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A stereoselective synthesis of the reported structure of polyporolide†

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Polyporolide, isolated from a basidiomycete, was assigned a 4-hydroxy-5-(1-hydroxyhexyl)-dihydrofuran-2-one structure with *anti*-placement of the three contiguous stereocenters. A stereoselective total synthesis of the reported structure of the natural product involving two different routes is presented. A comparison of the spectral data of the synthesized molecule indicates the need for structure revision of natural polyporolide.

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Introduction

The secondary metabolites generated by *Polyporus* species (basidiomycetes) are structurally diverse and biologically active. In 2006, Wei and co-workers isolated a new acetogenin, polyporolide **1** (Fig. 1) from the mycelial solid cultures of *Polyporus* strain SC0652.[1] They observed this strain to possess antibacterial activity against *E. coli*. Polyporolide showed weak activity against brine shrimps (*Artemia salina*) with LC_{50} of 424.5 μg mL^{-1}. The structure of **1** was established by extensive spectroscopic studies. The relative configuration in **1** was assigned based on the NMR data and NOESY studies. They observed that H-3 and H-4 were *anti*-configured. Similarly, H-4 and H-5 were *erythro*-configured as shown in Fig. 1.[1]

In the course of our synthetic studies directed toward the enantioselective synthesis of pharmacologically active natural products like paraconic acids and butyrolactones,[2] we became interested in synthesis of the newly isolated acetogenin, polyporolide **1**.

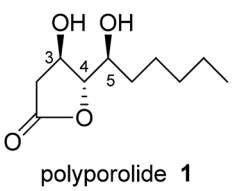
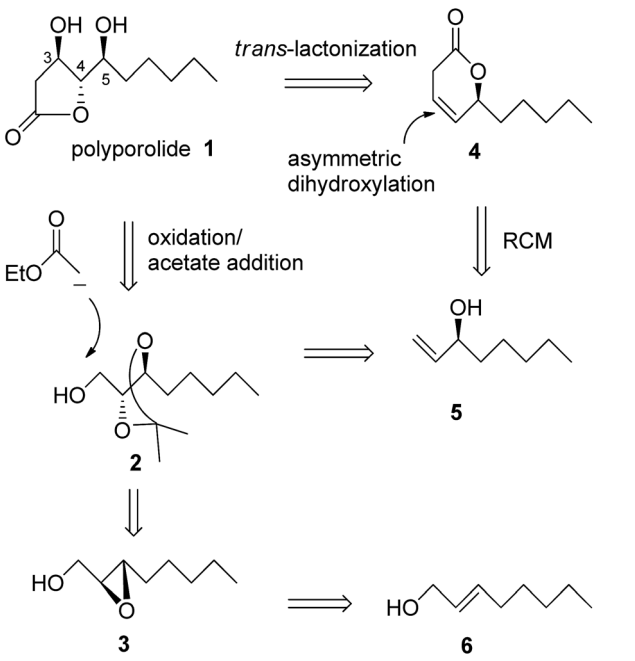


Fig. 1 Polyporolide **1**.

Results and discussion

Our detailed retrosynthetic approach for polyporolide **1** is outlined in Scheme 1. We visualized the γ-butyrolactone moiety in **1** can be accessed from **2** by aldol-type acetate anion addition and cyclization. Compound **2** with *anti*-diol group can be accessed from epoxide **3**. The latter can be derived from (*E*)-2-octen-1-ol **6** through Sharpless asymmetric epoxidation.[3] Alternatively, (*S*)-1-octen-3-ol **5** can be derived from **2**. From this, homoacrylate ester formation and ring closing metathesis would give **4**. *cis*-Dihydroxylation[4] of olefin **4** and *trans*-lactonization was expected to give **1**.



Scheme 1 Retrosynthetic analysis for polyporolide **1**.

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† Electronic supplementary information (ESI) available: Copies of ^{1}H and ^{13}C NMR spectra for all the compounds. See DOI: 10.1039/c5ra07930f

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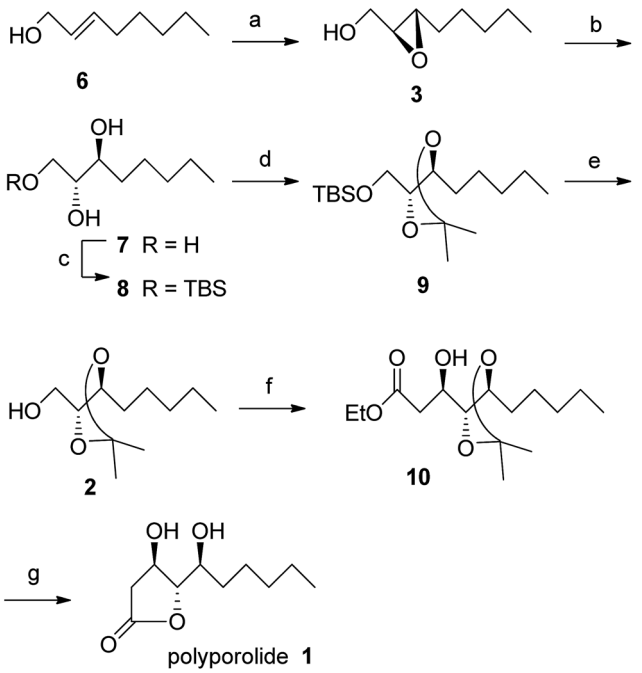
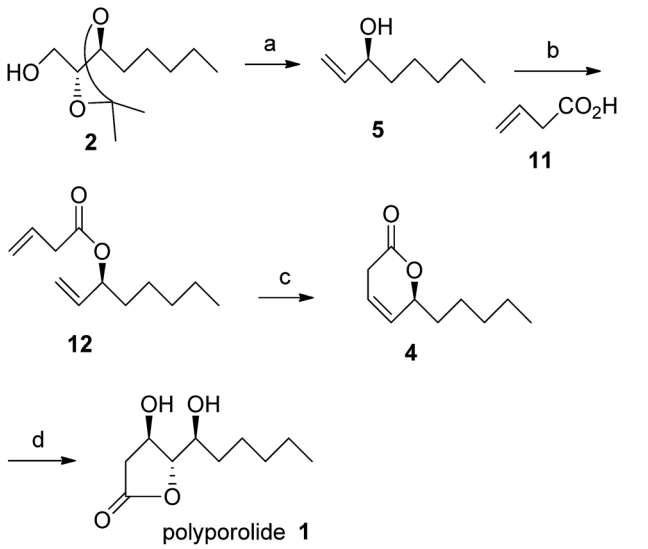
The forward synthesis of polyporolide started from known (*E*)-2-octen-1-ol **6**[5] (Scheme 2). The Sharpless asymmetric epoxidation,[3] of **6** in presence of (+)-DIPT, $Ti(Oi\text{-}Pr)_4$ and TBHP in CH_2Cl_2 at −30 °C furnished the epoxy alcohol **3** in 85% yield and excellent >98% ee.[6] Regioselective opening of epoxide ring under Payne rearrangement[7] conditions delivered the *anti*-triol **7** in 71% yield. Monoprotection of primary alcohol as silyl ether (**8**, 76%) and acetonide protection of the internal diol furnished **9** (82%). Removal of TBS protection with TBAF liberated the primary alcohol **2** in 86% yield. The two carbon homologation was planned through aldol-type acetate anion addition. We anticipated as reported in literature[8] the acetate anion addition on such vicinal acetonide containing aldehydes to deliver *anti*-C3/C4 steroegenic centres. DMP (Dess–Martin periodinane) oxidation of primary alcohol **2** to aldehyde and subsequent addition of lithiated ethyl acetate gave diastereoselectively **10** as single diastereomer in 54% yield over two steps. Removal of acetonide protection and *in situ* lactonization produced polyporolide **1** in 77% yield, $[\alpha]_D^{25} = +4.5$ ($c = 0.1$, MeOH). The IR spectral data of **1** was conclusive of γ-lactone structure ($\nu = 1770\ cm^{-1}$ for C=O). However, a comparison of ^{1}H-NMR and ^{13}C-NMR data for synthesized **1** with that reported for the natural product[1] showed discrepancy.

We explored an alternative strategy for polyporolide **1** as shown in Scheme 3. The acetonide alcohol **2** (from Scheme 2) was converted into iodide and subsequent zinc-mediated elimination provided (*S*)-1-octen-3-ol **5** in 80% yield from **2**.



Scheme 2 Synthesis of polyporolide **1**: reagents and conditions: (a) $Ti(O\text{-}iPr)_4$, TBHP, (+)-DIPT, CH_2Cl_2, −30 °C, 12 h, 85%; (b) 0.5N NaOH, 1,4-dioxane, reflux, 48 h, 71%; (c) TBSOTf, Et_3N, THF, 0 °C to rt, 5 min, 76%; (d) $(OMe)_2C(Me)_2$, *p*-TsOH·$2H_2O$, CH_2Cl_2, rt, 4 h, 82%; (e) TBAF, THF, 0 °C to rt, 3 h, 86%; (f) (i) DMP, CH_2Cl_2, rt, 3 h (ii) DIPA, *n*-BuLi, THF, −78 °C, 30 min, then EtOAc, −78 °C, 25 min, then aldehyde from **2**, −78 °C, 4 h, 54% (two steps); (g) 4N HCl, MeOH, reflux, 8 h, 77%.



Scheme 3 Alternative synthesis of polyporolide **1**: reagents and conditions: (a) (i) PPh_3, imidazole, I_2, THF, rt, 3 h, 93%, (ii) Zn, AcOH, Et_2O, rt, 4 h, 86%; (b) DCC, DMAP, CH_2Cl_2, **11**, 0 °C to rt, 6 h, 70%; (c) Grubbs-II cat. (1 mol%), CH_2Cl_2, reflux, 12 h, 96%; (d) $K_3Fe(CN)_6$, K_2CO_3, $MeSO_2NH_2$, $(DHQ)_2PHAL$, $K_2OsO_4 \cdot 2H_2O$, *t*-BuOH/H_2O (1 : 1), 0 °C, 24 h, 71%.

Esterification of **5** with 3-butenoic acid **11** under Steglich conditions[9] provided the diene **12** in 70% yield. The ring-closing metathesis[10] of diene **12** with Grubbs-II catalyst (1.0 mol%) gave δ-lactone **4** in excellent yields of 96%. The subsequent Sharpless asymmetric dihydroxylation[4] with $(DHQ)_2$-PHAL ligand gave the diol and *in situ trans*-lactonization (from 6-membered to 5-membered lactone) furnished polyporolide **1**, $[\alpha]_D^{25} = +4.7$ ($c =$

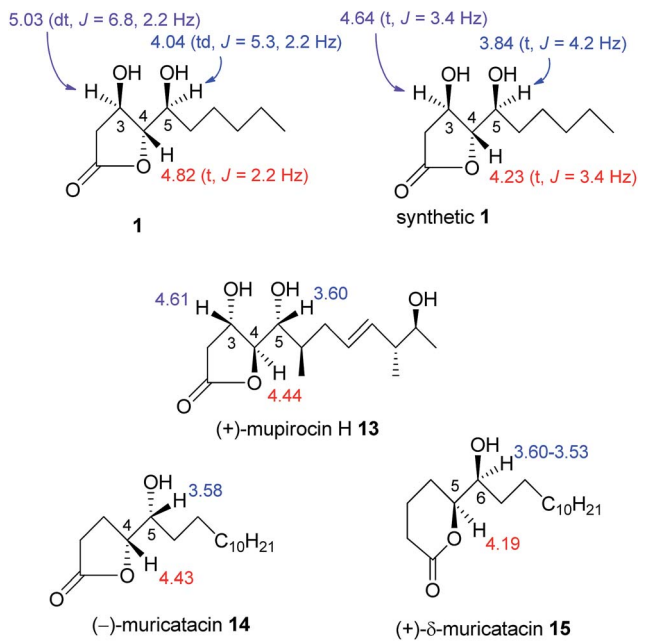


Fig. 2 Chemical shifts values (δ ppm) for molecules related to polyporolide **1**.

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0.1, MeOH). The spectral data of this was same as that prepared in Scheme 2.

The ^{1}H NMR data for C3, C4 and C5 protons (chemical shifts values, δ ppm) for polyporolide **1**,[1] synthetic **1**, and related compounds: (+)-mupirocin H **13**,[11] (−)-muricatacin **14**[12] and (+)-δ-muricatacin **15**[13] are shown in Fig. 2. Polyporolide **1** is assigned the *anti*-relative stereochemistry for C3, C4 and C5 contiguous protons (Fig. 1).[1] Similar relative stereochemistry exists in (+)-mupirocin H **13**. However, the chemical shifts values of reported **1** for C3, C4 and C5 protons as shown, completely mis-match with that in **13**. But there exists a good match of these protons shifts of **13** with that of synthetic **1**. A similar correlation can be extended for synthetic **1** with that of (−)-muricatacin **14** for C4 and C5 protons with regards to δ values. It can be further extended even to (+)-δ-muricatacin **15** for the C5 and C6 protons which are similar to C4 and C5 in polyporolide **1**. The ^{13}C NMR data for reported **1** for C3 (70.1), C4 (91.6) and C5 (71.4) do not match with that of synthetic **1** for C3 (67.9), C4 (91.6) and C5 (71.4), respectively. Thus, the synthetic **1** has the structure as depicted in Fig. 2. It is apparent from this mis-match of data of synthesised **1**, that the proposed structure of polyporolide needs revision.

Conclusions

In conclusion, a stereoselective synthesis of the reported structure of polyporolide **1** has been achieved in 7–9 steps and 12.3–13.5% overall yields. The key steps involve Sharpless epoxidation and diastereoselective aldol-type acetate anion addition. Alternatively ring-closing-metathesis, asymmetric dihydroxylation and *trans*-lactonizaton also yielded polyporolide **1**. The reported polyporolide **1** had specific rotation value of $[\alpha]_D^{20} = +13.1$ ($c = 0.2$, MeOH),[1] while the synthesized compound showed $[\alpha]_D^{25} = +4.7$ ($c = 0.1$, MeOH). A comparison of the spectral data of synthetic **1** with that of proposed structure and known similar molecules is conclusive of the need of structure revision for proposed polyporolide.

Experimental section

General information

Solvents were dried by standard procedures. Thin-layer chromatography was performed on EM 250 Kieselgel 60 F254 silica gel plates. The spots were visualized by staining with $KMnO_4$ or by using UV lamp. ^{1}H-NMR and ^{13}C-NMR were recorded on Varian 400, Bruker Avance^{III} 400 and 500 spectrometers and the chemical shifts are based on TMS peak at $\delta = 0.00$ pm for proton NMR and $CDCl_3$ peak at $\delta = 77.00$ ppm (t) in carbon NMR. IR spectra were obtained on Perkin Elmer Spectrum One FT-IR spectrometer. Optical rotations were measured with Jasco P-2000 digital polarimeter using Sodium D line (589 nm). HRMS were recorded using Micromass: Q-Tof micro (YA-105) spectrometer. Compound **6** was prepared following literature procedure.[5]

(2*S*,3*S*)-2,3-Epoxyoctan-1-ol (3).[6] To flame dried molecular sieves 4 Å (0.7 g) in CH_2Cl_2 (15 mL) were added (+)-diisopropyl L-tartrate (95 mg, 0.406 mmol, 0.2 equiv.) and $Ti(OiPr)_4$ (0.12 mL, 0.406 mmol, 0.2 equiv.). The suspension was cooled to −30 °C and allyl alcohol **6** (0.260 g, 2.03 mmol) was added. The reaction mixture was then stirred for an additional 30 min, and then *t*-BuOOH (3.8 M solution in decane, 1.1 mL, 4.1 mmol, 2 equiv.) was added. The reaction mixture was stirred to −30 °C for 12 h. After completion of reaction, the mixture was quenched with water (15 mL) and NaOH solution (30% aq.). It was then treated with saturated aq. NaCl (20 mL), and the resulting mixture was stirred vigorously for an additional 30 min at room temperature. The mixture was then vacuum filtered through a pad of celite, and the filter cake was washed with CH_2Cl_2 (50 mL). The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with water, brine, dried (Na_2SO_4) and concentrated. The residue was purified by silica gel column chromatography using petroleum ether/EtOAc (4 : 1) as eluent to afford **3** (0.248 g, 85%) as colorless oil. $[\alpha]_D^{25} = -41.2$ ($c = 0.7$, $CHCl_3$), lit.[6] $[\alpha]_D^{24} = -43.0$ ($c = 0.45$, $CHCl_3$). IR ($CHCl_3$): $\nu_{max} = 3424, 2952, 2929, 2859, 1457, 1158, 1109, 1045, 865, 704, 668$ cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ 3.91 (dd, $J = 12.6$, 2.4 Hz, 1H), 3.62 (dd, $J = 12.5$, 4.3 Hz, 1H), 2.97–2.90 (m, 2H), 1.71 (br. s, 1H, *OH*), 1.59–1.53 (m, 2H), 1.48–1.39 (m, 2H), 1.36–1.27 (m, 4H), 0.89 (t, $J = 7.1$ Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 61.7, 58.5, 56.02, 31.5, 31.46, 25.6, 22.5, 13.9 ppm.

(2*R*,3*S*)-Octane-1,2,3-triol (7). To a solution of epoxy alcohol **3** (0.5 g, 3.47 mmol) in 1,4-dioxane (10 mL) was added 0.5 N NaOH (2 mL) at room temperature. The mixture was stirred under reflux for 48 h, then cooled to room temperature and concentrated to a volume of 1.0 mL. The mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with water, brine, dried (Na_2SO_4) and concentrated. The reduced was purified by silica gel column chromatography using petroleum ether/EtOAc (1 : 1) to give compound **7** (0.399 g, 71%) as white solid. Mp 95–96 °C, $[\alpha]_D^{25} = -20.9$ ($c = 0.75$, EtOH), lit.[14] 104–105 °C, $[\alpha]_D^{20} = -21.4$ ($c = 0.98$, EtOH). IR ($CHCl_3$): $\nu_{max} = 3398, 3018, 2956, 2932, 2873, 2861, 1466, 1072, 916, 880, 671$ cm^{-1}. ^{1}H NMR (400 MHz, acetone-d6): δ 3.76–3.71 (m, 2H), 3.67–3.48 (m, 2H), 3.41 (dd, $J = 10.4$, 6.1 Hz, 1H), 1.68–1.52 (m, 2H), 1.43–1.27 (m, 6H), 0.88 (t, $J = 6.8$ Hz, 3H) ppm. ^{13}C NMR (125 MHz, acetone-d6): δ 74.1, 71.9, 63.1, 32.4, 31.3, 24.7, 21.9, 13.0 ppm. HRMS: m/z calcd for $C_8H_{18}O_3Na$ $[M + Na]^+$ 185.1154; found: 185.1151.

(2*R*,3*S*)-1-(*tert*-Butyldimethylsilyloxy)octane-2,3-diol (8). To a stirred solution of **7** (150 mg, 0.925 mmol) in dry THF (6 mL) at 0 °C were sequentially added Et_3N (0.52 mL, 3.7 mmol, 4.0 equiv.) and TBSOTf (0.330 mL, 1.437 mmol, 1.55 equiv.). The reaction mixture was stirred at room temperature for 5 min. It was then quenched with water (0.2 mL) and the aqueous layer extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with water, brine, dried (Na_2SO_4) and concentrated. The residue was purified by silica gel column chromatography using petroleum ether/EtOAc (17 : 3) as eluent to afford **8** (194.4 mg, 76%) as colorless oil. $[\alpha]_D^{25} = -5.2$ ($c = 0.4$, $CHCl_3$). IR ($CHCl_3$): $\nu_{max} = 3305, 2949, 2929, 2857, 1464, 1252, 1095, 1068, 912, 836, 666$ cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ 3.80–3.75 (m, 2H), 3.74–3.66 (m, 1H), 3.58–3.52 (m, 1H),

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1.9 (br. s, 2H, *OH*), 1.52–1.25 (m, 8H), 0.92–0.84 (m, 12H), 0.07 (s, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 73.5, 73.4, 64.1, 33.2, 32.1, 26.1, 25.9, 22.8, 18.4, 14.2, −5.2, −5.3 ppm. HRMS: *m*/*z* calcd for $C_{14}H_{32}O_3SiNa$ $[M + Na]^+$ 299.2013; found 299.2015.

(2*R*,3*S*)-1-(*tert*-Butyldimethylsilyloxy)-2,3-(isopropylidenedioxy) octane (9). To a solution of diol **8** (180 mg, 0.651 mmol) in CH_2Cl_2 (15 mL) was added *p*TsOH·$2H_2O$ (4 mg) and 2,2-dimethoxypropane (0.28 mL, 2.28 mmol, 3.5 equiv.). The reaction mixture was stirred at room temperature for 4 h and then quenched with saturated aq. $NaHCO_3$ (0.5 mL) and stirred for additional 15 min. The solution 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 silica gel column chromatography using petroleum ether/EtOAc (9 : 1) as eluent to afford **9** (169 mg, 82%) as colorless oil. $[\alpha]_D^{25} = -3.2$ (c = 0.3, $CHCl_3$). IR ($CHCl_3$): ν_{max} = 2957, 2931, 2859, 1464, 1380, 1364, 1260, 1097, 1046, 912, 839, 809, 777, 735, 672 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ 4.15–4.10 (m, 1H), 4.08–4.03 (m, 1H), 3.66 (dd, J = 10.2, 7.4 Hz, 1H), 3.57 (dd, J = 10.3, 5.0 Hz, 1H), 1.60–1.48 (m, 3H), 1.41 (s, 3H), 1.38–1.25 (m, 5H), 1.33 (s, 3H), 0.91–0.86 (m, 12H), 0.06 (s, 3H), 0.057 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 107.5, 77.9, 77.7, 62.1, 31.9, 29.0, 28.3, 26.4, 25.9, 25.6, 22.6, 18.2, 14.0, −5.4, −5.5 ppm. HRMS: *m*/*z* calcd for $C_{17}H_{36}O_3SiNa$ $[M + Na]^+$ 339.2326; found 339.2327.

(2*R*,3*S*)-2,3-(Isopropylidenedioxy)octan-1-ol (2). To a solution **9** (100 mg, 0.315 mmol) in dry THF (10 mL) was added TBAF (0.48 mL, 0.48 mmol, 1.5 equiv., 1 M solution in THF) at 0 °C and the mixture warmed to room temperature over 3 h. It was then quenched with water and stirred for 15 min. THF was removed under reduced pressure and the aqueous layer extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with water, brine, dried (Na_2SO_4) and concentrated. The residue was purified by silica gel column chromatography using petroleum ether/EtOAc (4 : 1) as eluent to give **2** (55 mg, 86%) as colorless oil. $[\alpha]_D^{25} = 6.2$ (c = 0.2, $CHCl_3$). IR ($CHCl_3$): ν_{max} = 3419, 2985, 2955, 2932, 2873, 1460, 1380, 1369, 1247, 1168, 1102, 1045, 881, 666 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$/TMS): δ 4.16–4.11 (m, 2H), 3.62–3.57 (m, 2H), 2.09 (br. s, 1H, *OH*), 1.57–1.23 (m, 8H), 1.46 (s, 3H), 1.35 (s, 3H), 0.88 (t, J = 7.0 Hz, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 108.0, 77.9, 77.01, 61.8, 31.8, 28.8, 28.2, 26.3, 25.5, 22.5, 14.0 ppm. HRMS: *m*/*z* calcd for $C_{11}H_{22}O_3Na$ $[M + Na]^+$ 225.1461; found 225.1452.

Ethyl(3*R*,4*S*,5*S*)-3-hydroxy-4,5-(isopropylidenedioxy)decanoate (10). To a solution of alcohol **2** (0.052 g, 0.256 mmol) in CH_2Cl_2 (10 mL) was added Dess–Martin periodinane (0.152 g, 0.358 mmol, 1.4 equiv.) in one portion and the reaction mixture stirred at room temperature for 3 h. The mixture was then filtered through a *celite* pad and the filtrate concentrated under reduced pressure. The residue was purified by silica gel column chromatography using petroleum ether/EtOAc (9 : 1) as eluent to afford the corresponding aldehyde (50 mg) as colorless oil. This was immediately used in the next reaction.

To a solution of iPr_2NH (0.08 mL, 0.563 mmol, 2.2 equiv.) in dry THF (10 mL) was added *n*BuLi (1.6 M in THF, 0.34 mL, 0.54 mmol, 2.1 equiv.) dropwise at −78 °C. The reaction mixture was stirred for 30 min at −78 °C. A solution of ethylacetate (0.05 mL, 0.512 mmol, 2 equiv.) in dry THF was added over 10 min, and the resulting soln. was stirred for another 15 min. Then, the solution of above aldehyde (50 mg) in THF was added slowly at −78 °C. The resulting mixture was stirred further for 4 h at the same temp., followed by quenching the reaction with saturated aq. NH_4Cl soln. The aqueous layer was extracted with EtOAc (3 × 10 mL) and the combined organic layers were washed with water, brine, dried (Na_2SO_4) and concentrated. The residue was purified by silica gel column chromatography using petroleum ether/EtOAc (4 : 1) as eluent to give **10** (40 mg, 54% from **2**) as colorless oil. $[\alpha]_D^{25} = -25.9$ (c = 0.1, $CHCl_3$). IR ($CHCl_3$): ν_{max} = 3437, 2956, 2931, 2873, 1725, 1463, 1379, 1248, 1165, 1097, 1042, 699 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ 4.21–4.15 (m, 3H), 4.07–4.02 (m, 1H), 3.88 (dd, J = 8.8, 5.7 Hz, 1H), 2.80 (dd, J = 17.1, 2.5 Hz, 1H), 2.49 (dd, J = 17.1, 9.0 Hz, 1H), 1.75–1.42 (m, 8H), 1.39 (s, 3H), 1.32 (s, 3H), 1.28 (t, J = 7.1 Hz, 3H), 0.89 (t, J = 6.9 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.5, 107.8, 79.0, 78.1, 66.6, 60.8, 38.4, 31.9, 29.3, 28.2, 26.3, 25.6, 22.6, 14.2, 14.0 ppm. HRMS: *m*/*z* calcd. for $C_{15}H_{28}O_5Na$ $[M + Na]^+$ 311.1829; found 3111.1821.

(4*R*,5*S*)-4-Hydroxy-5-[(*S*)-1-hydroxyhexyl]dihydrofuran-2(3*H*)-one (1). The ester **10** (30 mg, 0.104 mmol) was dissolved in methanol (10 mL) and 4 N HCl (2 mL) was added and refluxed for 8 h. The mixture was then cooled to room temperature and quenched with $NaHCO_3$ and filtered. The filtrate was concentrated and the residue purified by flash column chromatography using petroleum ether/EtOAc (1 : 1) as eluent to afford **1** (16.2 mg, 77%) as colorless oil. $[\alpha]_D^{25} = +4.5$ (c = 0.1, MeOH). IR ($CHCl_3$): ν_{max} = 3428, 2956, 2928, 2858, 1770, 1468, 1378, 1262, 1197, 1075, 1056, 1004, 910, 839, 649 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$/TMS): δ 4.64 (t, J = 3.4 Hz, 1H), 4.23 (t, J = 3.4 Hz, 1H), 3.84 (t, J = 4.2 Hz, 1H), 2.94 (dd, J = 18.2, 7.3 Hz, 1H), 2.55 (br. s, 2H, *OH*), 2.53 (dd, J = 18.2, 4.0 Hz, 1H), 1.62–1.51 (m, 3H), 1.32–1.25 (m, 5H), 0.90 (t, J = 6.5 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.1, 89.8, 71.5, 67.9, 38.5, 32.6, 31.6, 25.2, 22.5, 14.00 ppm. HRMS: *m*/*z* calcd for $C_{10}H_{19}O_4$ $[M + H]^+$ 203.1278; found 203.1279.

(*S*)-Oct-1-en-3-ol (5). To a mixture of triphenylphosphine (1.162 g, 4.43 mmol, 1.5 equiv.), imidazole (0.502 g, 7.38 mmol, 2.5 equiv.) and **2** (0.6 g, 2.95 mmol) in THF (30 mL) was added iodine (1.124 g, 4.43 mmol, 1.5 equiv.) portion wise at 0 °C. The resulting solution was stirred for 3 h at room temperature. The reaction was quenched by adding saturated aq. $Na_2S_2O_3$ and extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with water, brine, dried (Na_2SO_4) and concentrated. The residue was purified by silica gel column chromatography using petroleum ether/EtOAc (9 : 1) as eluent to afford the corresponding iodide (0.862 g, 93%) as colorless oil. This was used immediately in next reaction.

To a solution of iodide (0.84 g, 2.68 mmol) in Et_2O (10 mL) at room temperature was added Zn dust (1.49 g, 22.78 mmol, 8.5 equiv.) and acetic acid (2 mL). The mixture was stirred for 4 h and then quenched with 2 N HCl and stirred for 5 min. The suspension was extracted with Et_2O (3 × 30 mL) and the combined organic layers were washed with water, brine, dried (Na_2SO_4) and concentrated. The residue was purified by silica gel column chromatography using petroleum ether/CH_2Cl_2

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(4 : 1) as eluent to afford **5** (0.295 g, 86%) as colorless oil. $[\alpha]_D^{25}$ = +9.2 (c = 0.16, $CHCl_3$), lit.[15] $[\alpha]_D^{25}$ = +9.0 (c = 0.4, $CHCl_3$). IR ($CHCl_3$): ν_{max} = 3434, 2956, 2932, 2859, 1648, 1464, 1380, 1262, 1092, 1036, 925, 867 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$/TMS): δ = 5.87 (ddd, J = 17.2, 10.5, 6.4 Hz, 1H), 5.22 (td, J = 17.2, 1.4 Hz, 1H), 5.10 (td, J = 10.4, 1.3 Hz, 1H), 4.13–4.07 (m, 1H), 1.59–1.24 (m, 9H), 0.88 (t, J = 7.2 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.3, 114.6, 73.3, 37.0, 31.7, 25.0, 22.6, 14.0 ppm. HRMS: m/z calcd for $C_8H_{16}OK$ $[M + K]^+$ 167.0838; found 167.0839.

(*S*)-Oct-1-en-3-yl but-3-enoate (12). To a solution of the allylic alcohol **5** (0.34 g, 2.65 mmol) in CH_2Cl_2 (20 mL) were added 3-butenoic acid **11** (1.14 g, 13.25 mmol, 5.0 equiv.), DCC (1.094 g, 5.30 mmol, 2.0 equiv.) and DMAP (33 mg, 0.27 mmol, 10 mol%) at 0 °C. The mixture was warmed to room temperature and stirred for 6 h. It was then quenched with 2 N HCl. The suspension was extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic layers were washed with water, brine, dried (Na_2SO_4) and concentrated. The residue was purified by silica gel column chromatography using the petroleum ether/CH_2Cl_2 as eluent to afford **12** (0.364 g, 70%) as colorless oil. $[\alpha]_D^{25}$ = −5.2 (c = 0.2, $CHCl_3$). IR ($CHCl_3$): ν_{max} = 3085, 2956, 2933, 2862, 1741, 1644, 1467, 1426, 1379, 1323, 1252, 1293, 1174, 1094, 991, 923, 886 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$/TMS): δ 6.00–5.86 (m, 1H), 5.77 (ddd, J = 17.3, 10.5, 6.5 Hz, 1H), 5.29–5.12 (m, 5H), 3.11 (td, J = 7.0, 1.3 Hz, 2H), 1.70–1.50 (m, 2H), 1.42–1.20 (m, 6H), 0.88 (t, J = 6.3 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.8, 136.5, 130.4, 118.5, 116.6, 75.1, 39.4, 34.1, 31.5, 24.7, 22.5, 14.0 ppm. HRMS: m/z calcd for $C_{12}H_{20}O_2Na$ $[M + Na]^+$ 219.1361; found 219.1351.

(*S*)-6-Pentyl-3,6-dihydro-2*H*-pyran-2-one (4). To a stirred and degassed solution of **12** (100 mg, 0.51 mmol) in dry CH_2Cl_2 (70 mL) was added Grubbs second-generation catalyst (4.3 mg, 0.005 mmol, 1.0 mol%) at room temperature and the mixture refluxed for 12 h. It was then cooled and filtered through a small pad of silica gel and the filtrate concentrated. The residue was purified by silica gel column chromatography using petroleum ether/EtOAc (6 : 1) as eluent to give **4** (82.3 mg, 96%) as colorless oil. $[\alpha]_D^{25}$ = +35.2 (c = 0.24, $CHCl_3$). IR ($CHCl_3$): ν_{max} = 2956, 2932, 2861, 1735, 1467, 1382, 1240, 1165, 1118, 1057, 829, 704 cm^{-1}. ^1H NMR[16] (400 MHz, $CDCl_3$/TMS): δ 5.88–5.81 (m, 2H), 4.99–4.96 (m, 1H), 3.07–3.05 (m, 2H), 1.78–1.71 (m, 2H), 1.40–1.25 (m, 6H), 0.89 (t, J = 6.9 Hz, 3H) ppm. ^{13}C NMR[16] (100 MHz, $CDCl_3$): δ 169.2, 126.6, 121.4, 79.7, 35.6, 31.4, 29.9, 23.9, 22.5, 13.9 ppm.

(4*R*,5*S*)-4-Hydroxy-5-[(*S*)-1-hydroxyhexyl]dihydrofuran-2(3*H*)-one (1) from 4. To a mixture of $K_3Fe(CN)_6$ (0.942 g, 2.86 mmol, 3.0 equiv.), K_2CO_3 (0.396 g, 2.86 mmol, 3.0 equiv.), $MeSO_2NH_2$ (90.6 mg, 0.952 mmol, 1.0 equiv.), $(DHQ)_2PHAL$ (7.6 mg, 0.0096 mmol, 1.0 mol%) and $K_2OsO_4 \cdot 2H_2O$ (1.4 mg, 0.0038 mmol, 0.4 mol%) were added *t*-BuOH (3 mL) and water (5 mL). The mixture was stirred for 5 min and cooled at 0 °C in ice bath. To the cooled mixture, a solution of the olefin **4** (160 mg, 0.952 mmol) in *t*-BuOH (2 mL) was added. The reaction mixture was stirred at 0 °C for 24 h and then quenched with solid Na_2SO_3 and stirred for 30 min. The solution was extracted with EtOAc (3 × 20 mL) and the combined organic layers were washed with 2 N KOH (10 mL), brine, dried (Na_2SO_4) and concentrated. The residue was purified by silica gel column chromatography using petroleum ether/EtOAc (1 : 1) as an eluent to give **1** (0.156 g, 71%) as a colorless oil. $[\alpha]_D^{25}$ = +4.7 (c = 0.1, MeOH). Spectral data is same as before.

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