

An alternative stereoselective total synthesis of Verbalactone

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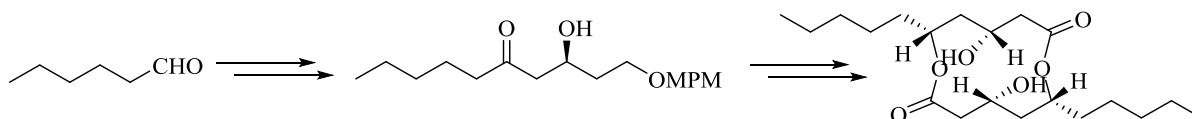
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Abstract

A simple and efficient synthesis of Verbalactone has been accomplished from inexpensive and commercially available starting material, hexanal. This concise synthesis utilizes stereoselective reduction of β -hydroxyketone using catecholborane, regioselective opening of epoxide and Yamaguchi reaction for the construction of the macrolactone.

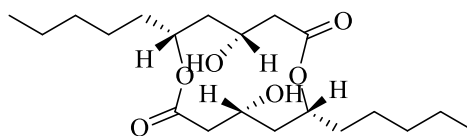


Keywords: Hexanal, regioselective epoxide opening, Yamaguchi macrolactonisation, stereoselective synthesis, Verbalactone

Introduction

Macrolides are large lactone ring molecules and these molecules are derived by the internal esterification of the corresponding hydroxy acids. Macrodiolides and macrocyclic monolactones are two types of macrolides. Researchers across the world concentrated towards the synthesis of both homo and hetero dimers (macro dilactones)¹⁻³ and macrocyclic monolactones⁴⁻⁶. Macrodiolides are interesting natural products which can be isolated from marine sponges and different fungi. These macrodiolides exhibited potent biological activities including antihelmintic,^{7,8} antifungal^{9,10} and phytotoxic activities¹¹.

Verbalactone **1** is a 12 membered C₂ symmetric dilactone and it was isolated from the roots of *Verbascum undulatum* Lam., a biennial plant of the genus *Verbascum* that belongs to the family Scrophulariaceae by Mitaku et al.¹² It showed antibacterial activity against Gram-positive (MIC=62.5 mg/cm³) and Gram-negative bacteria (MIC=125 mg/cm³). Verbalactone (**1**) is thus a dimeric lactone with C₂-symmetry and has a NMR profile similar to the monomer lactone of (3R,5R)-dihydroxydecanoic acid.¹³⁻¹⁶ The structure and absolute stereochemistry of verbalactone was determined as 4*R*,6*R*,10*R*,12*R* by the 1D and 2D NMR spectroscopic methods and chemical correlations. The NMR profile of **1** is similar to the NMR data of (3*R*,5*R*)-dihydroxydecanoic acid.¹³⁻¹⁶ The structure of verbalactone was shown in Figure 1.



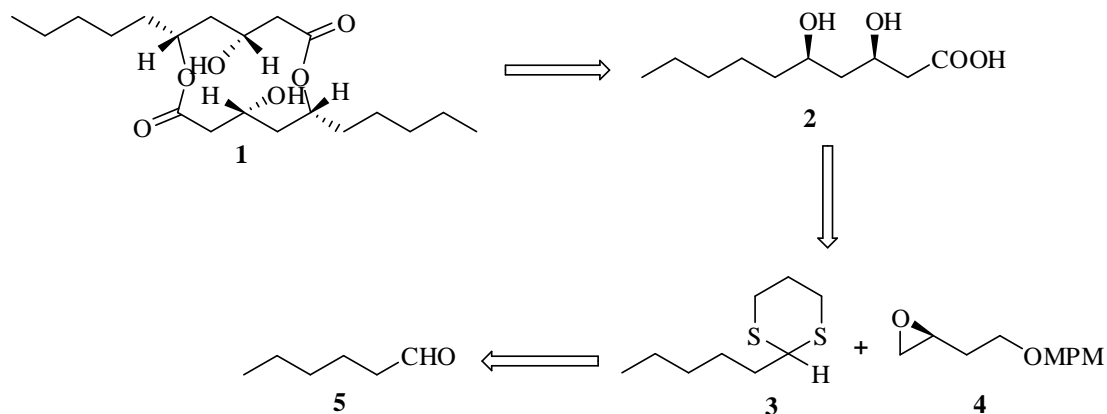
Verbalactone (**1**)

Figure 1

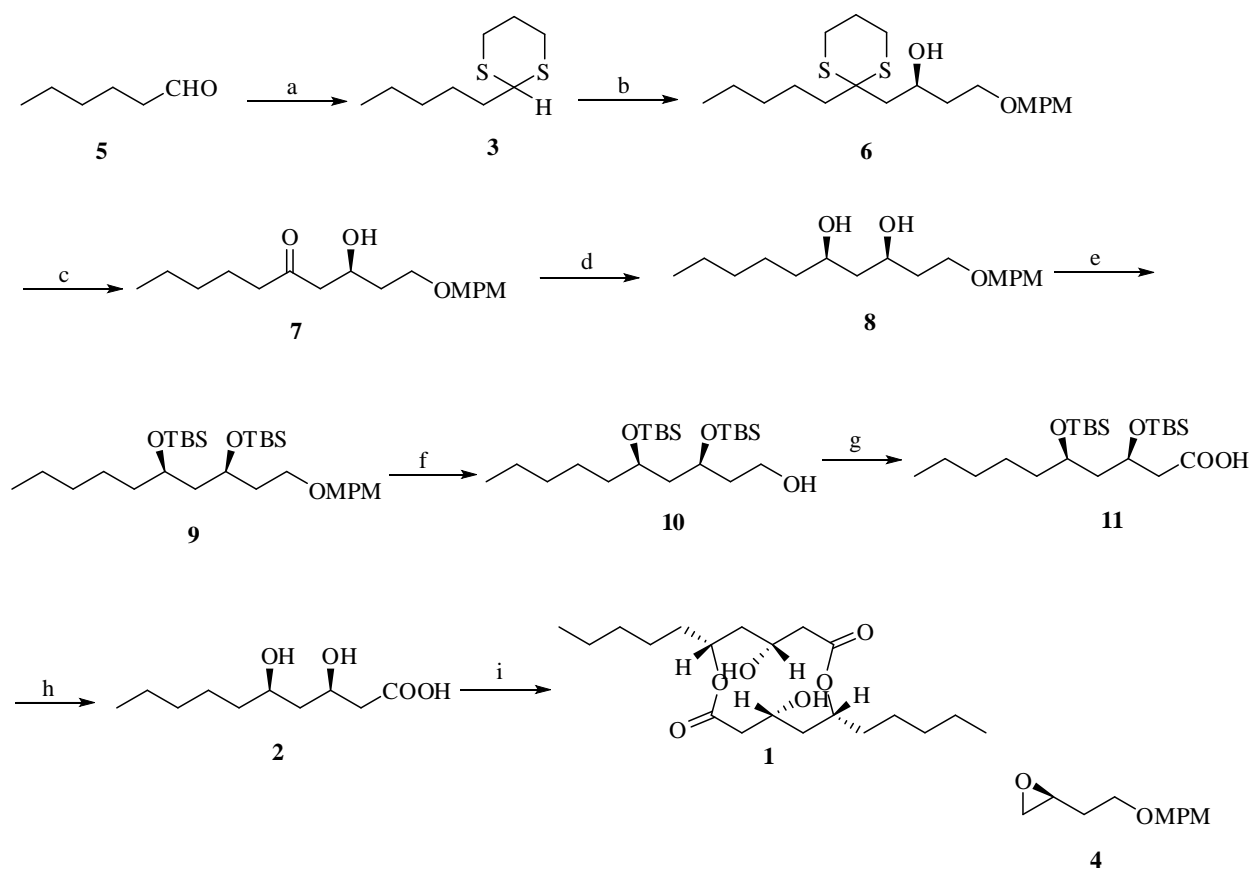
Meanwhile, several scientists reported the total synthesis of Verbalactone due to its interesting biologically active nature and stereochemical complexity.¹⁷⁻²⁷ The reported methods involve long reaction sequences, low yields and dependence of chiral pool resources were disadvantages. In continuation of our research work on the synthesis of biologically active natural products, herein we report an efficient straightforward and an alternative concise synthetic route for stereoselective total synthesis of Verbalactone starting from commercially available material hexanal with overall high yield.

Results and Discussion

Our retrosynthetic analysis of **1** is outlined in Scheme 1. Retrosynthetically (Scheme 1), the target molecule **1** could be obtained from dihydroxy acid **2** by Yamaguchi's macrolactonization. While compound **2** could be obtained from opening of epoxide **4** with 2-pentyl-1,3-dithiane **3**, the 1,3-dithiane **3** could be prepared from the aldehyde **5**.



Scheme 1. Retrosynthetic route of Verbalactone.



Reagents and conditions: (a) 1,3-propanedithiol, $\text{BF}_3 \cdot \text{OEt}_2$, CH_2Cl_2 , 0°C -rt, 12h. (b) **4**, *n*-BuLi, dry THF, -78°C to -20°C , 3h. (c) CaCO_3 , I_2 , THF/ H_2O (4:1), 0°C , 30 min (d) catecholborane, dry THF, -10°C , 4h, (e) TBSCl, Imidazole, CH_2Cl_2 , rt, 4h; (f) DDQ, CH_2Cl_2 : H_2O (19:1), rt, 3 h. (g) TEMPO, BIAB, H_2O : CH_2Cl_2 , (1:1), 0°C , 1 h. (h) TBAF, THF, 0°C to rt, 3 h. (i) 2,4,6-trichlorobenzoyl chloride, Et_3N , THF, rt, 2 h then DMAP, toluene, reflux, 6 h

Scheme 2. Stereoselective total synthesis of Verbalactone.

The synthesis (Scheme 2) was started from the commercially available hexanal **5**, which was converted as corresponding 1,3- dithiane using 1,3-propanedithiol and $\text{BF}_3 \cdot \text{OEt}_2$ in CH_2Cl_2 for 12 h. Later, 1,3- dithiane **3** on treatment with *n*-BuLi followed by the regioselective opening of known epoxide **4**²⁸ with resulting carbanion gave alcohol **6** in 77% yield. Later, the 1,3-dithioacetal group was removed from **6** to furnish the β -hydroxy

ketone **7**. For this transformation, we first tried with DDQ in aqueous MeCN. But in this reaction conditions the yield of the required compound is low (< 40%) and some of the Starting material remains unchanged. To overcome this, we next tried with CaCO₃, I₂, in THF/H₂O (4:1), in this method the reaction took place with good yield (74%). The stereoselective reduction of β-hydroxyl ketone **7** to the corresponding *syn* 1, 3-diol **8** was achieved using catecholborane (3.0 eq.) in THF at -10 °C in 84% yield with high diastereoselectivity (*syn*: *anti*, 99:1). The resulting diol **8** was masked as silylethers with TBSCl and imidazole in CH₂Cl₂ to give **9** (81%), which on selective cleavage of PMB ether in the presence of DDQ in aq. CH₂Cl₂ gave alcohol **10** in 78% yield. The alcohol **10** was oxidized to acid by treating with TEMPO and BIAB in aq. CH₂Cl₂ to afford acid **11** in 71% yield, which on desilylation with TBAF in dry THF afforded the dihydroxy acid **2**.

Finally, The resulting dihydroxy acid **2** was immediately subjected to macrolactonisation under Yamaguchi reaction conditions (2,4,6-trichlorobenzoyl chloride, Et₃N and DMAP) to afford the target molecule Verbalactone **1** in in 57% yield. The ¹H NMR, ¹³C NMR and optical rotation value of synthetic **1** were in good agreement with those of the previously reported natural product.²¹

Conclusions

In conclusion, a stereoselective total synthesis of Verbalactone **1** was accomplished by a versatile strategy. A combination of stereoselective reduction of β-hydroxyl ketone using catecholborane, regioselective ring opening of epoxide and Yamaguchi macrolactonisation were effectively utilized in accomplishing the synthesis.

Experimental Section

General. All chemicals and solvents were purchased from Sigma–Aldrich and Merck and used without further purification. All reactions were monitored by thin-layer chromatography (TLC) on silica Merck 60 F254 precoated aluminum plates. ¹H and ¹³C NMR spectra were recorded with 500, 300, 150, and 75 MHz Bruker spectrometer. Chemical shifts are reported in δ units (ppm) with tetramethylsilane (TMS) as a reference. All coupling constants (J) are reported in Hertz. Multiplicity is indicated as s (singlet), d (doublet), dd (double doublet), t (triplet), q (quartet), m (multiplet). FT-IR spectra were taken on IR spectrophotometer using NaCl optics. Mass spectra were performed on direct inlet system or LC by MSD trap SL, the HRMS data were obtained using Q-TOF mass spectrometry. Optical rotation values are recorded on digital polarimeter at 25 °C.

2-Pentyl-1,3-dithiane (3).²⁹ To a stirred solution of hexanal (5.0 mL, 49.07 mmol) in CH₂Cl₂ (20 mL) was added 1,3-propanedithiol (6.4 mL, 58.89 mmol). The mixture was cooled to 0 °C and BF₃·OEt₂ (3.0 mL, 24.53 mmol) was added dropwise. The mixture was allowed to warm to room temperature stirred for 12 h. After completion of reaction the reaction was quenched by the addition of saturated aqueous NaHCO₃. The mixture was diluted with CH₂Cl₂ and washed twice with 0.1 M NaOH then three times with brine. The combined aqueous phases were extracted twice with CH₂Cl₂ and the combined organic layers were dried over NaSO₄ then concentrated and purified by Flash chromatography (silica gel, 60–120 mesh, 4% EtOAc in pet. ether) afforded **3** (8.0 g 86%) as a colorless oil. ¹H NMR (300 MHz, CDCl₃): δ 4.05 (t, *J* 6.9 Hz, 1H), 2.91-2.80 (m, 4H), 2.15-2.09 (m, 1H), 1.90-1.82 (m, 1H), 1.76-1.72 (m, 2H), 1.51 (quintet, *J* 7.6 Hz, 2H), 1.33-1.25 (m, 4H), 0.89 (t, *J* 7.0 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 47.9, 35.6, 31.6, 30.7, 26.5, 26.3, 22.6, 14.2; IR (neat) 2930, 1422, 1275, 1182, 908 cm⁻¹; HRMS (ESI): *m/z* calcd for C₉H₁₈NaS₂: 213.0748; found: 213.0751 [M+Na]⁺.

(S)-4-(4-Methoxybenzyloxy)-1-(2-pentyl-1,3-dithian-2-yl)butan-2-ol (6). To a solution of **3** (5.0 g, 26.31 mmol) in dry THF (20 mL) was added *n*-BuLi (15.7 mL, 39.47 mmol, 2.5 N hexane solution) dropwise under N₂ atmosphere at -78 °C and stirred for 30 min. then the reaction mixture was sequentially treated with a solution of epoxide **4** (6.0 mL, 28.94 mmol) in dry THF (15 mL) at 10 min interval and stirred for an additional 3 h at -20 °C. After completion of reaction, Saturated NaHCO₃ solution (20 mL) followed by saturated NH₄Cl solution (20 mL) were added to the reaction mixture at -20 °C and allowed to warm to room temperature. The reaction mixture was extracted with EtOAc (2 x 50 mL). The organic layers were washed with water (50 mL), dried (Na₂SO₄), evaporated and the residue obtained was purified by column chromatography (60-120 Silica gel, 8% EtOAc in pet. ether) to give **6** (8.06 g, 77%) as a yellow syrup. [α]_D -18.7 (c 1.6, CHCl₃); ¹H NMR (CDCl₃, 300 MHz): δ 7.19 (d, 2H, *J* 8.6 Hz, Ar-H), 6.83 (d, 2H, *J* 8.6 Hz, Ar-H), 4.51 (d, 1H, *J* 11.7 Hz, -OCH₂Ph), 4.41 (d, 1H, *J* 11.7 Hz, -OCH₂Ph), 3.81 (s, 3H, -OCH₃), 3.75-3.79 (m, 1H, H-3), 3.48 (t, 2H, *J* 5.7 Hz, H-1, 1'), 3.05 (br s, 1H, -OH), 2.88-3.01 (m, 2H), 2.66-2.75 (m, 2H), 1.86-1.99 (m, 2H), 1.55-1.79 (m, 8H, 4 x CH₂), 1.26-1.34 (m, 4H, 2 x CH₂), 0.92 (t, 3H, *J* 5.7 Hz, -CH₃); ¹³C NMR (75 MHz, CDCl₃): δ 158.6, 129.8, 129.4, 114.3, 76.3, 69.1, 66.9, 62.3, 56.7, 44.8, 40.1, 38.3, 33.7, 27.3, 25.2, 23.3, 22.8, 14.6; IR (neat) 3373, 2984, 1372, 1175, 1082, 928 cm⁻¹; HRMS (ESI): *m/z* calcd for C₂₁H₃₄O₃NaS₂: 421.1847; found: 421.1852 [M+Na]⁺.

(S)-3-Hydroxy-1-(4-methoxybenzyloxy)decan-5-one (7). To a solution of compound **6** (4.1 g, 10.30 mmol) and CaCO₃ (8.24 g, 82.41 mmol) in THF/H₂O (v/v, 4:1, 100 mL) was added iodide (5.21 g, 20.6 mmol) at 0 °C. The resulting mixture was stirred at 0 °C for 30 min. The reaction was quenched by adding saturated aqueous Na₂S₂O₃, filtered through a pad of Celite, and then extracted with EtOAc (3 x 100 mL), water, brine, dried over Na₂SO₄ and concentrated in vacuo. Purification by flash chromatography (silica gel, 60-120 mesh, 15% EtOAc in pet. ether) to give compound **7** (2.34 g, 74% yield) as colorless oil: [α]_D -98.7 (c 1.6, CHCl₃); ¹H NMR (CDCl₃, 300 MHz): δ 7.22 (d, 2H, *J* 8.8 Hz, Ar-H), 6.79 (d, 2H, *J* 8.8 Hz, Ar-H), 4.47 (d, 1H, *J* 11.6 Hz, -OCH₂Ph), 4.39 (d, 1H, *J* 11.6 Hz, -OCH₂Ph), 3.79 (s, 3H, -OCH₃), 3.66-3.58 (m, 1H), 3.51 (t, 2H, *J* 6.1 Hz, 2.91 (br s, 1H, -OH), 2.68-2.54 (m, 2H), 2.06 (t, 2H, *J* 6.7 Hz, -CH₂), 1.52-1.39 (m, 4H, 2 x CH₂), 1.29-1.18 (m, 4H, 2 x CH₂), 0.89 (t, 3H, *J* 5.8 Hz, -CH₃); ¹³C NMR (75 MHz, CDCl₃): δ 206.7, 159.0, 129.7, 129.4, 114.1, 76.6, 68.3, 67.9, 56.6, 50.1, 40.9, 36.6, 32.9, 26.7, 14.1; HRMS (ESI): *m/z* calcd for C₁₈H₂₈O₄Na: 331.1885; found: 331.1890 [M+Na]⁺.

(3S,5R)-1-(4-Methoxybenzyloxy)decane-3,5-diol (8). To a stirred solution of compound **7** (2.25 g, 7.30 mmol) in dry tetrahydrofuran, freshly distilled catecholborane (2.3 mL, 21.9 mmol) was added at -10 °C (reaction mixture was kept in MeOH-ice bath). After 4 h, the reaction mixture was quenched by the addition of 1mL of anhydrous MeOH and 2mL of a saturated aqueous solution of sodium potassium tartarate. This mixture was allowed to stir at room temperature for 2 h. The layers were separated, and aqueous layer was extracted with ethyl acetate (3 x 30 ml). The organic extracts were washed with brine (30 ml) and dried over anhydrous Na₂SO₄, and purified by column chromatography (silica gel, 60-120 mesh, 25% EtOAc in pet. ether) to afford the diol **8** (1.9 g, 84%) as a liquid. [α]_D -38.1 (c 1.6, CHCl₃); ¹H NMR (CDCl₃, 300 MHz): δ 7.22 (d, 2H, *J* 8.8 Hz, Ar-H), 6.79 (d, 2H, *J* 8.8 Hz, Ar-H), 4.47 (d, 1H, *J* 11.6 Hz, -OCH₂Ph), 4.39 (d, 1H, *J* 11.6 Hz, -OCH₂Ph), 3.83 (s, 3H, -OCH₃), 3.76-3.64 (m, 2H), 3.43 (t, 2H, *J* 5.8 Hz), 3.03-2.88 (br s, 2H, 2 x -OH), 1.78-1.64 (m, 4H, 2 x -CH₂), 1.52-1.28 (m, 8H, 4 x CH₂), 0.83 (t, 3H, *J* 5.8 Hz, -CH₃); ¹³C NMR (75 MHz, CDCl₃): δ 158.7, 129.7, 129.5, 114.3, 76.7, 67.9, 67.5, 67.3, 56.1, 45.6, 36.3, 33.8, 32.7, 25.6, 14.2; HRMS (ESI): *m/z* calcd for C₁₈H₃₀O₄Na: 333.2042; found: 333.2047 [M+Na]⁺.

(5S,7R)-5-(2-(4-Methoxybenzyloxy)ethyl)-2,2,3,3,9,9,10,10-octamethyl-7-pentyl-4,8-dioxa-3,9-disilaundecane (9). A mixture of the above alcohol **8** (1.74 g, 5.61 mmol) and imidazole (1.52 g, 22.45 mmol) in dry CH₂Cl₂ (40 mL) was treated with TBSCl (2.10 g, 14.02 mmol) at 0 °C under nitrogen atmosphere and stirred at room temperature for 4 h. The reaction mixture was quenched with aq. NH₄Cl solution (10 mL) and extracted with CH₂Cl₂ (2 x 50 mL). The combined extracts were washed with water (30 mL), brine (30 mL), dried (Na₂SO₄) and concentrated. The residue was purified by column chromatography (60-120 Silica gel, 5% EtOAc in pet.

ether) to furnish **9** (2.44 g, 81%) as a colorless liquid. $[\alpha]_D$ -57.4 (c 0.76, CHCl_3); ^1H NMR (CDCl_3 , 300 MHz): δ 7.22 (d, 2H, J 8.8 Hz, Ar-H), 6.79 (d, 2H, J 8.8 Hz, Ar-H), 4.47 (d, 1H, J 11.6 Hz, $-\text{OCH}_2\text{Ph}$), 4.39 (d, 1H, J 11.6 Hz, $-\text{OCH}_2\text{Ph}$), 3.83 (s, 3H, $-\text{OCH}_3$), 3.52-3.41 (m, 2H), 3.41 (t, 2H, J 6.0 Hz), 1.74-1.56 (m, 6H, 3 x CH_2), 1.42-1.25 (m, 6H, 3 x $-\text{CH}_2$), 0.88 (t, 3H, J 5.8 Hz, $-\text{CH}_3$), 0.83 (s, 9H, *t*-butyl), 0.79 (s, 9H, *t*-butyl), 0.08 (s, 6H, 2 x $-\text{CH}_3$), 0.03 (s, 6H, 2 x $-\text{CH}_3$); ^{13}C NMR (75 MHz, CDCl_3): δ 158.6, 129.7, 129.4, 114.2, 113.2, 75.9, 70.3, 67.9, 67.6, 56.0, 46.1, 36.2, 33.7, 31.9, 26.6, 26.3, 25.7, 22.8, 17.9, 13.9, -4.3, -4.6; HRMS (ESI): m/z calcd for $\text{C}_{30}\text{H}_{58}\text{O}_4\text{NaSi}_2$: 561.3771; found: 561.3774 $[\text{M}+\text{Na}]^+$.

(3S,5R)-3,5-Bis(tert-butyl dimethylsilyloxy)decan-1-ol (10). To a solution of **9** (2.3 g, 4.27 mmol) in aq. CH_2Cl_2 (20 mL, 19:1), DDQ (1.16 g, 5.13 mmol) was added and stirred at room temperature for 3 h. The reaction mixture was quenched with sat. NaHCO_3 solution (30 mL), filtered and washed with CH_2Cl_2 (50 mL). The filtrate was washed with water (30 mL), brine (30 mL), dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by column chromatography (60-120 Silica gel, 15% EtOAc in pet. ether) to furnish **10** (1.39 g, 78%). $[\alpha]_D$ -57.4 (c 0.76, CHCl_3); ^1H NMR (CDCl_3 , 300 MHz): δ 3.72-3.61 (m, 2H), 3.57 (br s, 1H, $-\text{OH}$), 3.47 (m, 1H), 3.41 (m, 1H), 1.82-1.66 (m, 8H, 4 x CH_2), 1.39-1.21 (m, 2H, $-\text{CH}_2$), 1.19-1.11 (m, 2H, $-\text{CH}_2$), 0.87 (t, 3H, J 5.8 Hz, $-\text{CH}_3$), 0.81 (s, 9H, *t*-butyl), 0.79 (s, 9H, *t*-butyl), 0.07 (s, 6H, 2 x $-\text{CH}_3$), 0.01 (s, 6H, 2 x $-\text{CH}_3$); ^{13}C NMR (75 MHz, CDCl_3): δ 70.3, 69.0, 61.3, 46.3, 38.3, 35.2, 32.3, 26.3, 26.1, 25.3, 23.1, 19.1, 14.0, -4.4, -4.7; HRMS (ESI): m/z calcd for $\text{C}_{22}\text{H}_{50}\text{O}_3\text{NaSi}_2$: 441.3196; found: 441.3199 $[\text{M}+\text{Na}]^+$.

(3R,5R)-3,5-Bis(tert-butyl dimethylsilyloxy)decanoic acid (11). To a stirred solution of **10** (1.20 g, 2.87 mmol) in CH_2Cl_2 : H_2O (1:1, 10 mL), TEMPO (0.15 g, 0.97 mmol) and BIAB (2.77 g, 8.61 mmol) were added at 0 °C and stirred for 1 h. The reaction mixture was diluted with water (5 mL) and extracted with CH_2Cl_2 (2 x 20 mL). The organic layers were washed with brine (10 mL), dried (Na_2SO_4), evaporated and the residue purified by column chromatography (silica gel, 60-120 mesh, 20% EtOAc in pet. ether) to give acid **11** (0.88 g, 71%) as a colorless gummy oil. $[\alpha]_D$ -7.4 (c 0.9, CHCl_3). ^1H NMR (CDCl_3 , 300 MHz): δ 4.26-4.22 (m, 1 H); 3.73-3.67 (m, 1 H); 2.59 (dd, J 15.0, 5.0 Hz, 1 H); 2.45 (dd, J 15.0, 6.8 Hz, 1 H); 1.78-1.55 (m, 2 H); 1.45-1.12 (m, 8 H); 0.91 (t, 3H, J 7.1 Hz, $-\text{CH}_3$), 0.81 (s, 9H, *t*-butyl), 0.79 (s, 9H, *t*-butyl); 0.07 (s, 6 H); 0.04 (s, 6H). ^{13}C NMR (75 MHz, CDCl_3): δ 176.9, 69.3, 66.8, 44.4, 42.1, 37.3, 32.1, 29.8, 25.8, 25.7, 24.6, 22.6, 17.9, 17.8, 14.0, -4.2, -4.5, -4.8; HRMS (ESI): m/z calcd for $\text{C}_{22}\text{H}_{48}\text{O}_4\text{NaSi}_2$: 455.2989; found: 455.2994 $[\text{M}+\text{Na}]^+$.

(3R,5R)-3,5-Dihydroxydecanoic acid (2). To a cooled (0 °C) solution of **11** (0.72 g, 1.66 mmol) in dry THF (5 mL) under nitrogen atmosphere, TBAF (4.2 mL, 4.2 mmol) was added and stirred for 3 h. After completion of reaction, reaction mixture was diluted with water (5 mL) and extracted with ethyl acetate (2 x 20 mL). Organic layers were washed with water (2 x 10 mL), brine (10 mL), dried (Na_2SO_4), evaporated and purified the residue by column chromatography to give **2** (0.26 g, 78%) as semisolid which was directly used for next reaction without any purification.

Verbalactone (1). To a stirred solution of **2** (0.26 g, 1.27 mmol) and Et_3N (0.53 mL, 3.81 mmol) in dry THF (2 mL), a solution of 2, 4, 6-trichlorobenzoyl chloride (0.30 mL, 1.91 mmol) in dry THF (1 mL) was added. The resulting mixture was stirred for 2 h at room temperature under nitrogen atmosphere and evaporated to afford the mixed anhydride. It was diluted with toluene (10 mL) and filtered quickly through celite. The filtrate was added drop wise to a stirred solution of DMAP (1.54 g, 12.7 mmol) in toluene (35 mL) at 90 °C over a period of 6 h. After the complete addition, the reaction mixture was stirred at 100 °C for 2 h. It was cooled, washed with 7% aq NaHCO_3 (40 mL), 2M aqueous HCl (40 mL), brine (40 mL) and dried (Na_2SO_4). The organic layer was evaporated and the obtained residue purified by column chromatography (60-120 Silica gel, 15% EtOAc in pet. ether) to give **1** (0.13 g, 57%) as a syrup. $[\alpha]_D$ $+10.1$ (c 1.1, CHCl_3). ^1H -NMR (CDCl_3 , 300 MHz): δ 4.97-4.90 (m, 2 H, 2 x $-\text{CH}$); 4.11-4.04 (m, 2 H, 2 x $-\text{CH}$); 3.73 (br s, 2 x OH); 2.71 (d, 4 H, J 3.1 Hz, 2 x $-\text{CH}_2$); 2.04 (ddd, 2 H, J 15.3, 10.2, 3.1 Hz, 2 x $-\text{CH}$); 1.98 (td, 2 H, J 4.0, 15.0 Hz, 2 x $-\text{CH}$); 1.69-1.39 (m, 4 H, 2 x $-\text{CH}_2$); 1.37-

1.20 (m, 12 H, 6 x CH₂); 0.85 (t, 6H, *J* 6.3 Hz, 2 x –CH₃). ¹³CNMR (CDCl₃, 75 MHz): δ 173.1, 72.7, 64.9, 39.3, 38.1, 31.6, 31.5, 25.4, 22.5, 14.3; HRMS (ESI): *m/z* calcd for C₂₀H₃₆O₆Na: 395.2410; found: 395.2414 [M+Na]⁺.

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Supplementary Material

Copies of ¹H and ¹³C NMR spectra associated with this paper can be found in the online version.

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