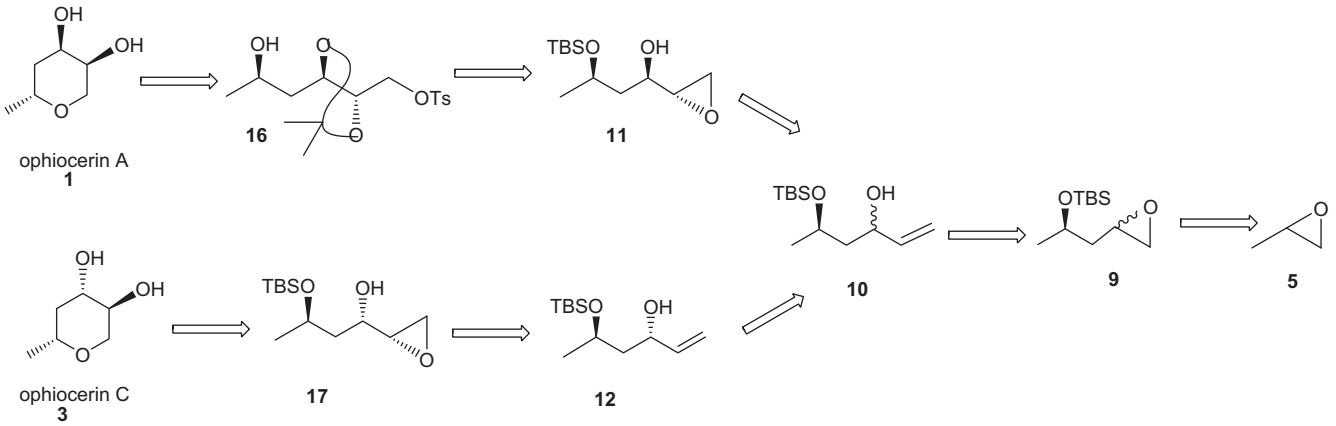
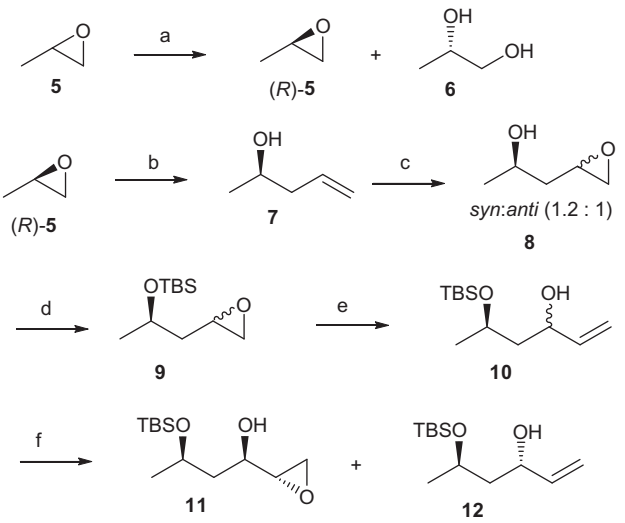


Scheme 1. Retrosynthetic analysis of ophiocerins A and C.

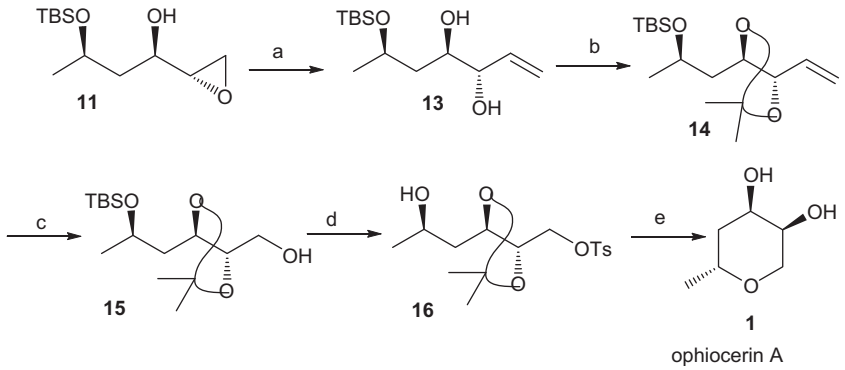


Scheme 2. Reagents and conditions: (a) (*R*,*R*)-salen-Co(III)-OAc (0.5 mol %), distd H_2O (0.55 equiv), 0 °C,14 h, (45% for (*R*)-**5**, 43% for **6**; (b) vinylmagnesium bromide, THF, CuI, −20 °C, 89%, 12 h; (c) *m*-CPBA, CH_2Cl_2, 0 °C to rt, 10 h, 96%; (d) TBDMSCl, imidazole, CH_2Cl_2, 0 °C to rt, 4 h, 95%; (e) $(CH_3)_3S^+ I^-$, *n*-BuLi, THF, −20 °C, 70%; (f) (−)-DIPT, Ti(O-*i*Pr)$_4$, TBHP, dry CH_2Cl_2, molecular sieves, 4 Å, −20 °C, 18 h, 48% for **11** and 42% for **12**.

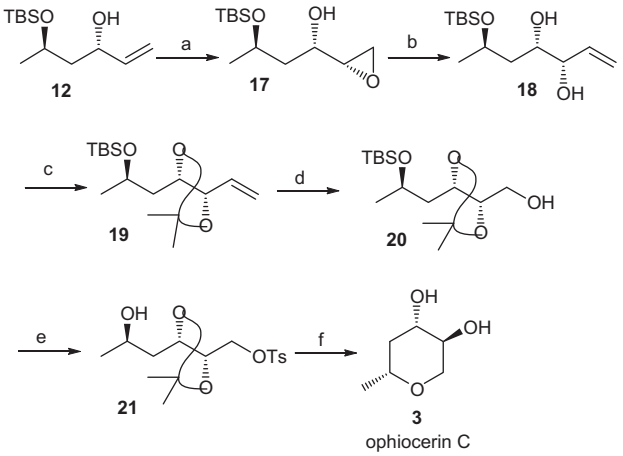
dimethylsulfonium methylide[13] (generated from trimethylsulfonium iodide and *n*-BuLi) to give allylic alcohol **10** in 70% yield, which is a common intermediate for the synthesis of both ophiocerins A and C. Thus, the treatment of **10** with titanium tetraisopropoxide and *tert*-butylhydroperoxide in the presence of (−)-DIPT under Sharpless asymmetric kinetic resolution conditions[12] provided the chiral epoxy alcohol **11** in 48% yield and >99% de and chiral allylic alcohol **12** in 42% yield and 98% de (determined from the ^1H and ^{13}C NMR).

For the synthesis of ophiocerin A, epoxide **11** was opened with an excess of dimethylsulfonium methylide to furnish diol **13** in 70% yield. Treatment of diol **13** with 2,2-dimethoxypropane in the presence of a catalytic amount of pyridinium 4-toluenesulfonate in acetone gave compound **14** in 80% yield, which upon olefinic oxidation using OsO_4 and $NaIO_4$ followed by subsequent reduction with $NaBH_4$[14] afforded alcohol **15** in 75% yield. Treatment of **15** with tosyl chloride followed by desilylation with tetrabutylammonium fluoride gave the secondary alcohol **16**. The base-induced cyclization of **16** with potassium *tert*-butoxide in diethyl ether at 0 °C, and the subsequent deprotection of acetonide using a catalytic amount of 4-toluenesulfonic acid in methanol furnished ophiocerin A (**1**) in 92% yield (Scheme 3). $[\alpha]_D^{25} = -23.4$ (*c* 0.1, CH_2C1_2); lit.[1] $[\alpha]_D^{25} = -24.0$ (*c* 0.1, CH_2Cl_2). The physical and spectroscopic data of **1** were in full agreement with the literature data.

For the synthesis of ophiocerin C **3**, the allylic alcohol **12** obtained by the chiral resolution of **10** was subjected to a Sharpless asymmetric epoxidation[9g,h,12] to give epoxide **17** in 60% yield as a single diastereomer, which was converted into ophiocerin C **3** following the same sequence of reactions as described for **1** (Scheme 4). Thus as shown in Scheme 4, epoxide **17** was opened with an excess of dimethylsulfonium methylide to furnish diol **18** in 72% yield. Treatment of diol **18** with 2,2-dimethoxypropane in the presence of a catalytic amount of pyridinium 4-toluenesulfonate in acetone afforded compound **19** in 85% yield, which upon olefinic oxidation followed by subsequent reduction gave alcohol **20** in 78% yield. Treatment of **20** with tosyl chloride followed by desilylation gave



Scheme 3. Reagents and conditions: (a) $(CH_3)_3S^+I^-$, *n*-BuLi, THF, −20 °C, 70%; (b) 2,2-DMP, PPTS, dry CH_3COCH_3, 40 °C,8 h, 80%; (c) (i) OsO_4, $NaIO_4$, Et_2O–H_2O, 24 h, rt; (ii) $NaBH_4$, MeOH, rt, 0.5 h, 75%; (d) (i)TsCl, NEt_3, DMAP (cat.), 3 h; (ii) TBAF, THF, 2 h, 85%; (e) (i) *t*-BuO^-K^+, Et_2O, 2 h; (ii) *p*-TSA, MeOH, rt, 2 h, 92%.



Scheme 4. Reagents and conditions: (a) (−)-DIPT, Ti(*O*-^{i}Pr)$_4$, TBHP, dry CH_2Cl_2, molecular sieves, 4 Å, −20 °C, 8 days, 60%; (b) $(CH_3)_3S^+I^-$, *n*-BuLi, THF, −20 °C, 72%; (c) 2,2-DMP, PPTS, dry CH_3COCH_3, 40 °C, 8 h, 85%; (d) (i) OsO_4, $NaIO_4$, Et_2O-H_2O, 24 h, rt; (ii) $NaBH_4$, MeOH, rt, 0.5 h, 78%; (e) (i) TsCl, NEt_3, DMAP (cat.), 3 h; (ii) TBAF, THF, 2 h, 82%; (f) (i) *t*-BuO$^-$K$^+$, Et_2O, 2 h; (ii) *p*-TSA, MeOH, rt, 2 h, 90%.

the secondary alcohol **21**, which upon base-induced cyclization with potassium *tert*-butoxide in diethyl ether at 0 °C, and subsequent deprotection of the acetonide using a catalytic amount of 4-toluenesulfonic acid in methanol furnished ophiocerin C **3** in 90% yield (Scheme 4). $[\alpha]_D^{25} = +43.4$ (*c* 0.1, CH_2Cl_2); lit.[1] $[\alpha]_D^{25} = +45.0$ (*c* 0.1, CH_2Cl_2). The physical and spectroscopic data of **3** were in full agreement with the literature data.

3. Conclusion

In conclusion, we have accomplished total synthesis of both ophiocerins A and C via a common intermediate using Jacobsen hydrolytic kinetic resolution and Sharpless kinetic resolution as the key steps and as a source of chirality. The generality of the method shown has significant potential for further extension to other isomers and related compounds. Further studies are in currently progress.

4. Experimental

4.1. 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. Optical rotations were measured at room temperature. IR spectra were recorded on an FT-IR instrument. ^{1}H NMR spectra were recorded on 200 MHz, 400 MHz, and 500 MHz and are reported in parts per million (δ) downfield relative to $CDCl_3$ as the internal standard and ^{13}C NMR spectra were recorded at 50 MHz, 100 MHz, and 125 MHz and assigned in parts per million (δ) relative to $CDCl_3$. Mass spectra were obtained with TSQ 70, Finningen MAT spectrometer. Column chromatography was performed on silica gel (100–200 and 230–400 mesh) using a mixture of petroleum ether and ethyl acetate as the eluent. Elemental analyses were carried out on a Carlo Erba CHNSO analyzer.

4.2. Preparation of (*R*)-propylene oxide (*R*)-5

The racemic propylene oxide **5** was resolved to (*R*)-propylene oxide (*R*)-**5** in high enantiomeric excess by the hydrolytic kinetic resolution method following a literature procedure.[10b] $[\alpha]_D^{25} = +11.2$ (neat); {lit[10b] $[\alpha]_D^{25} = -11.6$ (neat) for (*S*)-propylene oxide}.

4.3. Preparation of (*R*)-pent-4-en-2-ol 7

A round bottomed flask was charged with copper (I) iodide (3.28 g, 17.2 mmol), gently heated under vacuum, and slowly cooled with a flow of argon, after which dry THF (40 mL) was added. This suspension was cooled to −20 °C and vigorously stirred, and vinylmagnesium bromide (1 M in THF, 345 mL, 344.8 mmol) was injected into it. A solution of propylene oxide (*R*)-**5** (10 g, 172.18 mmol) in THF (20 mL) was added slowly to the above reagent, and the mixture was stirred at −20 °C for 12 h. The reaction mixture was quenched with a saturated aqueous solution of NH_4Cl. The organic layer was washed with brine, dried (Na_2SO_4), and concentrated to afford the crude homo allylic alcohol, which upon distillation provided alcohol **7** (13.2 g, 89%) as a colorless liquid (bp 115 °C, lit[15] bp 115 °C). $[\alpha]_D^{25} = -9.1$ (*c* 3.0, Et_2O); {lit.[15] $[\alpha]_D^{25} = -9.8$ (*c* 3.1, Et_2O)}; IR ($CHCl_3$, cm^{-1}): ν_{max} 3467, 3089, 2998, 2920, 1528, 1487, 1412, 1235, 1051, 994; ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.78–5.85 (m, 1H), 5.14 (d, *J* = 6.6 Hz, 1H), 5.10 (d, *J* = 2.4 Hz, 1H), 3.80–3.86 (m, 1H), 2.22–2.38 (m, 2H), 1.82 (s, 1H), 1.18 (d, *J* = 6.1 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 134.6, 116.6, 66.5, 43.2, 22.1.

4.4. Preparation of (2*R*)-1-(oxiran-2-yl)propan-2-ol 8

To a stirred solution of olefin **7** (3 g, 34.9 mmol) in CH_2Cl_2 (25 mL) at 0 °C was added *m*-CPBA (50%) (14.43 g, 41.8 mmol). The reaction mixture was stirred at room temperature for 10 h and quenched with a saturated $NaHCO_3$ solution, extracted with CH_2Cl_2, washed with saturated $NaHCO_3$ and brine, dried (Na_2SO_4), concentrated, and purified by silica gel column chromatography using pet ether/EtOAc (9:1) as eluent to yield epoxide **8** (3.41 g, 96%) as a colorless liquid in a diastereomeric mixture (1.2:1). $[\alpha]_D^{25} = -10.85$ (*c* 0.86, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): ν_{max} 3465, 3180, 2987, 2923, 2855, 1452, 1398, 1243, 1201, 1201, 984, 888; ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.06–4.10 (m, 1H), 3.02–3.05 (m, 1H), 2.81–2.84 (m, 1H), 2.52–2.54 (m, 1H), 1.82–1.86 (m, 1H), 1.71–1.74 (m, 1H), 1.18 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 66.5, 66.3, 49.6, 49.3, 47.2, 46.3, 42.9, 42.3, 25.7, 24.2 (both the diastereomers).

4.5. Preparation of *tert*-butyldimethyl(((2*R*)-1-(oxiran-2-yl)propan-2-yl)oxy)silane 9

To a stirred solution of alcohol **8** (12 g, 117.6 mmol) in CH_2Cl_2 (50 mL) was added imidazole (16.0 g, 235.0 mmol). To this solution *t*-butyldimethylchlorosilane (21.26 g, 141.0 mmol) was added at 0 °C and reaction was stirred at room temperature for 4 h. The reaction mixture was quenched with a saturated aqueous solution of NH_4Cl and extracted with CH_2Cl_2 (3 × 50 mL). The extract was washed with brine, dried (Na_2SO_4), and concentrated. Silica gel column chromatography of the crude product using pet ether/EtOAc (19:1) as eluent provided compound **9** (24.16 g, 95%) as a colorless liquid. IR ($CHCl_3$, cm^{-1}): ν_{max} 3060, 2985, 2903, 1885, 1472, 1420, 1377, 1289, 1101, 1005, 938, 898, 760; ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.03–4.10 (m, 1H), 3.03–3.06 (m, 1H), 2.79–2.83 (m, 1H), 2.44–2.54 (m, 1H), 1.67–1.75 (m, 1H), 1.49–1.55 (m, 1H), 1.18 (d, *J* = 6.3 Hz, 3H), 0.88 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 66.5, 66.3, 49.7, 49.1, 47.8, 46.5, 42.8, 42.4, 25.9, 24.6, 17.2, −3.6, −4.3, −4.8, −5.2. ((both the diastereomers).

4.6. Preparation of (5*R*)-5-((*tert*-butyldimethylsilyl)oxy)hex-1-en-3-ol 10

To a stirred solution of dry THF was added trimethylsulfonium iodide (13.91 g, 68.19 mmol) at −20 °C. The reaction mixture was stirred for 20 min followed by the addition of *n*-BuLi (42.6 mL,

1.6 M, 68.19 mmol). After 40 min, epoxide **9** (2.94 g, 13.61 mmol) in THF was added dropwise. The reaction mixture was stirred at −20 °C for 3 h and quenched by a saturated solution of ammonium chloride. The two phases were separated and the aqueous phase was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with water (2 × 50 mL), brine, dried over Na_2SO_4, and concentrated. The residual oil was purified by silica gel column chromatography using pet ether/EtOAc (7:3) as eluent to furnish the allylic alcohol **10** (2.19 g, 70%) as a colorless oil. IR ($CHCl_3$, cm^{-1}): ν_{max} 3415, 3018, 2950, 2963, 2865, 1624, 1427, 1465, 1348, 1262, 1057, 947; ^1H NMR (200 MHz, $CDCl_3$): δ 5.94–5.76 (m, 1H), 5.29–5.04 (m, 2H), 4.43–4.04 (m, 2H), 1.67–1.55 (m, 2H), 1.24–1.17 (m, 3H), 0.89 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 141.1, 140.7, 114.0, 113.8, 72.2, 69.6, 69.4, 67.1, 45.9, 44.4, 25.7, 24.5, 23.0, 17.9, −3.9, −4.4, −4.9, −5.0 (both the diastereomers).

4.7. Preparation of (1*R*,3*R*)-3-((*tert*-butyldimethylsilyl)oxy)-1-((*S*)-oxiran-2-yl)butan-1-ol 11 and (3*S*,5*R*)-5-((*tert*-butyldimethylsilyl)oxy)-hex-1-en-3-ol 12

To a mixture of 4 Å molecular sieves (1.0 g) and $Ti(O\text{-}^iPr)_4$ (2.7 mL, 9.086 mmol) in dry CH_2Cl_2 (60 mL), (−)-DIPT (2.08 mL,9.912 mmol) was added dropwise over 10 min at −20 °C. The mixture was stirred for 20 min at −20 °C and a solution of **10** (1.9 g, 8.26 mmol) in dry CH_2Cl_2 (40 mL) was added over 10 min. The reaction mixture was stirred for an additional 30 min at −20 °C after which TBHP (3.8 mL, 5 M solution in decane, 20.65 mmol) was added dropwise over 15 min. The reaction mixture was kept at −20 °C by a constant temperature bath and after 18 h the reaction was warmed to room temperature, and quenched with saturated Na_2SO_4 (30 mL). The mixture was then stirred vigorously for 2 h. The two phases were separated and the aqueous phase was extracted with CH_2Cl_2 (5 × 30 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated to dryness. The crude product was then purified by flash chromatography on silica gel using pet ether/EtOAc (95:5) as eluent to give chiral hydroxy olefin **12** (0.8 g, 42% yield, based on 45.4% conversion) as a colorless oil. Further elution with pet ether/EtOAc (4:1) gave epoxide **11** as a colorless oil (0.97 g, 48% yield, based on 54.6% conversion).

Data for **11**. $[\alpha]_D^{25} = -28.2$ (*c* 0.5, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): ν_{max} 3422, 2957, 2930, 2857, 1674, 1595, 1460, 1410, 1298, 1075, 1005, 963, 836; ^1H NMR (200 MHz, $CDCl_3$): δ 4.18–4.00 (m, 1H), 3.75–3.64 (m, 1H),3.44 (br s, 1H), 2.97–2.91 (m, 1H), 2.79–2.78 (m, 1H), 2.77 (m, 1H), 1.77–1.68 (m, 2H), 1.22 (d, *J* = 6.2 Hz, 3H), 0.90 (s, 9H), 0.11 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 70.5, 69.3, 54.3, 45.1, 42.6, 25.7, 24.3, 17.8, −3.9, −4.9; ESI[MS]: 269.07 [M^++Na]; Anal. Calcd for $C_{12}H_{26}O_3Si$; C, 58.49; H, 10.63; Found: C, 58.60; H, 10.51.

Data for **12**. $[\alpha]_D^{25} = -30.3$ (*c* 1.1, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): ν_{max} 3450, 3018, 2950, 2930, 2865, 1624, 1427, 1465, 1350, 1262, 1057, 947; ^1H NMR (200 MHz, $CDCl_3$): δ 5.93–5.79 (m, 1H), 5.32–5.05 (m, 2H), 4.45–4.42 (m, 1H), 4.22–4.18 (m, 1H), 1.69–1.61 (m, 2H), 1.24 (d, *J* = 6.2 Hz, 3H), 0.90 (s, 9H), 0.10 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 141.1, 113.8, 69.6, 67.2, 44.4, 25.8, 23.0, 17.9, −4.4, −5.0; Anal. Calcd for $C_{12}H_{26}O_2Si$ C, 62.55; H, 11.37; Found: C, 62.48; H, 11.41.

4.8. Preparation of (3*S*,4*R*,6*R*)-6-(*tert*-butyldimethylsilyloxy) hept-1-ene-3,4-diol 13

To a stirred solution of dry THF was added trimethylsulfonium iodide (1.23 g, 6.05 mmol) at −20 °C. The reaction mixture was stirred for 20 min after which was added *n*-BuLi (3.8 mL, 1.6 M, 6.05 mmol). After 40 min, epoxide **11** (0.3 g, 1.21 mmol) in THF was added dropwise. The reaction mixture was stirred at −20 °C for 3 h and then quenched by a saturated solution of ammonium chloride. The two phases were separated and the aqueous phase was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with water (2 × 50 mL), brine, dried over Na_2SO_4, and concentrated. The residual oil was purified by silica gel column chromatography using pet ether/EtOAc (7:3) as eluent to furnish diol **13** (0.22 g, 70%) as a colorless oil. $[\alpha]_D^{25} = -11.3$ (*c* 1.2, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): ν_{max} 3381, 2930, 1681, 1600, 1410, 1297, 1091, 926, 835, 727; ^1H NMR (200 MHz, $CDCl_3$): δ 5.93–5.79 (m, 1H), 5.39–5.21 (m, 2H), 4.15–4.05 (m, 2H), 3.86–3.78 (m, 1H), 2.75 (br s, 2H), 1.64–1.56 (m, 2H), 1.20 (d, *J* = 6.2 Hz, 3H), 0.91 (s, 9H), 0.13 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 136.4, 116.7, 75.4, 74.1, 70.1,39.6, 25.8, 24.5, 17.9, −3.9, −4.9; ESI[MS]: 283.10 [M^++Na]; Anal. Calcd For $C_{13}H_{28}O_3Si$; C, 59.95; H, 10.84; Found: C, 59.80; H, 10.61.

4.9. Preparation of *tert*-butyl-(((*R*)-1-((4*R*,5*S*)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl)-propan-2-yl)oxy) dimethylsilane 14

At first, 2,2-DMP (1.2 mL, 9.6 mmol) and PPTS (115 mg, 0.5 mmol) were added to a solution of diol **13** (1.25 g, 4.8 mmol) in acetone (30 mL), and the mixture was stirred at reflux for 8 h. The reaction was then quenched with satd aq $NaHCO_3$ (20 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography using pet-ether/EtOAc (19:1) to give **14** (1.15 g, 80%) as a pale yellow oil. $[\alpha]_D^{25} = -2.35$ (*c* 0.34, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): ν_{max} 2857, 1732, 1644, 1463, 1378, 1257, 1173, 1053, 898, 810; ^1H NMR (200 MHz, $CDCl_3$): δ 5.90–5.72 (m, 1H), 5.35–5.22 (m, 2H), 4.53–4.46 (m, 1H), 4.31–4.21 (m, 1H), 3.99–3.90 (m, 1H), 1.80–1.68 (m, 2H), 1.49 (s, 3H), 1.36 (s, 3H), 1.16 (d, *J* = 6.2 Hz, 3H), 0.89 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 134.5, 118.4, 108.1, 79.8, 75.2, 66.0, 40.1, 28.3, 25.8, 25.6, 23.4, 18.0, −4.4, −4.8; Anal. Calcd for $C_{16}H_{32}O_3Si$ C, 63.95; H, 10.73; Found: C, 63.81; H, 10.62.

4.10. Preparation of ((4*S*,5*R*)-5-((*R*)-2-(*tert*-butyldimethylsilyl oxy)propyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanol 15

A solution of **14** (156 mg,0.052 mmol) in Et_2O (25 mL) was added to a saturated aqueous solution of $NaIO_4$ (15 mL) containing OsO_4 (40 mg, 0.17 mmol), and this mixture was stirred at room temperature for 24 h. The mixture was diluted with Et_2O (15 mL) and H_2O (15 mL), and the organic layer was dried (Na_2SO_4), filtered, and concentrated. The residue was redissolved in MeOH (10 mL), and $NaBH_4$ (60 mg) was added. After 30 min the mixture was concentrated, and the residue was partitioned between Et_2O (50 mL) and H_2O (20 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated, and the residue was purified by silica gel column chromatography using pet ether/ethylacetate (19:1) as eluent to give **15** (119 mg, 75%) as a colorless liquid. $[\alpha]_D^{25} = -12.2$ (*c* 1.2, $CHCl_3$); IR (neat, cm^{-1}): ν_{max} 3465, 2913, 1456, 1252, 1049, 834; ^1H NMR (200 MHz, $CDCl_3$): δ 4.31–4.11 (m, 2H), 4.07–3.90 (m, 1H), 3.65–3.53 (m, 2H), 1.88–1.75 (m, 2H), 1.47 (s, 3H),1.36 (s, 3H),1.19 (d, *J* = 6.2 Hz, 3H), 0.89 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 109.0, 78.5, 72.5, 66.5, 63.6, 42.0, 30.9, 26.6, 25.8, 24.4, 17.8, −3.9, −4.8; Anal. Calcd for $C_{15}H_{32}O_4Si$: C, 59.17; H, 10.59; Found: C, 59.08; H, 10.43.

4.11. Preparation of ((4*S*,5*R*)-5-((*R*)-2-hydroxypropyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl 4-methylbenzenesulfonate 16

At first, Et_3N (1.0 mL, 7.2 mmol) and DMAP (44 mg, 0.4 mmol) were added to a solution of alcohol **15** (1.10 g, 3.6 mmol) in CH_2Cl_2 (10 mL) at rt, and the mixture was stirred for 10 min. Next, TsCl (0.9 g, 4.8 mmol) was added and stirring was continued at rt for

3 h. The reaction was quenched with satd aq NH_4Cl (20 mL), and the mixture was extracted with CH_2Cl_2 (5 × 15 mL). The combined organic layers were washed with H_2O and brine, then dried (Na_2SO_4), and concentrated under reduced pressure. The crude tosylate product was used in the next step without further purification.

A 1 M solution of TBAF in THF (5.2 mL, 5.23 mmol) was added to a stirred soln of crude tosylate (1.6 g, 3.49 mmol) in dry THF (10 mL) at rt, and the mixture was stirred for 2 h. The reaction was quenched with satd aq NH4Cl (20 mL), and the mixture was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed with H_2O and brine then dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified by silica gel column chromatography using pet-ether/EtOAc (5:1) as eluent to give **16** (1.05 g, 85%) as a light yellow oil. $[\alpha]_D^{25} = -6.0$ (*c* 0.43, $CHCl_3$); IR (neat, cm^{-1}): ν_{max} 3455, 2903, 1445, 1185, 790; ^1H NMR (200 MHz, $CDCl_3$): δ 7.80 (d, J = 8.2 Hz, 2H), 7.37 (d, J = 8.2 Hz, 2H), 4.40–4.22 (m, 2H), 4.05–3.88 (m, 3H), 2.46 (s, 3H), 1.73–1.49 (m, 2H), 1.35 (s, 3H),1.32 (s, 3H),1.18 (d, J = 6.2 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 145.0, 132.5, 129.9, 127.9, 109.2, 74.7, 71.8, 68.7, 64.7, 34.0, 29.8, 22.0, 21.6, 19.6; Anal. Calcd for $C_{16}H_{24}O_6S$: C, 55.80; H, 7.02; Found: C, 55.69; H, 6.99.

4.12. Preparation of ophiocerin A 1

A solution of tosylate **16** (90 mg, 0.26 mmol) in dry Et_2O (3 mL) was added to a stirred suspension of *t*-BuOK (87.85 mg, 0.78 mmol) in dry Et_2O (5 mL) at 0 °C, and the mixture was stirred for 2 h at 0 °C. The reaction was quenched with satd aq NH_4Cl (10 mL), and the mixture was extracted with Et_2O (4 × 5 mL). The combined organic layers were washed with H_2O and brine, then treated with PTSA (3 mg) and MeOH (5 mL) with stirring at rt for 2 h. The reaction was quenched with satd aq $NaHCO_3$ solution, and the solvents (MeOH and Et_2O) were evaporated under reduced pressure. The residue was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic layers were washed with H_2O and brine, then dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography using pet-ether/EtOAc (4:6) as eluent to give ophiocerin A **1** (31.7 mg, 92%) as a white solid. $[\alpha]_D^{25} = -23.4$ (*c* 0.1, CH_2Cl_2) lit.[1] $[\alpha]_D^{25} = -24.0$ (*c* 0.1, CH_2Cl_2); mp = 62–64 °C;IR (KBr, cm^{-1}): ν_{max} 3401, 2930, 1454, 1389, 1185, 1011; ^1H NMR (500 MHz, $CDCl_3$): δ 4.10 (m, 1H), 3.83 (ddq, J = 2.0, 6.4, 11.3 Hz, 1H), 3.71–3.78 (m, 2H), 3.60–3.53 (m, 1H), 1.89 (ddd, J = 2.1, 3.5, 14.3 Hz, 1H), 1.53 (ddd, J = 2.5, 11.0, 13.9 Hz, 1H), 1.16 (d, J = 6.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 67.3, 67.1, 67.0, 65.9, 39.0, 20.8.

4.13. Preparation of (1*S*,3*R*)-3-(*tert*-butyldimethylsilyloxy)-1-((*S*)-oxiran-2-yl)butan-1-ol 17

To a mixture of 4 Å molecular sieves (0.3 g) and $Ti(O\text{-}^iPr)_4$ (0.7 mL, 2.38 mmol) in dry CH_2Cl_2 (20 mL), (−)-DIPT (0.54 mL,2.60 mmol) was added dropwise over 10 min at −20 °C. The mixture was stirred for 20 min at −20 °C after which a solution of **12** (0.5 g, 2.17 mmol) in dry CH_2Cl_2 (20 mL) was added over 10 min. The reaction mixture was stirred for an additional 30 min at −20 °C after which TBHP (1.0 mL, 5 M solution in decane, 5.42 mmol) was added dropwise over 15 min. The reaction mixture was kept at −20 °C by a constant temperature bath and after 8 days the reaction was warmed to room temperature, and quenched with saturated Na_2SO_4 (15 mL). The mixture was then stirred vigorously for 2 h. The two phases were separated and the aqueous phase was extracted with CH_2Cl_2 (5 × 20 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated to dryness. The crude product was then purified by flash chromatography on silica gel using pet ether–EtOAc (95:5) as eluent to give chiral hydroxy olefin **17** (0.32 g, 60% yield) as a colorless liquid. $[\alpha]_D^{25} = -18.1$ (*c* 3.2, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 4.28–4.14 (m, 1H), 3.83–3.74 (m, 1H), 3.01–2.95 (m, 1H), 2.81–2.76 (m, 1H), 2.74–2.70 (m, 1H), 1.82–1.55 (m, 2H), 1.21 (d, J = 6.2 Hz, 3H), 0.89 (s, 9H), 0.09 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 68.3, 66.1, 55.6, 44.5, 42.1, 25.8, 23.5, 17.9, −4.5, −5.0; Anal. Calcd for $C_{12}H_{26}O_3Si$: C, 58.49; H, 10.63; Found: C, 58.41; H, 10.55.

4.14. Preparation of (3*S*,4*S*,6*R*)-6-(*tert*-butyldimethylsilyloxy) hept-1-ene-3,4-diol 18

Compound **18** was synthesized using the same procedure as described for compound **13**. $[\alpha]_D^{25} = -28.6$ (*c* 0.8, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 5.95–5.78 (m, 1H), 5.40–5.20 (m, 2H), 4.29–4.20 (m, 1H), 3.91–3.85 (m, 2H), 2.77 (br s, 2H), 1.83–1.69 (m, 1H), 1.59–1.48 (m, 1H), 1.24 (d, J = 6.2 Hz, 3H), 0.89 (s, 9H), 0.09 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 137.6, 117.1, 76.4, 71.0, 67.4, 40.0, 25.7, 22.7, 17.9, −4.5, −5.1 Anal. Calcd For $C_{13}H_{28}O_3Si$; C, 59.95; H, 10.84; Found: C, 59.83; H, 10.68.

4.15. Preparation of *tert*-butyl-((*R*)-1-((4*S*,5*S*)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl)propan-2-yloxy)dimethylsilane 19

Compound **19** was synthesized using the same procedure as described for compound **14**. $[\alpha]_D^{25} = -16.9$ (*c* 0.4, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 5.87–5.70 (m, 1H), 5.39–5.22 (m, 2H), 4.07–3.99 (m, 1H), 3.92–3.79 (m, 2H), 1.61–1.55 (m, 2H), 1.42 (s, 3H), 1.40 (s, 3H), 1.16 (d, J = 6.2 Hz, 3H), 0.89 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 135.0, 118.9, 108.5, 82.8, 77.1, 65.5, 41.6, 27.4, 26.9, 25.8, 24.6, 18.0, −4.4, −4.9 Anal. Calcd for $C_{16}H_{32}O_3Si$ C, 63.95; H, 10.73; Found: C, 63.86; H, 10.63.

4.16. Preparation of ((4*S*,5*S*)-5-((*R*)-2-(*tert*-butyldimethylsilyl oxy)propyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanol 20

Compound **20** was synthesized using the same procedure as described for compound **15**. $[\alpha]_D^{25} = -22.6$ (*c* 0.2, $CHCl_3$), lit.[7c] $[\alpha]_D^{27} - 21.0$ (*c* 0.2, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 4.08–4.01 (m, 2H), 3.80–3.55 (m, 3H), 1.95 (br s, 1H), 1.61–1.55 (m, 2H), 1.42 (s, 3H), 1.38 (s, 3H),1.16 (d, J = 6.2 Hz, 3H), 0.89 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 108.6, 81.5, 73.7, 65.6, 61.9, 42.8, 27.4, 26.9, 25.8, 24.7, 18.0, −4.4, −4.9;

4.17. Preparation of ((4*S*,5*S*)-5-((*R*)-2-hydroxypropyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl 4-methylbenzenesulfonate 21

Compound **21** was synthesized using the same procedure as described for compound **16**. $[\alpha]_D^{25} = +3.2$ (*c* 0.3, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 7.79 (d, J = 8.2 Hz, 2H), 7.35 (d, J = 8.2 Hz, 2H), 4.14–4.11 (m, 2H), 4.09–4.05 (m, 1H), 4.02–3.99 (m, 1H), 3.88–3.85 (m, 1H), 2.47 (s, 3H), 1.71–1.68 (m, 2H), 1.37 (s, 3H),1.31 (s, 3H),1.21 (d, J = J = 6.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 145.1, 132.6, 129.9, 127.9, 109.5, 78.0, 75.3, 68.9, 65.0, 41.0, 27.2, 26.6, 23.8, 21.6.

4.18. Preparation of ophiocerin C 3

Ophiocerin **C** was synthesized using the same procedure as described for ophiocerin **A**. $[\alpha]_D^{25} = +42.4$, lit.[1] $[\alpha]_D^{25} = +45.0$ (*c* 0.1, CH_2Cl_2); mp = 81–83 °C ^1H NMR (200 MHz, $CDCl_3$): δ 3.97 (dd, J = 5.0, 11.3 Hz, 1H), 3.65–3.45 (m, 3H), 3.16 (dd, J = 9.9, 11.0 Hz, 1H), 2.00 (ddd, J = 1.8, 4.3, 12.6 Hz, 1H), 1.38 (ddd, J = 11.1, 11.1, 12.8 Hz, 1H), 1.22 (d, J = 6.2 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 73.3, 72.7,72.2, 69.6, 40.5, 21.2.

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