Tetrahedron: *Asymmetry* 19 (2008) 2092–2095

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Stereoselective total synthesis of ophiocerin D from D-xylose

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ARTICLE INFO

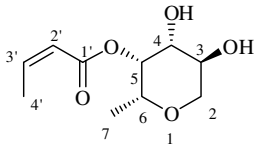
Article history:
Received 4 August 2008
Accepted 19 August 2008

ABSTRACT

A stereoselective total synthesis of ophiocerin D is reported by a combination of a 'chiron' approach and an asymmetric synthesis, from D-xylose. Of the four stereogenic centers, the vic diols C3/C4 and C5/C6 were obtained by Sharpless asymmetric dihydroxylation and from D-xylose, respectively.

1. Introduction

The chemical investigations on freshwater aquatic fungi by Gloer et al.[1] resulted in the isolation of tetrahydropyran derivatives ophiocerins A–C and ophiocerin D **1** from *Ophioceras venezuelense* (Magnaporthaceae).[2] The structural analysis of ophiocerin A–D was arrived at by Gloer et a1.[1] from spectroscopic studies, while the absolute stereochemistry was assigned by CD spectrometry by the use of the excitation chirality method.[3] These new tetrahydropyran derivatives[4] appear to be the first isolated natural products from the above genus. The substituted tetrahydropyran moiety is a part structure of a wide variety of natural products with diversified biological functions.[5] In continuation of our efforts on the synthesis of natural products[6] from carbohydrates, herein, we report the total synthesis **1** from a D-xylose derivative (Scheme 1).



ophiocerin D **1**

2. Results and discussion

The retrosynthetic analysis of **1** indicated that it could be prepared from **2** and butynoic acid **3**, while **2** could in turn be prepared from D-xylose derivative **4**. Thus, the synthetic strategy would be to (a) deoxygenate C-5 to a methyl group, (b) retention of C3/C4 for C5/C6 of **1**, and (c) introduction of a C3/C4 diol on the Wittig product made from the 1,2-diol of **4**.

Accordingly, the known[7] alcohol **5** on protection with benzyl bromide gave **6** (87%). Diacetonide **6** on acid (5% H_2SO_4, THF) catalyzed hydrolysis at room temperature gave diol **7**, which on oxidative cleavage (H_5IO_6 in aq EtOAc) at room temperature afforded the aldehyde **8**. Wittig olefination of aldehyde **8** furnished the ester **9** in 75% yield. Treatment of **9** with TBDMSCl and imidazole in CH_2Cl_2 gave TBS ether **10** (92%), $[\alpha]_D = -12.8$. (*c* 1.2, $CHCl_3$). Asymmetric dihydroxylation[8] of ester **10** with AD-mix-α gave the diol **11** (62%), which on protection with MOMCl in the presence of DIPEA afforded the MOM ether **12** in 91% yield, $[\alpha]_D = +41.6$ (*c* 2.2, $CHCl_3$).

Having established all the four stereocenters, next it was aimed at the cyclization and introduction of an isocrotonyl side chain at the C-5 OH group. Accordingly, ester **12** on reduction with LAH in THF at room temperature gave the alcohol **13** (89%), which on further reaction with *p*-TsCl (Et_3N, CH_2Cl_2) furnished tosylate **14** (68%). Tosylate **14** was exposed to TBAF[9] at room temperature to result in desilylation and concomitant cyclization in one-pot to give the cyclized product **15** in 78% yield. TBAF in the present study acted as a desilylating agent, as well as a base to promote a facile cyclization reaction (Scheme 2).

For the introduction of the side chain, the benzyl group in **15** was removed by hydrogenation using $Pd(OH)_2$ in MeOH to give the alcohol **2** (87%), $[\alpha]_D = -2.7$ (*c* 2.0, $CHCl_3$). Further, acylation of **2** with 2-butynoic acid **3** under Yamaguchi[10] reaction conditions gave **16** in 79% yield, which on selective hydrogenation in the presence of Lindlar catalyst afforded **17** in 75% yield, $[\alpha]_D = +34.4$ (*c* 0.2, $CHCl_3$). Finally, PPTS catalyzed deprotection of the MOM groups in **17** furnished ophiocerin D **1** in 71% yield. The specific rotation value $[\alpha]_D = +38.4$ (*c* 0.1, $CHCl_3$) of synthetic **1** was matching with that of the natural product $[\alpha]_D = +40$ (*c* 0.1, $CHCl_3$).

3. Conclusion

Thus, the present study describes the total synthesis of ophiocerin D **1** by a combination of a chiron approach and an asymmetric synthesis, wherein the C3/C4 and C5/C6 stereocenters were

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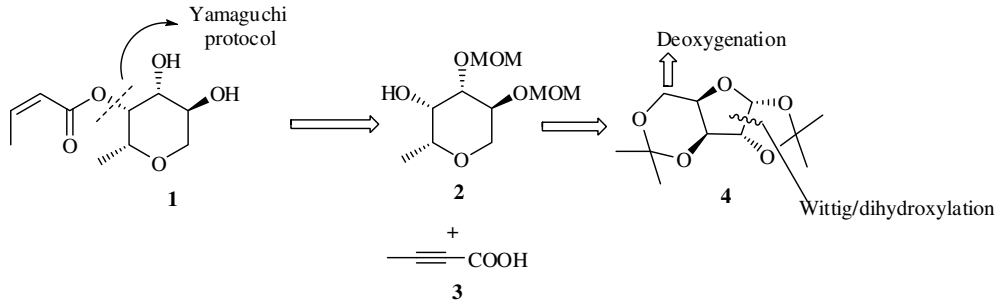
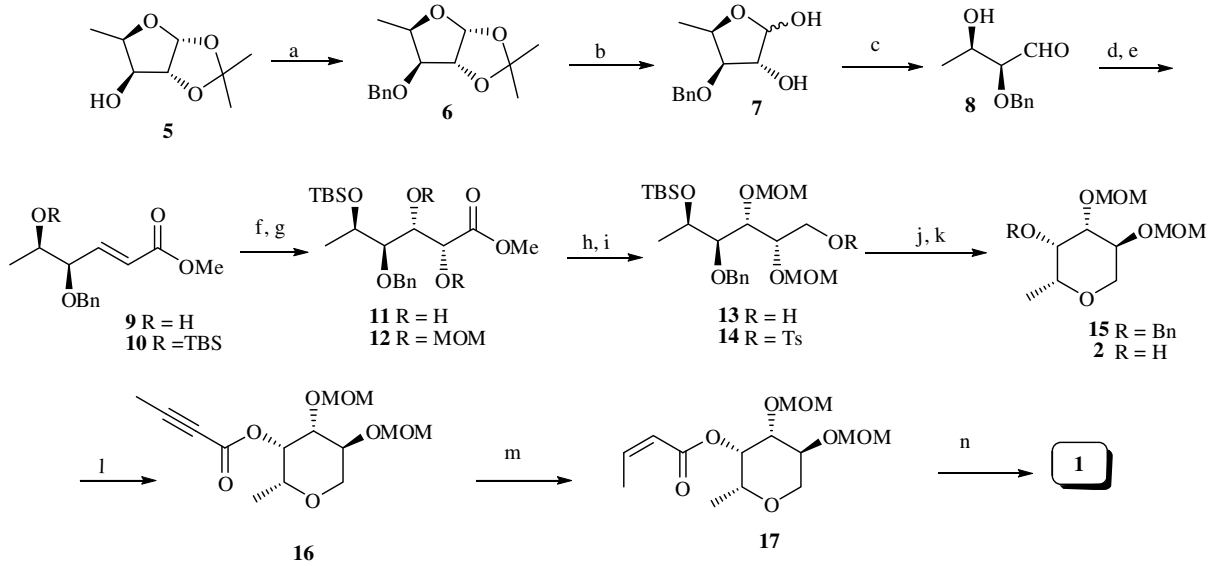
doi:10.1016/j.tetasy.2008.08.016



Scheme 1.



Scheme 2. Reagents and conditions: (a) BnBr, NaH, THF, 0 °C–rt; (b) 5% H_2SO_4, THF, 40 °C; (c) H_5IO_6, EtOAc/H_2O, rt; (d) $Ph_3P{=}CHCO_2Me$, benzene, reflux; (e) TBDMSCl, imidazole, CH_2Cl_2, rt; (f) AD-mix-α, *t*-BuOH/H_2O, 0 °C–rt; (g) MOMCl, DIPEA, CH_2Cl_2, rt; (h) LAH, THF, 0 °C–rt; (i) *p*-TsCl, Et3N, CH_2Cl_2, 0 °C–rt; (j) TBAF, THF, rt; (k) H_2, $Pd(OH)_2$, MeOH, rt; (l) 2-butynoic acid, 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, DMAP, toluene, rt; (m) Lindlar catalyst, MeOH, rt; (n) PPTS, *t*-BuOH, 70 °C.

obtained by asymmetric dihydroxylation and from D-xylose, respectively. Furthermore, TBAF acted as a mild base to afford a one-pot desilylation/cyclization. Thus, this strategy is adoptable for the generation of a library of stereoisomers.

4. Experimental

4.1. General methods

Solvents were dried over standard drying agents and freshly distilled prior to use. Chemicals were purchased and used without further purification. All column chromatographic separations were performed using silica gel (Acme's, 60–120 mesh). Organic solutions were dried over anhydrous Na_2SO_4 and concentrated below 40 °C in vacuo. ^{1}H NMR (200 MHz, 300 MHz, and 400 MHz) and ^{13}C NMR (50 MHz and 75 MHz) spectra were measured with a Varian Gemini FT-200 MHz spectrometer, Bruker Avance 300 MHz, Unity 400 MHz, and Inova-500 MHz with tetramethylsilane as an internal standard for solutions in deuteriochloroform. *J* values are given in hertz. IR spectra were recorded on at Perkin–Elmer IR-683 spectrophotometer with NaCl optics. Optical rotations were measured with JASCO DIP 300 digital polarimeter at 25 °C. Mass spectra were recorded on CEC-21-11013 or Fannigan Mat 1210 double focusing mass spectrometers operating at a direct inlet system or LC/MSD Trap SL (Agilent Technologies).

4.1.1. (3a*R*,5*R*,6*S*,6a*R*)-2,2,5-Trimethyl perhydrofuro[2,3-*d*]-[1,3]-dioxol-6-yl-benzyl ether 6

To a cooled (0 °C) suspension of NaH (0.82 g, 34.4 mmol, 60% w/w dispersion in paraffin oil) in THF (15 mL), a solution of **5** (5 g, 28.7 mmol) in THF (10 mL) was added dropwise. After 15 min, BnBr (4.9 g, 28.7 mmol) was added at 0 °C and stirred at room temperature for 6 h. The reaction mixture was quenched with satd aq NH_4Cl solution (20 mL) and extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with water (50 mL), brine (50 mL), dried (Na_2SO_4), and evaporated. The crude product was purified by column chromatography (silica gel, 60–120 mesh, EtOAC/hexane, 2:8) to afford **6** (6.2 g, 87%) as a light yellow syrup. $[\alpha]_D = -50.9$ (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.32 (d, 3H, J = 6.2 Hz, $-CH_3$), 1.41 (s, 3H, $-CH_3$), 1.50 (s, 3H, $-CH_3$) 4.21–4.26 (m, 1H, –CH), 3.62 (d, 1H, J = 2.9 Hz, –CH), 4.51 (d, 1H, J = 12.4 Hz, $-CHC_6H_5$) 4.55 (d, 1H, J = 3.6 Hz, –CH), 4.65 (d, 1H, J = 12.4 Hz, $-CHC_6H_5$) 5.80 (d, 1H, J = 4.0 Hz, –CH), 7.20–7.31 (m, 5H, $-C_6H_5$); IR (neat): 2978, 2920, 2870, 1453, 1064 cm^{-1}; ESIMS: 271 $[M+Na]^+$.

4.1.2. (4*R*,5*R*,*E*)-Methyl 4-(benzyloxy)-5-hydroxyhex-2-enoate 9

To a solution of **6** (6.0 g, 24.1 mmol) in THF (30 mL), 5% H_2SO_4 (30 mL) was added and the reaction mixture stirred at 40 °C for 10 h. The reaction mixture was neutralized with solid $NaHCO_3$ (30 g) and extracted with EtOAc (3 × 100 mL). The combined

organic layers were dried (Na_2SO_4) and evaporated. The crude was filtered through 60–120 mesh silica gel (1:1 EtOAc/hexane) to afford (3*R*,4*R*,5*R*)-4-(benzyloxy)-5-methyltetrahydro-2,3-furandiol **7** (3.5 g, 71%) as a yellow syrup.

To a stirred solution of **7** (3.0 g, 13.3 mmol) in EtOAc/water (1:1, 10 mL), periodic acid (6.0 g, 26.7 mmol) was added at 0 °C and stirred for 2 h at room temperature. The reaction mixture was extracted with EtOAc (2 × 50 mL) and washed with water (2 × 50 mL). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to afford (2*S*,3*R*)-2-(benzyloxy)-3-hydroxybutanal **8** which was used as such for the next reaction.

A solution of aldehyde **8** (2.8 g, 8.1 mmol) in benzene was added to a solution of (methoxycarbonylmethylene)triphenyl phosphorane (3.1 g, 9.7 mmol) in benzene (30 mL) at reflux and stirred for 5 h. The solvent was evaporated and residue purified by column chromatography (silica gel, 60–120 mesh, EtOAc/hexane, 1:4) to afford **9** (2 g, 75%) as a pale yellow syrup. $[\alpha]_D = -22.8$ (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 1.15 (d, 3H, *J* = 5.8 Hz, $-CH_3$), 2.56 (br s, 1H, OH), 3.64–3.69 (m, 2H, 2 × –CH), 3.76 (s, 3H, $-OCH_3$), 4.34 (d, 1H, *J* = 11.3 Hz, $-CH-C_6H_5$), 4.63 (d, 1H, *J* = 11.3 Hz, $CH-C_6H_5$), 6.01 (d, *J* = 15.7 Hz, olefinic), 6.79 (dd, 1H, *J* = 6.9, 15.7 Hz, olefinic), 7.21–7.30 (m, 5H, $-C_6H_5$); ^{13}C NMR (75 MHz, $CDCl_3$): 166.19, 144.56, 137.31, 128.01, 124.26, 83.32, 71.54, 69.52, 51.74, 18.25; IR (neat): 3403, 2926, 2864, 1706, 1451 cm^{-1}; HRMS *m/z* $[M+Na]^+$ calcd 273.1102 found 273.1108 for $C_{14}H_{18}O_4Na$.

4.1.3. (4*R*,5*R*,*E*)-Methyl 4-(benzyloxy)-5-(isopropyldimethylsilyloxy)-hex-2-enoate 10

To a stirred solution of **9** (1.8 g, 7.2 mmol) in anhydrous CH_2Cl_2 (20 mL) imidazole (0.55 g, 6.4 mmol) was added at 0 °C. After 15 min, TBDMSCl (1.08 g, 7.2 mmol) was added and reaction mixture stirred at room temperature for 5 h. The reaction mixture was quenched with satd aq NH_4Cl (25 mL) and extracted with CH_2Cl_2 (2 × 25 mL). The organic layer was washed with water (2 × 25 mL), dried (Na_2SO_4), evaporated, and the residue purified by column chromatography (silica gel, 60–120 mesh, EtOAC/hexane, 1:10) to afford **10** (2.4 g, 92%) as a light yellow syrup. $[\alpha]_D = -12.8$ (*c* 1.2, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 0.23 (s, 6H, 2 × $-CH_3$), 0.82 (s, 9H, 3 × $-CH_3$), 1.01 (d, 3H, *J* = 5.8 Hz, $-CH_3$), 3.73 (s, 3H, $-OCH_3$), 3.75–3.82 (m, 2H, –CH), 4.41 (d, 1H, *J* = 12.1 Hz, $-CHC_6H_5$), 4.62 (d, 1H, *J* = 12.1 Hz, $-CHC_6H_5$) 6.07 (d, 1H, *J* = 16.1 Hz, olefinic), 6.81 (dd, 1H, *J* = 4.7, 16.1 Hz, olefinic), 7.22–7.32 (m, 5H, $-C_6H_5$); ^{13}C NMR (75 MHz, $CDCl_3$): 166.67, 145.64, 138.01, 128.33, 127.96, 122.61, 81.79, 71.56, 69.70, 51.56, 25.76, 18.74, −4.80; IR (neat): 2926, 2864, 1716, 1251, 889 cm^{-1}; ESIMS: 365 $[M+H]^+$.

4.1.4. (2*R*,3*R*,4*R*,5*R*)-Methyl 4-(benzyloxy)-2,3-dihydroxy-5-(isopropyldimethylsily-loxy)hexanoate 11

A well-stirred solution of AD-mix-α (5.8 g, 7.5 mmol) in *t*-BuOH/H_2O (1:1, 20 mL) was treated with methane sulfonamide (0.35 g, 3.7 mmol) at room temperature. After 30 min, the clear yellow solution was cooled to 0 °C and a solution of ester **10** (1.5 g, 3.7 mmol) in *t*-BuOH (5 mL) was added. The reaction mixture was stirred vigorously at 0 °C for 27 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 a crude residue, which was purified by column chromatography (silica gel, 60–120 mesh, 30:70% EtOAc/hexane) to afford **11** (1.0 g in 62%) as a yellow syrup. $[\alpha]_D = +12.8$ (*c* 1.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ 0.03 (s, 6H, 2 × $-CH_3$), 0.86 (s, 9H, 3 × $-CH_3$), 1.28 (d, 3H, *J* = 6.4 Hz, $-CH_3$), 2.93 (br s, 1H, –OH), 3.55 (dd, 1H, *J* = 3.7, 9.4 Hz, –CH), 3.82 (s, 3H, OCH_3), 3.91 (t, 1H, *J* = 1.5, 3.0 Hz, –CH), 4.01 (dd, 1H, *J* = 4.1, 6.4 Hz, –CH), 4.06–4.09 (m, 1H, –CH), 4.32 (br s, 1H, –OH), 4.68 (d, 1H, *J* = 11.3 Hz, $-CHC_6H_5$), 4.53 (d, 1H, *J* = 11.3 Hz, $-CHC_6H_5$), 7.22–7.31 (m, 5H, $-C_6H_5$); ^{13}C NMR (75 MHz, $CDCl_3$): δ −4.53, 18.48, 25.76, 27.17, 52.61, 61.77, 69.99, 72.29, 73.63, 80.85, 127.89, 128.42, 129.97, 137.77, 173.38; IR (neat): 3444, 3065, 2927, 1761, 1252 cm^{-1}; HRMS *m/z* $[M+Na]^+$; calcd 399.2202, found 399.2209 for $C_{20}H_{35}O_6Si$.

4.1.5. (2*R*,3*S*,4*R*,5*R*)-Methyl 4-(benzyloxy)-5-(isopropyldimethylsilyloxy)-2,3-bis-(methoxymethoxy)hexanoate 12

To a cooled (0 °C) solution of **11** (2.0 g, 5.0 mmol) in CH_2Cl_2 (10 mL), DIPEA (3.9 mL, 30.3 mmol) and MOM-Cl (0.813 g, 10.1 mmol) were added sequentially and stirred at room temperature for 6 h. The reaction mixture was evaporated and purified the residue by column chromatography (silica gel, 60–120 mesh, EtOAc/hexane, 1:5) to afford **12** (2.2 g, 91%) as a yellow syrup. $[\alpha]_D = +41.6$ (*c* 2.2, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 0.04 (s, 6H, 2 × $-CH_3$), 0.87 (s, 9H, 3 × $-CH_3$), 1.26 (d, 3H, *J* = 6.6 Hz, $-CH_3$), 3.29 (s, 3H, $-OCH_3$), 3.36 (s, 3H, $-OCH_3$), 3.41 (dd, 1H, *J* = 3.6, 5.8 Hz, –CH), 3.67 (s, 3H, $-OCH_3$), 4.05 (dd, 1H, *J* = 3.6, 6.6 Hz, –CH), 4.18 (dd, 1H, *J* = 2.9, 5.8 Hz, –CH) 4.39 (d, 1H, *J* = 2.9 Hz, –CH), 4.54–4.58 (m, 2H, $-OCH_2$), 4.62 (d, 1H, *J* = 11.7 Hz, $-CHC_6H_5$), 4.66–4.70 (m, 2H, –OCH), 4.72 (d, 1H, *J* = 11.7 Hz, $-CHC_6H_5$), 7.21–7.30 (m, 5H, $-C_6H_5$); ^{13}C NMR (75 MHz, $CDCl_3$): δ −4.2, 21.12, 25.01, 52.41, 56.21, 68.41, 73.25, 75.82, 79.08, 82.54, 97.12, 127.12, 128.72, 128.48, 138.24, 173.8; IR (Neat): 2210, 1750, 1440, 1223, 1032, 867 cm^{-1}; HRMS: *m/z* $[M+Na]^+$ calcd 509.2546, found 509.2540 for $C_{24}H_{42}O_8Na$.

4.1.6. (2*R*,3*R*,4*R*,5*R*)-4-(Benzyloxy)-5-(isopropyldimethylsilyloxy)-2,3-bis(methoxymethoxy)hexan-ol 13

To a stirred suspension of LAH (0.19 g, 5.1 mmol) in dry THF (5 mL) at 0 °C, a solution of **12** (1.5 g, 3.0 mmol) in dry THF (15 mL) was added. After 1 h, satd aq Na_2SO_4 solution (30 mL) was added to the reaction mixture and stirred for an additional 30 min. It was filtered through Celite and the residue was washed with EtOAc (2 × 70 mL). The filtrate was evaporated and the residue purified by column chromatography (silica gel, 60–120 mesh, 1:5 EtOAc/hexane) to afford **13** (1.7 g, 89%) as a pale yellow liquid. $[\alpha]_D = -30.4$ (*c* 2.4, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): 0.06 (s, 6H, 2 × $-CH_3$), 0.91 (s, 9H, 3 × $-CH_3$), 1.25 (d, 3H, *J* = 6.6 Hz, $-CH_2$), 3.41(s, 6H, 2 × $-OCH_3$), 3.41–3.44 (m, 1H, –CH), 3.71–3.73 (m, 2H, 2 × –CH), 3.82–3.85 (m, 1H, –CH), 3.91–3.94 (m, 1H, –CH), 4.11–4.14 (m, 1H, –CH), 4.59–4.63 (m, 2H, $-OCH_2$), 4.71 (s, 2H, $-CH_2C_6H_5$), 4.73–4.81 (m, 2H, $-OCH_2$), 7.25–7.32 (m, 5H, $-C_6H_5$); ^{13}C NMR (75 MHz, $CDCl_3$): δ −4.29, 20.70, 25.88, 55.72, 62.66, 68.90, 71.12, 73.24, 81.03, 83.95, 97.08, 97.48, 127.34, 128.15, 128.21, 138.12; IR (neat): 3446, 2923, 2853, 1643, 1102 cm^{-1}; HRMS *m/z* $[M+Na]^+$ calcd 481.2597, found 481.2594 for $C_{23}H_{42}O_7NaSi$.

4.1.7. (2*R*,3*R*,4*R*,5*S*)-3-(Benzyloxy)-4,5-bis(methoxymethoxy)-2-methyl-tetrahydro-2*H*-pyran 15

To a solution of **13** (1.7 g, 3.7 mmol) in CH_2Cl_2 (15 mL) at 0 °C, Et_3N (0.7 mL, 5.5 mmol) and tosyl chloride (0.84 g, 4.4 mmol) were added sequentially and stirred at room temperature for 6 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 filtered through silica gel (60–120 mesh, EtOAc/hexane, 1:4) to furnish (2*R*,3*R*,4*S*,5*R*)-4-(benzyloxy)-5-(isopropyldimethylsilyloxy)-2,3-di(methoxymethoxy)hexyl 4-methyl-1-benzenesulfonate **14** (1.5 g, 68%) as a pale yellow oil.

To a stirred solution of **14** (1.5 g, 2.4 mmol) in dry THF (5 mL) at 0 °C, *n*-$Bu_4N^+F^-$ in THF (6.1 mL, 6.1 mmol) was added and then stirred at room temperature for 8 h. The reaction mixture was evapo-

rated and the residue purified by column chromatography (silica gel, 60–120 mesh, EtOAc/hexane, 6:4) to afford **15** (0.63 g, 78%) as a pale yellow syrup. $[\alpha]_D = -100.7$ (*c* 1.4, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ 1.14 (d, 3H, *J* = 6.2 Hz, $-CH_3$), 3.06 (d, 1H, *J* = 6.2 Hz, –CH), 3.33 (s, 3H, $-OCH_3$), 3.35–3.38 (m, 1H, –CH), 3.39 (s, 3H, $-OCH_3$), 3.41–3.47 (m, 1H, –CH), 3.57–3.62 (m, 2H, 2 × –CH), 4.03 (dd, 1H, *J* = 5.5, 14.3 Hz, –CH), 4.59 (d, 1H, *J* = 11.1 Hz, $-CHC_6H_5$), 4.62–4.75 (m, 4H, $-OCH_2$), 4.92 (d, 1H, *J* = 11.1 Hz $-CHC_6H_5$), 7.46–7.23 (m, 5H, C_6H_5); ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.13, 52.59, 55.66, 69.10, 73.94, 78.07, 80.18, 96.24, 97.29, 127.59, 127.61, 138.51; IR (neat): 2955, 2858, 1521, 1465, 1241 cm^{-1}; HRMS *m/z* $[M+Na]^+$ calcd 349.1627, found 349.1631; for $C_{17}H_{26}O_6Na$.

4.1.8. (2*R*,3S,4S,5S)-4,5-Bis(methoxymethoxy)-2-methyl tetrahydro-2*H*-3-pyranol 2

To a solution of **15** (0.3 g, 0.9 mmol) in dry MeOH (5 mL), a catalytic amount of $Pd(OH)_2$ (20%) was added and the reaction mixture stirred at room temperature under hydrogen atmosphere for 5 h. It was filtered and washed with ethyl acetate (20 mL). The filtrate was evaporated under reduced pressure and purified by column chromatography (silica gel, 60–120 mesh, EtOAC/hexane, 3:2) to afford **2** (0.19 g, 87%) as a colorless liquid. $[\alpha]_D = -2.7$ (*c* 2.0, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 1.21 (d, 3H, *J* = 6.6 Hz, $-CH_3$), 2.20 (br s, 1H, –OH), 3.09–3.12 (m, 1H, –CH), 3.32 (*s*, 3H, $-OCH_3$), 3.40 (s, 3H, $-OCH_3$), 3.45 (dd, 1H, *J* = 1.1, 5.5 Hz, –CH), 3.75–3.89 (m, 2H, –CH), 4.01 (dd, 1H, *J* = 5.5, 11 Hz, –CH), 4.80–4.58 (m, 4H, 2 × $-CH_2$), ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.71, 55.42, 55.64, 68.92, 71.19, 74.42, 80.21, 96.12, 97.2; IR (Neat): 3400, 1180, 1095, 1065 cm^{-1}; HRMS: *m/z* $[M+Na]^+$ calcd for $C_{10}H_{20}O_6Na$: 259.1157; found: 259.1160 for $C_{10}H_{20}O_6Na$.

4.1.9. (2*R*,3S,4*R*,5S)-4,5-Bis(methoxymethoxy)-2-methyl-tetrahydro-2*H*-pyran-3-yl but-2-ynoate 16

To a solution of **15** (0.05 g, 0.21 mmol) and Et_3N (0.058 g, 0.42 mmol) in dry THF (3 mL) at 0 °C, 2,4,6-trichlorobenzoyl chloride (0.051 g, 0.21 mmol) was added dropwise and stirred at room temperature for 2 h. The reaction mixture was evaporated and the residue dissolved in toluene (2 mL). A solution of **2** (0.017 g, 0.21 mmol) and DMAP (0.051 g, 0.42 mmol) in dry toluene (2 mL) was added to the reaction mixture and stirred at room temperature for 12 h. It was filtered through Celite and washed with toluene (2 × 5 mL). The filtrate was evaporated and the residue purified by column chromatography (silica gel, 60–120 mesh, EtOAc/hexane, 3:7) to afford **16** (0.05 mg, 79%) $[\alpha]_D = +13.5$ (*c* 0.2, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 1.14 (d, 3H, *J* = 6.2 Hz, CH_3), 2.30 (s, 3H, $-CH_3$), 3.17 (m, 1H, –CH), 3.34 (s, 3H, $-OCH_3$), 3.35 (s, 3H, $-OCH_3$), 3.65–3.69 (m, 2H, 2 × –CH), 3.78 (dd, 1H, *J* = 5.4, 9.7 Hz, –CH), 4.03 (dd, 1H, *J* = 5.0, 10.9 Hz –CH), 4.56–4.62 (m, 2H, $-OCH_2$), 4.67–4.75 (m, 2H, OCH_2) 5.28 (dd, 1H, *J* = 1.7, 3.5 Hz, –CH), IR (neat) 2931, 2858, 1735, 1515, 1247, 1463 cm^{-1}; HRMS *m/z* $[M+Na]^+$ calcd 325.1263, found 325.1269; for $C_{14}H_{22}O_7Na$.

4.1.10. (*Z*)-[(2*R*,3S,4*R*,5S)-4,5-Bis(methoxymethoxy)-2-methyl-tetrahydro-2*H*-pyran-3-yl]but-2-enoate 17

To a solution of **16** (0.02 mg, 0.625 mmol) in dry MeOH (2 mL), catalytic amount of Lindlar catalyst was added and the reaction mixture was stirred at room temperature under a hydrogen atmosphere for 3 h. The reaction mixture was filtered and washed with ethyl acetate (10 mL). The filtrate was evaporated under reduced pressure and purified the residue by column chromatography (silica gel, 60–120 mesh, EtOAc/hexane, 1:4) to afford **17** (0.015 mg, 75%) as a colorless oil, $[\alpha]_D = +34.4$ (*c* 0.2, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 1.10 (d, 3H, *J* = 6.6 Hz, CH_3), 2.15 (dd, 3H, *J* = 1.8, 7.3 Hz, $-CH_3$), 3.17 (dd, 1H, *J* = 9.9, 10.6 Hz, –CH), 3.33 (s, 3H, $-OCH_3$), 3.35 (s, 3H, $-OCH_3$), 3.60 (dd, 1H, *J* = 6.2, 12.8 Hz, –CH), 3.69 (dd, 1H, *J* = 3.3, 9.5 Hz, –CH), 3.77 (dd, 1H, *J* = 5.1, 9.9 Hz,), 4.06 (dd, 1H, *J* = 5.1, 10.6 Hz, –CH), 4.66 (dq, 4H, *J* = 6.6 Hz, $-CH_2$), 5.21 (dd, 1H, *J* = 1.1, 3.3 Hz, –CH), 5.91 (dd, 1H, *J* = 1.8, 11.3 Hz, olefinic), 6.31 (dq, 1H, *J* = 7.3, 11.3 Hz, olefinic); ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.57, 16.77, 55.44, 55.60, 69.17, 70.40, 72.85, 73.68, 95.09, 97.19, 120.32, 145.92, 166.01; IR (neat): 2980, 2857, 1710, 1097 cm^{-1}; HRMS *m/z* $[M+Na]^+$; calcd 327.1419, found 327.1421 for $C_{24}H_{24}O_7Na$.

4.1.11. Ophiocerin D: (2*R*,3*R*,4*S*,5*S*)-4,5-dihydroxy-2-methyl-tetrahydro-2*H*-3-pyranyl(*Z*)-2-butenoate 1

To a solution of **17** (0.01 g, 0.03 mmol) in *t*-butanol (2 mL), PPTS (0.024 g, 0.09 mmol) was added and stirred at 70 °C for 4 h. The reaction mixture was concentrated and the residue dissolved in EtOAc (20 mL). It was washed with water (2 mL), brine (2 mL), and dried (Na_2SO_4). The solvent was evaporated and the residue purified by column chromatography (silica gel, 60–120 mesh, EtOAc/hexane, 1:1) to afford **1** (0.005 g, 71%) as a white solid; mp 94–97 °C [lit.[1] mp 96–98 °C); $[\alpha]_D = +38.4$ (*c* 0.1, $CHCl_3$) {lit.[1] $[\alpha]_D = +40$ (*c* 0.1, $CHCl_3$)}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.17 (d, 3H, *J* = 6.5 Hz, $-CH_3$), 2.12 (dd, 3H, *J* = 1.5, 7.3 Hz, $-CH_3$), 3.16 (dd, 1H, *J* = 10.0, 10.9 Hz, –CH), 3.59–3.67 (m, 2H, 2 × –CH), 3.86 (ddd, 1H, *J* = 5.3, 9.2, 10.0 Hz, –CH), 3.99 (dd, 1H, *J* = 5.3, 10.9 Hz, –CH), 5.14 (dd, 1H, *J* = 1.1, 3.4 Hz, –CH), 5.87 (dq, 1H, *J* = 1.5, 11.5 Hz, olefinic), 6.45 (dq, 1H, *J* = 7.3, 11.5 Hz, olefinic); ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.52, 16.61, 67.12, 69.41, 73.71, 75.42, 76.95, 119.61, 147.12, 166.92; IR (neat): 3422, 1710, 1640, 1440, 1181, 1099, 1076 cm^{-1}; HRMS: *m/z* $[M+Na]^+$ calcd for $C_{10}H_{16}O_5Na$: 239.0895; found 239.0906 for $C_{10}H_{16}O_5Na$.

Acknowledgment

One of the authors (D.K.) thanks the CSIR, New Delhi, India, for financial support in the form of a fellowship.

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