Stereoselective Total Synthesis of Botryolide E and Ophiocerin C

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A highly stereoselective approach to the total synthesis of the γ-lactone derivative botryolide E and tetrahydropyran derivative ophiocerin C *via* a common polyketide precursor by means of *Prins* cyclization and *MacMillan* α-aminoxylation sequence is described. The method can conveniently be utilized for the preparation of further related γ-lactone and tetrahydropyran derivatives.

Introduction. – The natural products containing γ-lactone moieties are known to possess a variety of biological features [1], such as cytotoxic [2], antitumor [3], and cyclooxygenase or phospholipase A2 inhibition activities [4]. These compounds are of either bacterial or fungal origin. Botryolide E (**1**; *Fig. 1*), a γ-lactone, has been isolated from cultures of the fungicolous *Botryotrichum* sp. (NRRL 38180) by *Gloer* and co-workers in 2008 [5], and it exhibited an antibacterial activity against *Bacillus subtilis* (MTCC 441), *Staphylococcus aureus* (MTCC 96), and *Escherichia coli* (MTCC 443), and an antifungal activity against *Aspergillus niger* (MTCC 1344) and *Saccharomyces cerevisiae* (MTCC 171). The structure and relative configuration was established by a NMR and ESI-MS analysis.

Another class of natural products, ophiocerins A – D (*Fig. 2*), which represent a new type of tetrahydropyran derivatives, are isolated from cultures of the aquatic fungus *Ophioceras venezuelenser*. The isolations, structures, absolute and relative configurations of these compounds were reported by *Reategui et al.* in 2005 [6].

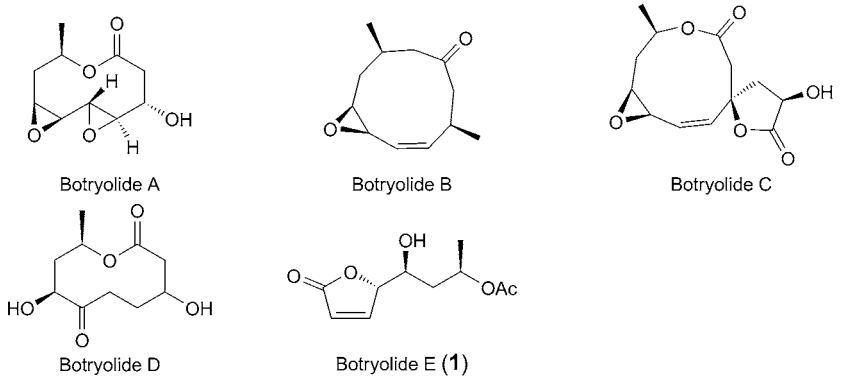


Fig. 1. *Structures of botryolides A – E*

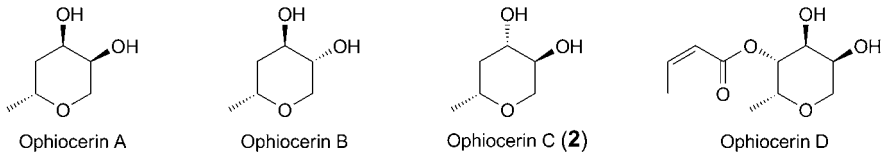


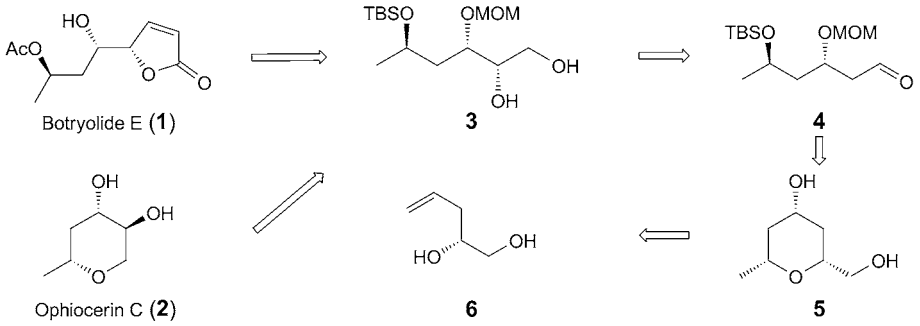
Fig. 2. *Structures of ophiocerins A – D*

Antagonistic effects among competing aquatic fungi have been reported from a chemical standpoint [7]. The substituted tetrahydropyran moiety occurs in a wide variety of natural products with diversified biological functions [8]. In continuation of our efforts towards the synthesis of natural products, herein, we report a new total synthesis of botryolide E (**1**) [9], and ophiocerin C (**2**) [10] *via* a common intermediate **3** using our recently developed methodology of *Prins* cyclization and *MacMillan* α-aminoxylation sequence [11].

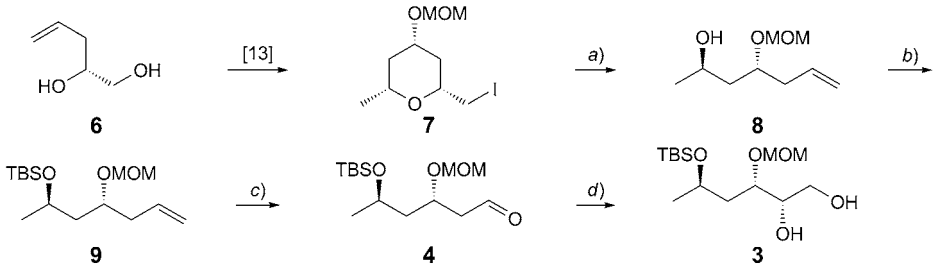
Results and Discussion. – The retrosynthetic analysis of botryolide E (**1**) and ophiocerin C (**2**) is outlined in *Scheme 1*. It is envisaged that the target molecules **1** and **2** could be prepared from the common intermediate **3**, which was proposed to be formed by the *MacMillan* α-aminoxylation of **4**. The tetrahydropyran core **5** could be obtained *via Prins* cyclization between homoallylic alcohol **6** and acetaldehyde. We envisioned that the polyhydroxy compound **3** would be a common chiral synthon for accessing **1** and **2** *via* lactonization and S_N2 cyclization, respectively.

The synthesis of botryolide E (**1**) was started with a *Prins* cyclization [12] between the known homoallylic alcohol **6** and MeCHO. The (iodomethyl)-pyran **7** was obtained from **6** in four steps [13]. Reductive opening of **7** gave alcohol **8** with the *anti*-1,3-diol system. Protection of the secondary OH group in **8** as ^{t}BuMe$_2$Si (TBS) ether using ^{t}BuMe$_2$SiCl (TBSCl) and 1*H*-imidazole in CH_2Cl_2 furnished **9** in 94% yield. Ozonolytic cleavage of olefinic bond of **9**, followed by α-aminoxylation using nitrosobenzene and L-proline in MeCN, followed by treatment with $NaBH_4$ in MeOH, gave the crude α-aminoxy alcohol, which on treatment with 30 mol-% $CuSO_4 \cdot 5\,H_2O$, furnished diol **3** [14] in 65% yield for two steps (*Scheme 2*).

Scheme 1. *Retrosynthetic Analysis of Botryolide E and Ophiocerin C*



Scheme 2

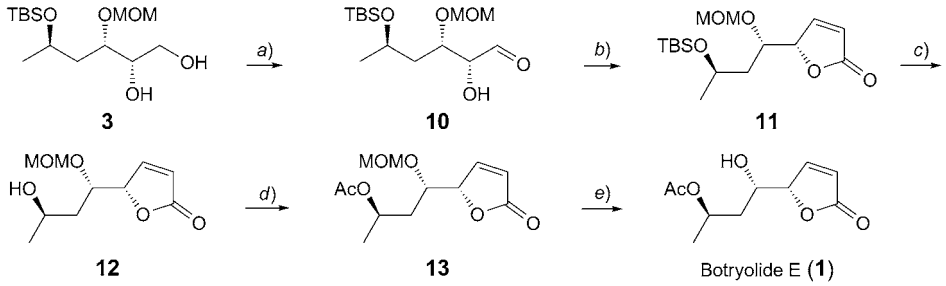


a) Zn, EtOH, $NaHCO_3$, reflux, 2 h; 92%. *b*) ^{t}BuMe$_2$SiCl (TBSCl), 1*H*-imidazole, CH_2Cl_2, 0° – r.t., 4 h; 94%. *c*) O_3, Ph_3P, CH_2Cl_2, −78°. *d*) PhNO, L-Proline, MeCN, 3 h, −20°, then $NaBH_4$, MeOH, $(AcO)_2Cu$, 12 h, r.t.; 65%.

Selective oxidation of diol **3** with (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) [15] and NaClO in CH_2Cl_2 provided α-hydroxy aldehyde **10**, which was subjected to (*Z*)-selective *Wittig* olefination [16], and subsequent lactonization using NaH and $(ArO)_2P(O)CH_2CO_2Et$ in THF afforded γ-butenolactone **11** in 82% yield. Deprotection of TBS ether with NH_4F in MeOH furnished compound **12** in 79% yield, which, on acetylation with Ac_2O and pyridine in CH_2Cl_2, afforded compound **13** in 88% yield. Finally, deprotection of the methoxymethyl (MOM) ether with Me_3SiBr (TMSBr) in CH_2Cl_2 gave botryolide E (**1**) in 73% yield [17] (*Scheme 3*). The spectroscopic and analytical data for the synthetic compound are in accordance with those reported in the literature [5][9].

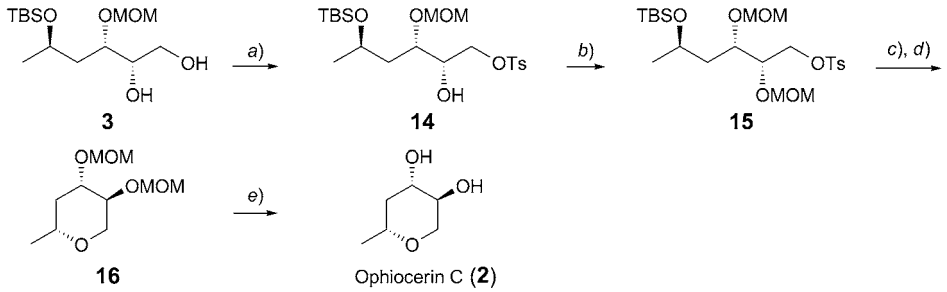
After successful completion of the synthesis of botryolide E (**1**), we attempted the synthesis of ophiocerin C (**2**) *via* the common intermediate **3** as depicted in *Scheme 4*. Selective tosylation of diol **3** using TsCl, Et_3N, and a catalytic amount of dibutyltin oxide (Bu_2SnO) in CH_2Cl_2 afforded compound **14** in 92% yield. Protection of the secondary OH group in **14** as MOM ether using MOMCl and EtN^{i}Pr$_2$ resulted in

Scheme 3



a) TEMPO (=(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl), NaClO, KBr, CH_2Cl_2, 0°, 3 h, 75%. *b*) NaH, (2-^{i}Pr-$C_6H_4O)_2P(O)CH_2CO_2Et$, THF, −78° – r.t., 4 h; 82%. *c*) NH_4F, MeOH, reflux, 12 h; 79%. *d*) Ac_2O, Py, CH_2Cl_2, 4 h; 88%. *e*) Me_3SiBr (TMSBr), CH_2Cl_2, 3 h, −40° – r.t.; 73%.

Scheme 4



a) TsCl, Et_3N, CH_2Cl_2, 0 °– r.t., 3 h; 92%. *b*) $MeOCH_2Cl$ (MOMCl), EtN^iPr_2, 4-(dimethylamino)pyridine (DMAP), CH_2Cl_2, 0° – r.t., 3 h; 90%. *c*) Bu_4NF, THF, 4 h. *d*) NaH, THF, 0° – r.t., 3 h; 72% for two steps. *e*) TMSBr, CH_2Cl_2, 2 h, r.t.; 76%.

compound **15** in 90% yield. The Bu_4NF-mediated desilylation, followed by S_N2 cyclization [18] of **15** using NaH in THF, afforded the tetrahydropyran derivative **16** in 72% yield. Removal of the MOM groups with Me_3SiBr in CH_2Cl_2 gave ophiocerin C (**2**) in 76% yield. The spectroscopic and analytical data for the synthetic compound are in accordance with those reported in the literature [6][10].

Conclusions. – In summary, we have described a new stereoselective approach to botryolide E (**1**) and ophiocerin C (**2**) *via* a common intermediate **3**. *Prins* cyclization, *MacMillan* α-aminoxylation, (*Z*)-selective *Wittig* olefination, and lactonization were the key steps in this synthesis.

N. M. R. and *A. M. R.* thank *CSIR*, New Delhi, for the award of a fellowship.

Experimental Part

General. All reagents were reagent-grade and used without further purification, unless specified otherwise. Solvents for reactions were distilled prior to use: THF, toluene and Et_2O were distilled from Na and benzophenone ketyl; MeOH from Mg and I_2; and CH_2Cl_2 from CaH_2. All air- or moisture-sensitive reactions were conducted under N_2 or Ar in flame-dried or oven-dried glassware with magnetic stirring. Column chromatography (CC): SiO_2 (60–120 or 100–200 mesh) packed in glass columns. Technical-grade AcOEt and petroleum ether used for CC were distilled prior to use. Optical rotation: *Jasco-DIP-360* digital polarimeter using a 1-ml cell with a 1-dm path length. FT-IR Spectra: *PerkinElmer* FT-IR as KBr pellets in $CHCl_3$, neat (as mentioned); $\tilde{\nu}$ in cm^{-1}. ^1H- and ^{13}C-NMR spectra: *Varian Gemini 200*, *Bruker Avance 300* or *Varian Innova 500* at 200, 300, or 500 MHz and r.t.; in $CDCl_3$ or (D_6)benzene; δ in ppm rel. to Me_4Si as internal standard, *J* in Hz. ESI- and HR-ESI-MS: *Finnigan MAT 1020B*; in *m*/*z*.

*(2*R*,4*R*)-4-(Methoxymethoxy)hept-6-en-2-ol* (**8**). To a soln. of **7** [13] (2.5 g, 8.30 mmol) in EtOH (60 ml), commercial Zn dust (10.83 g, 166.6 mmol) was added. The mixture was heated at 80° for 2 h and then cooled to 25°. Addition of solid NH_4Cl (6.5 g) and Et_2O (100 ml), followed by stirring for 5 min, gave a gray suspension, which was filtered through a pad of *Celite*, and the filtrate was concentrated *in vacuo*. Purification by CC gave **8** (1.33 g, 92%). Colorless liquid. R_f (AcOEt/hexane 3:7) 0.6. $[\alpha]_D^{27} = -69.50$ ($c = 1.30$, $CHCl_3$). IR (KBr): 3443, 3076, 2934, 1641, 1442, 1373, 1099, 1039. ^1H-NMR ($CDCl_3$, 300 MHz): 1.15 (*d*, *J* = 6.6, 3 H); 1.49–1.55 (*m*, 2 H); 2.20–2.37 (*m*, 2 H); 2.55 (br., OH); 3.38 (*s*, 3 H); 3.73–3.88 (*m*, 1 H); 3.92–4.09 (*m*, 1 H); 4.57–4.67 (*m*, 2 H); 5.01–5.10 (*m*, 2 H); 5.64–5.85 (*m*, 1 H).

^{13}C-NMR ($CDCl_3$, 75 MHz): 23.3; 39.3; 42.8; 55.8; 64.0; 75.2; 96.2; 117.5; 134.2. ESI-MS: 175 ($[M+H]^+$), 192 ($[M+NH_4]^+$).

*(4*R*,6*R*)-7-{[(*tert*-Butyl)(dimethyl)silyl]oxy}-4-(methoxymethoxy)hept-1-ene* (**9**). To a soln. of **8** (1.28 g, 7.35 mmol) in dry CH_2Cl_2 (20 ml) were added 4-(dimethylamino)pyridine (DMAP; 20 mg), and 1*H*-imidazole (1.20 g, 17.64 mmol) in one portion, followed by ^{t}BuMe$_2$SiCl (TBSCl; 1.32 g, 8.80 mmol) in two portions at 0°. The mixture was stirred for 4 h while slowly bringing it up to r.t. The reaction was quenched with the sat. NH_4Cl soln. (20 ml), and the mixture was extracted with CH_2Cl_2 (2 × 20 ml), washed with brine (20 ml), dried (Na_2SO_4), and concentrated *in vacuo*. Purification of the crude by CC (SiO_2) afforded **9** (1.98 g, 94%). Colorless oil. R_f (AcOEt/hexane 1:9) 0.7. $[\alpha]_D^{27} = -19.31$ ($c = 4.32$, $CHCl_3$). IR (KBr): 2932, 2892, 2858, 1466, 1374, 1253, 1148, 1097, 1043, 916, 833, 773. ^{1}H-NMR ($CDCl_3$, 300 MHz): 0.05 (*s*, 6 H); 0.88 (*s*, 9 H); 1.14 (*d*, *J* = 6.0, 3 H); 1.48–1.54 (*m*, 2 H); 2.27–2.32 (*m*, 2 H); 3.34 (*s*, 3 H); 3.64–3.75 (*m*, 1 H); 3.88–4.01 (*m*, 1 H); 4.63 (*s*, 2 H); 5.02–5.07 (*m*, 2 H); 5.70–5.84 (*m*, 1 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): −4.7; −3.9; 17.9; 24.4; 25.8; 39.7; 44.9; 55.4; 65.6; 75.1; 96.1; 117.0; 134.5. ESI-MS: 289 ($[M+H]^+$), 311 ($[M+Na]^+$).

*(2*S*,3*S*,5*R*)-5-{[(*tert*-Butyl)(dimethyl)silyl]oxy}-3-(methoxymethoxy)hexane-1,2-diol* (**3**). O_3 was bubbled through a soln. of **9** (1.92 g, 6.6 mmol) in CH_2Cl_2 (20 ml) at −78°, until no starting material was observed (TLC). The mixture was purged with N_2 to remove the excess O_3 and cooled to 0°, and Ph_3P (3.49 g, 13.32 mmol) was added. The mixture was stirred for 2 h and then concentrated *in vacuo*. After adding hexane, the mixture was filtered through *Celite* pad, and the residue washed with hexane. The filtrate was dried (Na_2SO_4), concentrated under reduced pressure, and the crude aldehyde **4** was used for the next reaction without further purification.

To a precooled (−20°) MeCN (50 ml) soln. of crude **4** and nitrosobenzene (PhNO) (0.713 g, 6.6 mmol) was added L-proline (0.23 g, 2.0 mmol). The mixture was stirred at the same temp. for 12 h, followed by the addition of MeOH (100 ml) and $NaBH_4$ (0.453 g, 13.32 mmol) to the mixture, which was stirred for 30 min, then $CuSO_4 \cdot 5\ H_2O$ (1.28 g, 5.1 mmol) was added at 0°. The mixture was allowed to stir for 10 h at this temp. Then, MeOH was removed *in vacuo*, then H_2O (50 ml) was added, the mixture was extracted with $CHCl_3$ (3 × 60 ml), and the combined org. phases were dried (Na_2SO_4) and concentrated to give the crude diol, which was then purified by CC (SiO_2) to give **3** (1.33 g, 65%). Colorless oil. R_f (AcOEt/hexane 5:5) 0.4. $[\alpha]_D^{27} = -12.28$ ($c = 1.75$, $CHCl_3$). IR (KBr): 3416, 2931, 2891, 2892, 2857, 1683, 1602, 1465, 1379, 1253, 1150, 1034, 834, 775. ^{1}H-NMR ($CDCl_3$, 300 MHz): 0.06 (*s*, 3 H); 0.08 (*s*, 3 H); 0.89 (*s*, 9 H); 1.18 (*d*, *J* = 6.2, 3 H); 1.48–1.75 (*m*, 2 H); 2.32 (br., OH); 3.43 (*s*, 3 H); 3.53–3.75 (*m*, 4 H); 3.92–4.14 (*m*, 1 H); 4.63–4.76 (*m*, 2 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): −4.6; −3.7; 17.9; 24.5; 25.8; 41.6; 55.8; 63.5; 65.3; 73.9; 79.6; 97.6. HR-ESI-MS: 309.2091 ($[M+H]^+$), $C_{14}H_{33}O_5Si^+$; calc. 309.2091).

*(5*S*)-5-((2*S*,3*R*)-3-{[(*tert*-Butyl)(dimethyl)silyl]oxy}-2-(methoxymethoxy)butyl)furan-2(5*H*)-one* (**11**). To a soln. of **3** (0.43 g, 1.39 mmol) in CH_2Cl_2 (10 ml), cooled to 0° under N_2, were added sat. aq. $NaHCO_3$ (10 ml), (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO; 21 mg, 0.134 mmol), and KBr (182 mg, 2.45 mmol). The mixture was stirred at 0° for 10 min, and then 5% NaClO aq. (3.6 ml, 2.45 mmol) was added. After stirring for 20 min, the reaction was quenched with sat. aq. $Na_2S_2O_3$, and the mixture was extracted with AcOEt. The combined org. layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give a crude product, which was purified by CC (SiO_2) to afford crude **10** (0.32 g 75%) as a colorless oil. The aldehyde **10**, containing unidentified side-products, was used in the next step without purification.

To a soln. of (2-^{i}Pr-C$_6$H$_4$O)$_2$P(O)CH$_2$COOEt (0.44 g, 1.08 mmol) in THF (10 ml) was added 60% NaH (50 mg, 1.83 mmol) under N_2. The reaction mixture was stirred at r.t. for 30 min, then cooled to −78°. A soln. of **10** (0.32 g, 0.91 mmol) in THF (3 ml) was added to the mixture, which was stirred at r.t. for 3 h, and then Et_2O and H_2O (10 ml) were added. The resulting mixture was extracted with Et_2O, and the combined org. layer was washed with brine, dried ($NaSO_4$), filtered, and concentrated *in vacuo* to give a crude product, which was purified by CC (SiO_2) to afford (247 mg, 82%) of **11**. Colorless oil. R_f (AcOEt/hexane 3:7) 0.65. $[\alpha]_D^{27} = -64.6$ ($c = 1.61$, $CHCl_3$). IR (KBr): 2955, 2930, 2856, 1758, 1156, 1038, 833, 775. ^{1}H-NMR ($CDCl_3$, 300 MHz): 0.05 (*s*, 3 H); 0.07 (*s*, 3 H); 0.88 (*s*, 9 H); 1.15 (*d*, *J* = 6.0, 3 H); 1.36–1.57 (*m*, 2 H); 3.38 (*m*, 3 H); 3.91–4.08 (*m*, 1 H); 4.64–4.77 (*m*, 2 H); 5.20–5.26 (*m*, 1 H); 6.19 (*dd*, *J* = 2.0, 5.6, 1 H); 7.51 (*dd*, *J* = 1.5, 5.6, 1 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): −4.6; −3.7; 24.5; 25.8;

29.6; 40.5; 55.8; 64.9; 75.6; 84.5; 97.7; 122.7; 153.9; 174.7. HR-ESI-MS: 353.17547 ($[M+Na]^+$, $C_{16}H_{30}NaO_5Si^+$; calc. 353.17547).

(5S)-5-[(1S,3R)-3-Hydroxy-1-(methoxymethoxy)butyl]furan-2(5H)-one (**12**). To a soln. of **11** (0.20 g, 0.6 mmol) in dry MeOH (10 ml) was added NH_4F (224 mg, 6.0 mmol). The mixture was refluxed for 12 h. After completion of the reaction, MeOH was removed *in vacuo*, H_2O was added, and the mixture was extracted with AcOEt (3×5 ml), dried (Na_2SO_4), and concentrated *in vacuo*. Purification by CC afforded **12** (103 mg, 79%). Colorless oil. R_f (AcOEt/hexane 7:3) 0.4. $[\alpha]_D^{27}=+40.1$ ($c=0.66$, $CHCl_3$). IR (KBr): 3452, 2964, 1753, 1157, 1097, 1035. ^{1}H-NMR ($CDCl_3$, 300 MHz): 1.23 (*d*, $J=$ 6.0, 3 H); 1.44–1.54 (*m*, 1 H); 1.59–1.70 (*m*, 1 H); 3.41 (*s*, 3 H); 3.95–4.09 (*m*, 2 H); 4.70 (*m*, 2 H); 5.09–5.15 (*m*, 1 H); 6.20 (*dd*, $J=2.2$, 6.0, 1 H); 7.47 (*dd*, $J=1.5$, 6.0, 1 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 23.5; 39.9; 56.1; 63.3; 75.5; 85.0; 97.9; 122.9; 153.2; 172.5. HR-ESI-MS: 239.08897 ($[M+Na]^+$), $C_{10}H_{16}NaO_5^+$; calc. 239.08899).

(5S)-5-[(1S,3R)-3-(Acetyloxy)-1-(methoxymethoxy)butyl]furan-2(5H)-one (**13**). To a soln. of **12** (72 mg, 0.3 mmol) in dry CH_2Cl_2 (2 ml) at 0°, Et_3N (92 µl, 0.66 mmol) and DMAP (cat.) were added. The mixture was stirred for 15 min, then Ac_2O (40 µl, 0.4 mmol) was added slowly, and the mixture was warmed to r.t. After stirring for 4 h, the mixture was diluted with CH_2Cl_2 (5 ml), and the reaction was quenched by addition of H_2O (3 ml). The org. layer was washed with brine (2×5 ml), dried (Na_2SO_4), concentrated, and the residue was purified by CC to afford pure **13** (5.41g, 91%). R_f (AcOEt/hexane 6:4) 0.6. $[\alpha]_D^{27}=+19.31$ ($c=4.32$, $CHCl_3$). IR (KBr): 2924, 2853, 1737, 1460, 1373, 1245, 1160, 1093, 1033. ^{1}H-NMR ($CDCl_3$, 300 MHz): 1.23 (*d*, $J=6.79$, 3 H); 1.44–1.55 (*m*, 1 H); 1.60–1.72 (*m*, 1 H); 3.36 (*s*, 3 H); 3.89–4.00 (*m*, 1 H); 4.97–5.06 (*m*, 1 H); 6.22 (*dd*, $J=2.2$, 1 H); 7.53 (*dd*, $J=1.5$, 6.0, 1 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 20.6; 29.6; 36.6; 56.2; 66.9; 74.4; 83.8; 97.9; 123.0; 153.5; 170.6; 172.5. HR-ESI-MS: 281.0993 ($[M+Na]^+$, $C_{12}H_{18}NaO_6^+$; calc. 281.0995).

(5S)-5-[(1S,3R)-3-(Acetyloxy)-1-Hydroxybutyl]furan-2-(5H)-one (**1**). Me_3SiBr (TMSBr; 35 µl, 0.271 mmol) was added dropwise to a cold (−40°) stirred soln. of **13** (35 mg, 0.135 mmol) in CH_2Cl_2 (3 ml). The mixture was stirred at −40° for 1 h and at 0° for additional 2 h, poured into sat. aq. $NaHCO_3$ soln., and extracted with CH_2Cl_2. The extract was dried (Na_2SO_4) and concentrated, and the residue was subjected to CC to give **1** (21 mg, 73%). Colorless liquid. R_f (AcOEt/hexane 3:7) 0.4. $[\alpha]_D^{27}=-38.2$ ($c=$ 0.05, $CHCl_3$). IR (KBr): 3446, 2926, 1738, 1374, 1248. ^{1}H-NMR ($CDCl_3$, 300 MHz): 1.27 (*d*, $J=6.0$, 3 H); 1.72–1.81 (*m*, 1 H); 1.85–1.94 (*m*, H); 2.03 (*s*, 3 H); 3.83–3.96 (*m*, 1 H); 5.0–5.17 (*m*, 1 H); 6.19 (*dd*, $J=2.2$, 6.0, 1 H); 7.48 (*dd*, $J=1.5$, 6.0, 1 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 20.1; 21.3; 39.1; 68.6; 68.8; 85.42; 122.7; 153.76; 170.8; 172.7. HR-ESI-MS: 237.0734 ($[M+$ $Na]^+$, $C_{10}H_{14}NaO_5^+$; calc. 237.0733).

*(2S,3S,5R)-5-{[(*tert*-Butyl)(dimethyl)silyl]oxy}-2-hydroxy-3-(methoxymethoxy)hexyl 4-Methylbenzenesulfonate* (**14**). To a soln. of **3** (0.21 g, 0.68 mmol) in dry CH_2Cl_2 (5 ml), Et_3N (284 µl, 2.03 mmol) and Bu_2SnO (cat.) were added. After 15 min. at 0° TsCl (0.194 g, 1.02 mmol) was added. The mixture was allowed to warm to r.t. and stirred for 3 h. After completion of the reaction, H_2O was added, and the mixture was extracted with CH_2Cl_2 (3×10 ml). The org. layer was washed with sat. $NaHCO_3$ (5 ml) and H_2O (5 ml). The combined org. phases were dried (Na_2SO_4) and concentrated under reduced pressure. Flash CC of the crude afforded **14** (1.95 g, 95%). Gummy liquid. R_f (AcOEt/hexane 3:7) 0.55. $[\alpha]_D^{27}=$ −7.58 ($c=1.45$, $CHCl_3$). IR (KBr): 3448, 2955, 2930, 2856, 1364, 1179, 1035, 833, 773. ^{1}H-NMR ($CDCl_3$, 300 MHz): 0.04 (*s*, 3 H); 0.06 (s, 3 H); 0.87 (*s*, 9 H); 1.15 (*d*, $J=6.0$, 3 H); 1.49–1.56 (*m*, 1 H); 1.58–1.68 (*m*, 1 H); 2.46 (*m*, 1 H); 3.33 (*s*, 3 H); 3.65–3.78 (*m*, 2 H); 3.88–4.04 (*m*, 2 H); 4.06–4.14 (*m*, 1 H); 4.58–4.65 (*m*, 2 H); 7.33 (*d*, $J=8.3$, 2 H); 7.79 (*d*, $J=8.0$, 2 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): −4.7; −3.9; 17.9; 21.6; 24.6; 25.8; 40.1; 55.6; 55.8; 65.2; 69.7; 75.5; 96.3; 96.7; 97.5; 120.9; 127.9; 129.7; 142.0; 114.7. HR-ESI-MS: 463.2186 ($[M+H]^+$, $C_{21}H_{39}O_7SSi^+$; calc. 463.2180).

*(2S,3S,5R)-5-{[(*tert*-Butyl)(dimethyl)silyl]oxy}-2,3-bis(methoxymethoxy)hexyl 4-Methylbenzenesulfonate* (**15**). To **14** (250 mg, 0.541 mmol) in anh. CH_2Cl_2 (6 ml) at 0° were added EtN^iPr_2 (564 µl, 3.24 mmol), DMAP (cat.), and MOMCl (121 µl, 1.61 mmol) successively, the resulting mixture was stirred for 3 h at r.t., and then the reaction was quenched by adding H_2O (10 ml), and the mixture was extracted with CH_2Cl_2 (3×10 ml). The org. extracts were washed with brine (10 ml), dried (Na_2SO_4), and concentrated under reduced pressure to remove the solvent, and the crude was purified by CC to afford pure **15** (1.85 g, 90%). Colorless liquid. R_f (AcOEt/hexane 3:7) 0.5. $[\alpha]_D^{27}=-35.6$ ($c=0.65$, $CHCl_3$). IR (KBr): 2970, 2926, 1357, 1178, 1092, 975. ^{1}H-NMR ($CDCl_3$, 300 MHz): 0.03 (*s*, 3 H); 0.05 (*s*,

3 H); 0.86 (*s*, 9 H); 1.13 (*d*, *J* = 6.0, 3 H); 1.28–1.34 (*m*, 1 H); 1.59–1.71 (*m*, 1 H); 2.46 (*s*, 3 H); 3.28 (*s*, 3 H); 3.32 (*s*, 3 H); 3.71–4.15 (*m*, 5 H); 4.50–4.64 (*m*, 4 H); 7.33 (*d*, *J* = 8.3, 2 H), 7.78 (*d*, *J* = 8.3, 2 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): −4.7; −3.9; 17.9; 21.6; 24.6; 25.8; 40.1; 55.6; 55.8; 65.2; 69.7; 75.5; 96.3; 96.7; 97.5; 120.9; 127.9; 129.7; 142.0; 144.7.

*(2*R*,4*S*,5*S*)-3,4,5,6-Tetrahydro-4,5-bis(methoxymethoxy)-2-methyltetrahydro-2*H*-pyran* (**16**). To a stirred soln. of **15** (190 mg, 0.375 mmol) in dry THF (5 ml) at 0°, Bu_4NF in THF (0.938 ml, 0.938 mmol) was added, and then the mixture was stirred at r.t. for 4 h. After completion of the reaction, H_2O was added, and the mixture was extracted with AcOEt and concentrated to afford a crude alcohol. The crude was further subjected to cyclization. To the alcohol in THF (2 ml) at 0° was added NaH (20 mg, 0.938 mmol), and the mixture was stirred for 2 h. H_2O (2 ml) was added, and the mixture was extracted with AcOEt, dried (Na_2SO_4), evaporated, and the residue was purified by CC to afford **16** (59 mg, 72%). Colorless oil. R_f (AcOEt/hexane 3:7) 0.4. $[\alpha]_D^{27} = -33.8$ ($c = 0.90$, $CHCl_3$). IR (KBr): 2926, 2854, 1710, 1605, 1164, 1035. ^{1}H-NMR ($CDCl_3$, 300 MHz): 1.20 (*d*, *J* = 6.7, 3 H); 1.22–1.38 (*m*, 2 H); 2.02–2.12 (*m*, 1 H); 3.35 (*s*, 3 H); 3.39 (*s*, 3 H); 3.42–3.65 (*s*, 3 H); 4.01–4.13 (*m*, 2 H); 4.79–4.63 (*m*, 4 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 21.2; 39.4; 55.2; 55.3; 68.8; 72.2; 76.6; 77.1; 95.8; 96.9. HR-ESI-MS: 243.1203 ($[M + Na]^+$, $C_{10}H_{20}NaO_5^+$; calc. 243.1202).

*(3*S*,4*S*,6*R*)-6-Methyltetrahydro-2*H*-pyran-3,4-diol* (**2**). TMSBr (107 µl, 0.81 mmol) was added dropwise to a cold (−40°) stirred soln. of **16** (45 mg, 0.204 mmol) in CH_2Cl_2 (3 ml). The mixture was stirred at −40° for 0.5 h and at 0° for additional 4 h, poured into sat. aq. $NaHCO_3$ soln., and extracted with CH_2Cl_2. The extract was dried (Na_2SO_4), concentrated, and the residue was subjected to CC to afford **2** (20 mg, 76%). White solid. R_f (60% AcOEt/hexane) 0.3. M.p. 81–83°. $[\alpha]_D^{27} = +45.6$ ($c = 0.1$, CH_2Cl_2). IR (KBr): 3413, 1460, 1380, 1262, 1136, 1080, 1006. ^{1}H-NMR ($CDCl_3$, 300 MHz): 1.20 (*d*, *J* = 6.0, 3 H); 1.90–1.98 (*m*, 2 H); 3.08 (*m*, 1 H); 3.38–3.56 (*m*, 3 H); 3.89 (*dd*, *J* = 5.2, 11.3, 1 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 21.1; 40.4; 69.5; 72.2; 72.6; 73.3. HR-ESI-MS: 155.0691 ($[M + Na]^+$, $C_6H_{12}NaO_3^+$; calc. 155.0684).

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