Substrate-Controlled Stereoselective Synthesis of Ophiocerin C

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Abstract: A novel stereoselective total synthesis of ophiocerin C was accomplished starting from L-(+)-tartaric acid. The C3,C4 *vic*-diol moiety was obtained from tartaric acid, and the stereogenic centre at C6 was created by substrate-controlled epoxidation and subsequent regioselective cleavage of the epoxide ring.

Key words: Wittig reactions, tartaric acid, epoxidations, ring opening, ophiocerin C, stereoselective synthesis

The ophiocerins A–D (**1**–**4**, Figure 1) are natural products with a tetrahydropyran skeleton, isolated from the freshwater fungus *Ophioceras venezuelense* (Magnaporthaceae) by Shearer and co-workers.[1,2] The absolute stereochemistry of **1**–**4** was assigned through circular dichroism spectroscopy by the exciton chirality method.[3,4] The substituted pyran moiety[5] is found in a wide variety of natural products that show a broad spectrum of biological activities.[6] Because of the interesting array of substituents on their tetrahydropyran rings, ophiocerins have attracted the attention of synthetic organic chemists.[7]

By retrosynthetic analysis (Scheme 1), we envisaged that ophiocerin C (**3**) could be prepared from the dioxolane **12**, which could, in turn, be obtained from olefin **8** by a substrate-controlled stereoselective epoxidation and subsequent regioselective opening of the epoxide ring. The final cyclization could be achieved by nucleophilic substitution.

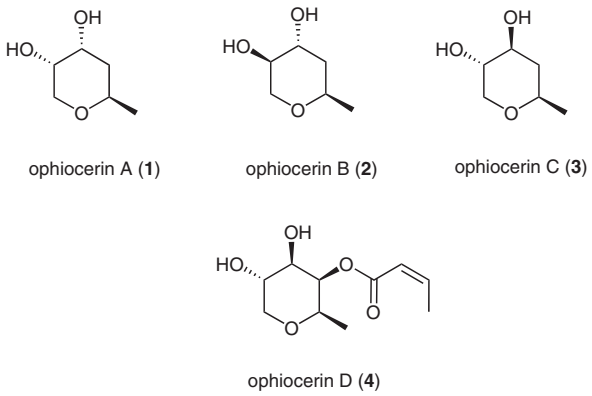
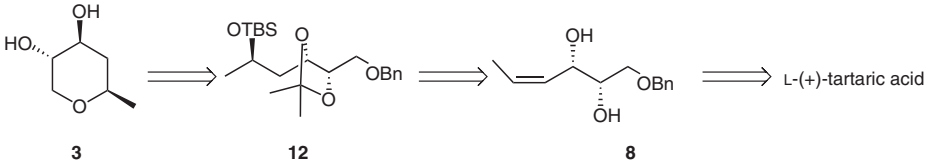


Figure 1 Ophiocerins A–D

According to our synthetic strategy, alcohol **6** was prepared from L-(+)-tartaric acid.[8] Compound **6** was subjected to Swern oxidation give the corresponding aldehyde, which underwent Wittig olefination by ethylidene(triphenyl)phosphorane to give the olefin **7** in 85% yield for the two steps (Scheme 2).

Treatment of compound **7** with a catalytic amount of 4-toluenesulfonic acid in methanol followed by epoxidation of the resulting allylic alcohol **8** gave the *threo*-2,3-epoxy alcohol **9** in 90% yield.[9] The epoxide **9** was treated with Red-Al [sodium bis(2-methoxyethoxy)dihydridoaluminum] to afford the triol **10** in 92% yield by regioselective ring opening.[10] The triol **10** was monosilylated with *tert*-butyl(dimethyl)silyl chloride, and the resulting diol **11** was protected by treatment with 2,2-dimethoxypropane and a catalytic amount of pyridinium 4-toluenesulfonate in dichloromethane to give the acetonide **12** in 94% yield. Debenzylation of **12** by hydrogenation over palladium/carbon gave the primary alcohol **13** quantitatively. Esterification of **13** with tosyl chloride afforded the *O*-tosyl derivative **14**. Desilylation of **14** with tetrabutylammonium fluoride gave the secondary alcohol **15.** Base-induced cyclization of **15** with potassium *tert*-butoxide in diethyl ether at 0 °C,[7a] and subsequent deprotection of the acetonide using a catalytic amount of 4-toluenesulfonic acid in methanol gave ophiocerin C (**3**) in 12 steps and 44% overall yield. The analytical data for **3** were in agreement with those reported in the literature.[1]

In conclusion, we have developed a concise and efficient stereocontrolled and stereoselective synthesis of ophiocerin C in a high overall yield; the application of this strategy to the synthesis of the other ophiocerins is underway.



Scheme 1 Retrosynthetic analysis of ophiocerin C

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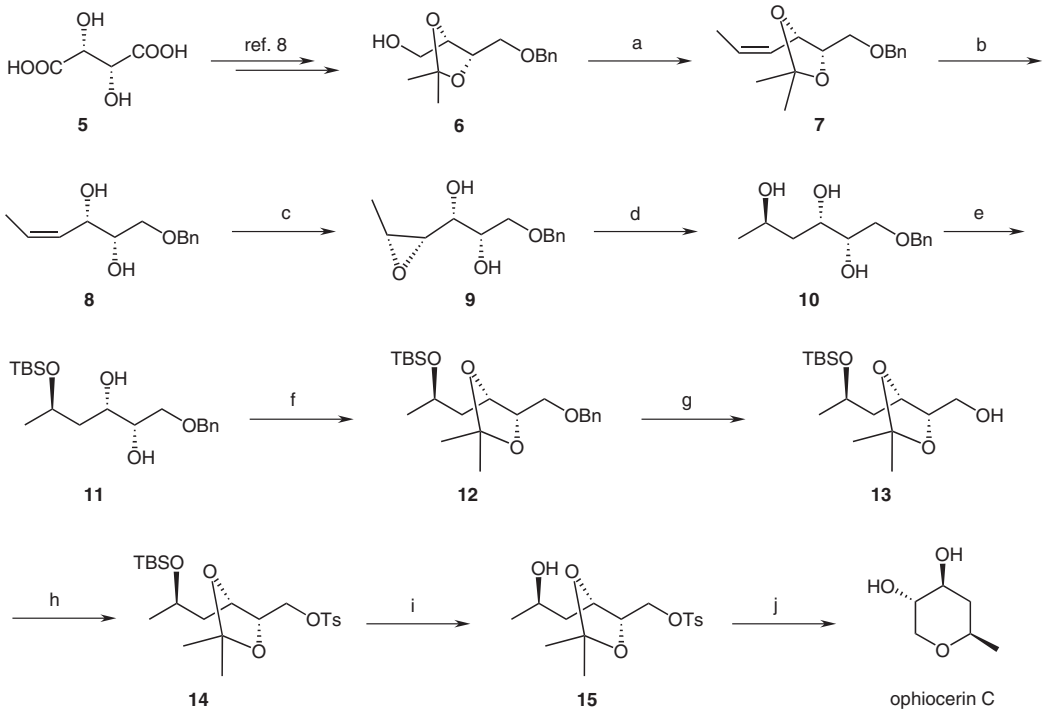

Scheme 2 *Reagents and conditions:* (a) (1) $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C to r.t., 2 h; (2) $Ph_3P^+C_2H_5I^-$, *t*-BuOK, THF, 0 °C, 1 h, 85% (2 steps); (b) PTSA, MeOH, r.t., 2 h, 90%; (c) MCPBA, $NaHCO_3$, CH_2Cl_2, 0 °C to r.t., 10 h, 90%; (d) Red-Al, THF, 0 °C to r.t., 5 h, 92%; (e) TBDMSCl, imidazole, CH_2Cl_2, r.t., 3 h, 90%; (f) $Me_2C(OMe)_2$, PPTS, CH_2Cl_2, r.t., 3 h, 94%; (g) H_2, 10% Pd/C, EtOAc, r.t., 2 h, 96%; (h) TsCl, TEA, DMAP (cat.), CH_2Cl_2, r.t., 3 h, 92%; (i) TBAF, THF, r.t., 2 h, 90%; (j) (1) *t*-BuOK, Et_2O, 0 °C, 2 h; (2) PTSA (cat.), MeOH, r.t., 2 h, 88% (2 steps).

All commercial reagents were used without further purification, and all solvents were purified by standard techniques. The crude products were purified by column chromatography on silica gel (60–120 mesh) with EtOAc and hexane as eluents. IR spectra were recorded on a Perkin-Elmer 683 spectrometer. Optical rotations were measured on Perkin-Elmer Model 343 polarimeter with $CHCl_3$ as the solvent. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ on Varian Gemini 200 and Bruker 300 NMR spectrophotometers; chemical shifts (δ) are quoted in parts per million and are referred to TMS as the internal standard. Coupling constants (*J*) are quoted in Hz. ESI HRMS were recorded on a high-resolution QSTAR XL hybrid MS/MS system (Applied Biosystems), and the sample solns were prepared in MeOH.

(4*S*,5*R*)-4-[(Benzyloxy)methyl]-2,2-dimethyl-5-[(1*Z*)-prop-1-en-1-yl]-1,3-dioxolane (7)

A soln of DMSO (3.1 mL, 43.7 mmol) in CH_2Cl_2 (15 mL) was added to a stirred soln of $(COCl)_2$ (3.5 mL, 39.7 mmol) in CH_2Cl_2 (15 mL) at –78 °C. After 20 min, a soln of **6** (5.0 g, 19.8 mmol) in CH_2Cl_2 (20 mL) was added at –78 °C. The mixture was stirred for another 20 min at –78 °C and then Et_3N (13.7 mL, 99.2 mmol) was added, also at –78 °C. The mixture was brought to r.t. and stirred for 30 min. Sat. aq NH_4Cl (50 mL) was added to quench the reaction and the resulting mixture was extracted with CH_2Cl_2 (3 × 20 mL). The organic layer was washed with H_2O and brine then dried (Na_2SO_4) and concentrated in vacuo. The crude aldehyde was used in the next step without further purification.

t-BuOK (6.72 g, 59.5 mmol) was added to a stirred soln of $Ph_3P^+EtI^-$ (24.82 g, 59.5 mmol) in THF (200 mL), and the mixture was stirred for 30 min at 0 °C. A soln of the crude aldehyde in THF (20 mL) was then added through a cannula, and the resulting mixture was stirred for 1 h. The reaction was quenched with sat. aq NH_4Cl (100 mL) and the mixture was extracted with Et_2O (3 × 40 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography [silica gel, EtOAc–hexane (1:9)] to give compound **7** as a colorless oil; yield: 85% (2 steps); $[\alpha]_D^{27}$ +3.2 (*c* 1.4, $CHCl_3$).

IR (neat): 3026, 2938, 1663, 1494, 1452, 740, 698 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.33–7.26 (m, 5 H), 5.70 (m, 1 H), 5.38 (m, 1 H), 4.65 (m, 1 H), 4.57 (ABq, 2 H), 3.77 (m, 1 H), 3.57 (dd, *J* = 10.5, 3.7 Hz, 1 H), 3.51 (dd, *J* = 10.5, 5.3 Hz, 1 H), 1.68 (d, *J* = 6.8 Hz, 3 H), 1.40 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.2, 137.9, 130.4, 128.33, 127.5, 127.0, 109.1, 80.3, 73.5, 73.1, 69.1, 27.1, 26.9, 13.3.

ESI-HRMS: *m/z* $[M + Na]^+$ calcd for $C_{16}H_{22}NaO_3$: 285.3366; found: 285.3362.

(2*R*,3*R*,4*Z*)-1-(Benzyloxy)-4-hexene-2,3-diol (8)

PTSA (238 mg, 1.4 mmol) was added to a stirred soln of acetonide **7** (3.60 g, 13.9 mmol) in MeOH (25 mL) at r.t., and the mixture was stirred for 2 h. The reaction was then quenched with sat. aq $NaHCO_3$ (20 mL) and the MeOH was removed. The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL), and the combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography [silica gel, EtOAc–hexane (4:6)] to give a white solid; yield: 90%; mp 55–56 °C; $[\alpha]_D^{27}$ +4.7 (*c* 0.9, $CHCl_3$).

IR (KBr): 3412, 3917, 1658, 1450, 1110, 1045, 736, 698 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.21 (m, 5 H), 5.63 (m, 1 H), 5.40 (m, 1 H), 4.51 (s, 2 H), 4.40 (m, 1 H), 3.61–3.49 (m, 2 H), 3.42 (m, 1 H), 2.90 (br s, 2 H, OH), 1.67 (d, *J* = 7.0 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 137.5, 128.9, 128.8, 128.3, 127.8, 127.7, 73.6, 73.5, 71.1, 67.9, 13.5.

ESI-HRMS: *m/z* $[M + Na]^+$ calcd for $C_{13}H_{18}NaO_3$: 245.2720; found: 245.2724.

2,3-Anhydro-6-*O*-benzyl-1-deoxy-D-galactitol (9)

A stirred soln of diol **8** (2.47 g, 11.1 mmol) in CH_2Cl_2 (30 mL) was cooled to 0 °C and then $NaHCO_3$ (1.21 g, 14.4 mmol) and MCPBA (2.48 g, 14.4 mmol) were added successively at 0 °C, and the mixture was stirred at r.t. for 10 h. The reaction was quenched with sat. aq $NaHCO_3$. The mixture was extracted with CH_2Cl_2 (3 × 20 mL), and the combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by column chromatography [silica gel, EtOAc–hexane (1:1)] to give a white solid; yield: 90%; mp 49–50 °C; $[\alpha]_D^{26}$ +3.4 (*c* 0.6, $CHCl_3$).

IR (KBr): 3319, 2928, 1452, 1129, 1057, 742 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.38–7.31 (m, 5 H), 4.54 (s, 2 H), 3.78 (m, 1 H), 3.59–3.53 (m, 3 H), 3.14–3.03 (m, 2 H), 2.71 (br s, 2 H, OH), 1.31 (d, *J* = 5.3 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 137.5, 128.3, 127.7, 127.6, 73.4, 71.3, 71.1, 69.7, 57.9, 53.2, 13.6.

ESI-HRMS: *m/z* $[M + Na]^+$ calcd for $C_{13}H_{18}NaO_4$: 261.2710; found: 261.2718.

6-*O*-Benzyl-1,3-dideoxy-D-*xylo*-hexitol (10)

A 65% w/v soln of Red-Al in toluene (8.3 mL, 26.7 mmol) was added to a stirred soln of **9** (2.11 g, 8.9 mmol) in THF (30 mL) under N_2 at 0 °C. The mixture was allowed to warm to r.t. over 1 h and stirred for a further 4 h. The reaction was quenched with sat. aq NH_4Cl (30 mL), and the mixture was filtered through Celite. The filtrate was extracted with CH_2Cl_2 (3 × 20 mL) and the organic layer was washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by column chromatography [silica gel, EtOAc–hexane (2:1)] to give a colorless oil; yield 92%; $[\alpha]_D^{26}$ –3.4 (*c* 0.6, $CHCl_3$).

IR (neat): 3388, 2924, 1459, 1052, 767 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.28 (m, 5 H), 4.54 (ABq, 2 H), 4.15 (dd, *J* = 7.5, 14.3 Hz, 2 H), 3.91 (br s, 1 H), 3.69–3.54 (m, 3 H), 1.80 (m, 1 H), 1.61 (m, 1 H), 1.18 (d, *J* = 6.0 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 137.5, 128.4, 127.8, 127.7, 73.4, 72.8, 71.9, 69.2, 64.7, 41.4, 23.4.

ESI-HRMS: *m/z* $[M + Na]^+$ calcd for $C_{13}H_{20}NaO_4$: 263.2868; found: 263.2863.

6-*O*-Benzyl-2-*O*-[*tert*-butyl(dimethyl)silyl]-1,3-dideoxy-D-*xylo*-hexitol (11)

Imidazole (1.36 g, 20.0 mmol) and TBDMSCl (2.26 g, 15.0 mmol) were added to a stirred soln of triol **10** (3.0 g, 12.5 mmol) in CH_2Cl_2 (30 mL) at r.t., and the resulting mixture was stirred for 3 h. The reaction was quenched with sat. aq NH_4Cl (20 mL), and the mixture was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed with H_2O, brine, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by column chromatography [silica gel, EtOAc–hexane (3:7)] to give a pale yellow oil; yield: 90%; $[\alpha]_D^{26}$ –6.1 (*c* 0.8, $CHCl_3$).

IR (neat): 3442, 2929, 1462, 1252, 1076, 834, 737 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.38–7.21 (m, 5 H), 4.53 (ABq, 2 H), 4.16 (m, 1 H), 3.90 (m, 1 H), 3.58–3.47 (m, 3 H), 3.12 (br s, 1 H, OH), 2.56 (br s, 1 H, OH), 1.73 (m, 1 H), 1.41 (m, 1 H), 1.20 (d, *J* = 5.8 Hz, 3 H), 0.89 (s, 9 H), 0.08 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 137.8, 128.4, 127.7, 73.5, 73.1, 72.1, 68.5, 66.7, 41.2, 25.7, 23.1, 17.9, –4.5, –5.0.

ESI-HRMS: *m/z* $[M + Na]^+$ calcd for $C_{19}H_{34}NaO_4Si$: 400.5386; found: 400.5384.

6-*O*-Benzyl-2-*O*-[*tert*-butyl(dimethyl)silyl]-1,3-dideoxy-4,5-*O*-(1-methylethylidene)-D-*xylo*-hexitol (12)

$Me_2C(OMe)_2$ (2.4 mL, 19.2 mmol) and PPTS (230 mg, 1.0 mmol) were added to a soln of diol **11** (3.40 g, 9.6 mmol) in CH_2Cl_2 (30 mL), and the mixture was stirred at r.t. for 3 h. The reaction was then quenched with sat. aq $NaHCO_3$ (20 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL) and the combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by column chromatography [silica gel, EtOAc–hexane (1:9)] to give a pale yellow oil; yield: 94%; $[\alpha]_D^{27}$ –16.3 (*c* 1.8, $CHCl_3$)

IR (neat): 2931, 1456, 1252, 1096, 834, 736 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.38–7.19 (m, 5 H), 4.56 (ABq, 2 H), 4.06–3.91 (m, 2 H), 3.69 (m, 1 H), 3.57–3.47 (m, 2 H), 1.68–1.45 (m, 2 H), 1.37 (s, 3 H), 1.34 (s, 3 H), 1.15 (d, *J* = 6.0 Hz, 3 H), 0.87 (s, 9 H), 0.05 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.0, 128.3, 127.6, 127.5, 108.6, 80.1, 74.8, 73.5, 70.4, 65.5, 43.0, 27.4, 26.8, 25.8, 24.7, 18.0, –4.4, –4.9.

ESI-HRMS: *m/z* $[M + Na]^+$ calcd for $C_{22}H_{38}NaO_4Si$: 417.6130; found: 417.6126.

2-*O*-[*tert*-Butyl(dimethyl)silyl]-1,3-dideoxy-4,5-*O*-(1-methylethylidene)-D-*xylo*-hexitol (13)

A soln of **12** (0.90 g, 2.3 mmol) in EtOAc (5 mL) was treated with 10% Pd/C (121 mg, 0.1 mmol) under H_2 pressure for 2 h. Then the mixture was then filtered through Celite, which was washed with EtOAc (10 mL). The combined organic layers were concentrated in vacuo to give a residue that was purified by column chromatography [silica gel, EtOAc–hexane (3:7)] to give a colorless oil; yield: 96%; $[\alpha]_D^{27}$ –21 (*c* 0.2, $CHCl_3$).

IR (neat): 3456, 2931, 1465, 1252, 1049, 834 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 4.04–3.94 (m, 2 H), 3.72 (m, 1 H), 3.64–3.49 (m, 2 H), 1.90 (br s, 1 H, OH), 1.62–1.47 (m, 2 H), 1.38 (s, 3 H), 1.35 (s, 3 H), 1.16 (d, *J* = 5.9 Hz, 3 H), 0.88 (s, 9 H), 0.06 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 108.6, 81.5, 73.6, 65.6, 61.9, 42.8, 27.4, 26.9, 25.8, 24.7, 18.0, –4.4, –4.9.

ESI-HRMS: *m/z* $[M + Na]^+$ calcd for $C_{15}H_{32}NaO_4Si$: 327.4886; found: 327.4891.

2-*O*-[*tert*-Butyl(dimethyl)silyl]-1,3-dideoxy-4,5-*O*-(1-methylethylidene)-6-*O*-[(4-methylphenyl)sulfonyl]-D-*xylo*-hexitol (14)

Et_3N (0.5 mL, 3.6 mmol) and DMAP (22 mg, 0.2 mmol) were added to a soln of alcohol **13** (555 mg, 1.8 mmol) in CH_2Cl_2 (5 mL) at r.t., and the mixture was stirred for 10 min. TsCl (451 mg, 2.4 mmol) was then added and stirring was continued at r.t. for 3 h. The reaction was quenched with sat. aq NH_4Cl (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 under reduced pressure. The residue was purified by column chromatography [silica gel, EtOAc–hexane (3:7)] to give a pale yellow oil; yield: 92%; $[\alpha]_D^{27}$ –16.8 (*c* 0.5, $CHCl_3$)

IR (neat): 2930, 1463, 1252, 1180, 834, 777 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.79 (d, *J* = 8.3 Hz, 2 H), 7.33 (d, *J* = 7.9 Hz, 2 H), 4.11 (m, 1 H), 4.05–3.92 (m, 3 H), 3.72 (m, 1 H), 2.44 (s, 3 H), 1.61–1.49 (m, 2 H), 1.35 (s, 3 H), 1.29 (s, 3 H), 1.13 (d, *J* = 6.0 Hz, 3 H), 0.86 (s, 9 H), 0.04 (s, 3 H), 0.03 (s, 3 H)

^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.6, 133.2, 129.8, 128.1, 109.2, 78.2, 74.3, 68.7, 65.2, 42.8, 27.5, 26.7, 24.9, 24.8, 21.7, 18.1, –4.2, –4.8.

ESI-HRMS: *m/z* $[M + Na]^+$ calcd for $C_{22}H_{38}NaO_6SSi$: 481.6710; found: 481.6716.

1,3-Dideoxy-4,5-*O*-(1-methylethylidene)-6-*O*-[(4-methylphenyl)sulfonyl]-D-*xylo*-hexitol (15)

A 1 M soln of TBAF in THF (0.7 mL, 0.7 mmol) was added to a stirred soln of **14** (250 mg, 0.5 mmol) in dry THF (10 mL) at r.t., and the mixture was stirred for 2 h. The reaction was quenched with sat. aq NH_4Cl (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 column chromatography [silica gel, EtOAc–hexane (1:5)] to give a colorless oil; yield: 90%; $[\alpha]_D^{27}$ +2 (*c* 0.2, $CHCl_3$).

IR (neat): 3443, 2926, 1456, 1178, 780 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.78 (d, *J* = 8.3 Hz, 2 H), 7.34 (d, *J* = 8.3 Hz, 2 H), 4.19–3.89 (m, 4 H), 3.82 (m, 1 H), 2.47 (s, 3 H), 1.74–1.64 (m, 2 H), 1.36 (s, 3 H), 1.30 (s, 3 H), 1.21 (d, *J* = 6.2 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 145.0, 135.1, 129.8, 127.9, 109.5, 77.9, 75.2, 68.8, 65.0, 40.9, 29.6, 27.1, 26.5, 21.6.

ESI-HRMS: *m/z* $[M + Na]^+$ calcd for $C_{16}H_{24}NaO_6S$: 367.4094; found: 367.4097.

Ophioerin C (3)

A soln of the tosylate **15** (151 mg, 0.4 mmol) in dry Et_2O (3 mL) was added to a stirred suspension of *t*-BuOK (99.4 mg, 0.9 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 sat. aq NH_4Cl (20 mL), and the mixture was extracted with Et_2O (2 × 5 mL). The combined organic layers were washed with H_2O and brine then treated with PTSA (10 mg) and MeOH (10 mL) with stirring at r.t. for 2 h. The reaction was quenched with sat. aq $NaHCO_3$ soln, 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 column chromatography [silica gel, EtOAc–hexane (6:4)] to give a white solid; yield: 88% (2 steps); m.p. 82–83 °C; $[\alpha]_D^{26}$ +42 (*c* 0.1, $CHCl_3$)

IR (KBr): 3390, 2921, 1460, 1376, 1176, 1025 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 3.90 (dd, *J* = 5.3, 11.3 Hz, 1 H), 3.58–3.36 (m, 3 H), 3.08 (dd, *J* = 10.5, 11.3 Hz, 1 H), 1.94 (ddd, *J* = 1.5, 4.5, 12.8 Hz, 1 H), 1.31 (ddd, *J* = 10.8, 10.8, 12.8 Hz, 1 H), 1.17 (d, *J* = 6.1 Hz, 3 H)

^{13}C NMR (75 MHz, $CDCl_3$): δ = 73.3, 72.6, 72.3, 69.6, 40.5, 21.2.

ESI-HRMS: *m/z* $[M + Na]^+$ calcd for $C_6H_{12}NaO_3$: 155.1476; found: 155.1472.

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