

Synthesis of 3,5-dihydroxy-2,4-dimethylheptanoic acid δ -lactone in enantiomerically pure form

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The paper is dedicated to Dr. A. V. Rama Rao on the occasion of his 70th birthday

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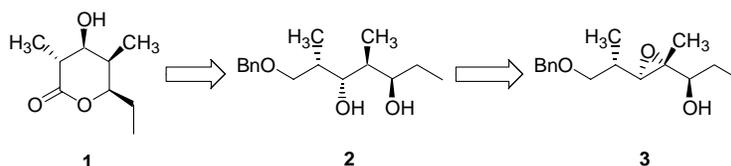
Abstract

Radical-mediated opening of a chiral trisubstituted epoxy alcohol using cp_2TiCl was followed by diastereoselective reduction of the resulting olefinic diol to build all the chiral centers of 3,5-dihydroxy-2,4-dimethylheptanoic acid δ -lactone **1** in their desired stereochemistries leading to the total synthesis of this highly substituted δ -lactone.

Keywords: 3,5-Dihydroxy-2,4-dimethylheptanoic acid, δ -lactone, Sharpless kinetic resolution, epoxide opening; 2-methyl-1,3-diol

Introduction

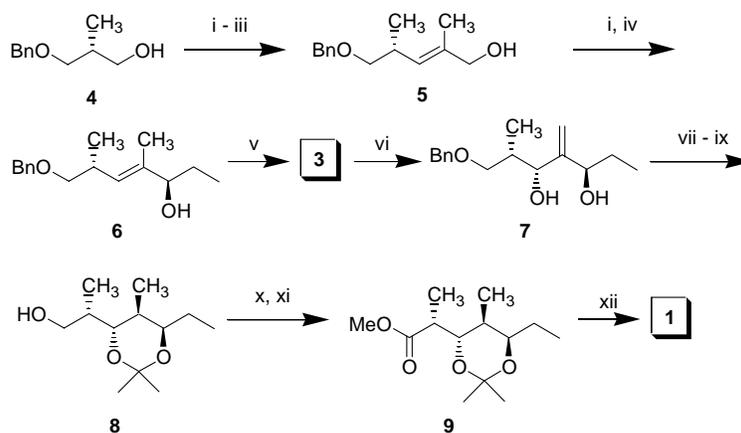
The 14-membered polyketide-derived macrolide antibiotic, erythromycin, produced by *Saccharopolyspora erythraea*, is used to treat infections caused by Gram-positive bacteria.¹ It is composed of a 14-membered macrolactone ring, to which are attached two deoxysugars. During the biosynthesis of erythromycin, synthesis of the macrolactone ring occurs first, which involves the intermediate formation of 3,5-dihydroxy-2,4-dimethylheptanoic acid δ -lactone **1**.¹ The discovery of this type of molecule supports the widely accepted hypothesis of step by step functionalization of the growing polyketide chains in the biosynthesis of macrolides.² A general strategy for the synthesis of this type of lactone will help to prepare material for use as standards during the mechanistic studies of the polyketide synthases and related biological studies.³



Enantiomerically pure 1,3-diols like, for example, compound **2**, are useful chiral building blocks in the synthesis of various naturally occurring macrolide antibiotics having polypropionate chain structures.⁴ We envisioned that this type of chiral building block could be obtained from trisubstituted epoxy alcohol **3** by radical mediated anti-Markovnikov opening at the more substituted carbon, using cp_2TiCl , a method developed by us earlier^{5,6} and used in the synthesis of many polyketide natural products. In this paper, we describe the synthesis of 3,5-dihydroxy-2,4-dimethylheptanoic acid δ -lactone **1**,⁷ a triketide product, previously isolated from a mutant *S. erythraea* strain,¹ utilizing the chiral building block **2** as the precursor.

Results and Discussion

The actual synthesis is outlined in scheme 1. Starting with (2*R*)-3-benzyloxy-2-methyl-1-propanol **4**,⁸ the allylic alcohol **5**⁹ was prepared in three steps in 80% overall yield – Swern oxidation¹⁰ of **4** to an aldehyde, a three-carbon stabilized Wittig olefination to give exclusively the *E*-isomer of the α,β -unsaturated ester intermediate and finally reduction of the ester group with LiAlH_4 . Swern oxidation of **5** was followed by Grignard addition with ethylmagnesium bromide to give the required isomer **6** in 60% yield. The other unwanted diastereoisomer could be separated easily by silica gel column chromatographically and the stereochemistry of the required allylic alcohol **6** was confirmed by Sharpless kinetic resolution of the mixture of allylic alcohols obtained in the Grignard addition step.¹¹ As the diastereomers could be separated at the allylic alcohol stage itself, the purified diastereomer **6** was used for the Sharpless epoxidation reaction to get the chiral epoxide **3** in 70% yield. With the trisubstituted chiral epoxide **3** in hand, the stage was now set to carry out the radical-mediated ring opening reaction. However, treatment of **3** with cp_2TiCl , generated in situ according to the procedure reported earlier,^{5,6} did not give the desired 2-methyl-1,3-diol moiety and instead it gave exclusively a β -hydride elimination product **7** in 70% yield. The formation of such olefins during Ti(III)-mediated epoxide opening reaction has been observed earlier by us in certain sterically hindered substrates^{4b,12,13} and also by others.¹⁴



Scheme 1. i) Swern oxidation (ref. 9); ii) $\text{Ph}_3\text{P}=\text{C}(\text{CH}_3)\text{CO}_2\text{Et}$, CH_2Cl_2 , rt, 12 h; iii) LiAlH_4 , Et_2O , $0\text{ }^\circ\text{C}$, 5 min; iv) EtMgBr , Et_2O , $0\text{ }^\circ\text{C}$, 15 min; v) $\text{Ti}(\text{O}^i\text{Pr})_4$, (-)-DET, TBHP (3.64 M in Toluene), CH_2Cl_2 , $-23\text{ }^\circ\text{C}$, 1.5 h; vi) cp_2TiCl_2 , Zn dust, THF, $-20\text{ }^\circ\text{C}$ to rt, 6 h; vii) H_2 , 10% Pd/C, *n*-BuNH₂, EtOAc, rt, 3 h; viii) 2,2-dimethoxypropane, CSA (Cat), CH_2Cl_2 , $0\text{ }^\circ\text{C}$ to rt, 1 h; ix) H_2 , 10% Pd/C, EtOAc, rt, 30 min; x) $\text{RuCl}_3 \cdot 3\text{H}_2\text{O}$, NaIO_4 , CH_3CN , CCl_4 , H_2O (1 : 1 : 1.5), $0\text{ }^\circ\text{C}$, 30 min; xi) CH_2N_2 , Et_2O , $0\text{ }^\circ\text{C}$, 5 min; xii) $\text{AcOH} - \text{H}_2\text{O}$ (4 : 1), $0\text{ }^\circ\text{C}$ to rt, 9 h.

Next, the olefin **7** was subjected to hydrogenation with H_2 using 10% Pd/C as catalyst in the presence of 0.5% *n*-BuNH₂ in EtOAc.¹⁵ This allowed the reduction of the double bond selectively keeping the *O*-Bn moiety intact to furnish the diol intermediate. This was necessary to avoid the formation of any triol, which would have complicated the subsequent acetonide protection step. Acetonide protection of the diol was followed by debenylation to yield the desired primary alcohols **8** as the major product with 30% overall yield from **7** in three steps. The diastereomers (3:2 ratio, determined by ¹H NMR method) could be separated at this stage. The ¹³C NMR spectra of the major isomer **8** showed that the *gem* dimethyls of the acetonide ring resonated at δ 23.67 and 25.04 and the ketal carbon at δ 100.39, proving *anti*-relationship between the 1,3-hydroxyls with a twist boat conformation of the acetonide.¹⁶ However, the stereochemistry at the C2' position in the acetonide **8** was still not known. The coupling constants between C1'-H and C2'-H, and between C2'-H and C3'-H could be used to assign the stereochemistry of C2'-CH₃.¹⁷ But, the very close proximity of the protons attached to C1' and C3', which were also coupled to too many protons, made it very difficult to derive the desired coupling constants by decoupling experiments. The same difficulty was also encountered for compound **9**. It was, therefore, decided to transform the acetonide **8** and its C2'-CH₃ isomer, separately, into their corresponding lactones, as one of them was expected to furnish the target molecule.

Thus, the major isomer **8** was subjected to oxidation with $\text{RuCl}_3 \cdot 3\text{H}_2\text{O}$ and NaIO_4 to acid followed by esterification with CH_2N_2 to furnish the methyl ester **9** in 40% yield. Acid treatment of the ester **9** deprotected its acetonide ring with concomitant cyclization furnishing the targeted lactone **1** in 70% yield.¹⁸ Our synthetic δ -lactone **1** showed rotation $[\alpha]_D^{22} +108^\circ$ (*c* 0.21, CHCl_3)

almost matching with the reported one $[\alpha]_D +114^\circ$ (c 1.33, CHCl_3).⁷ Furthermore, the spectroscopic data, namely NMR, IR and mass spectra of our synthetic product were in conformity with those published earlier.⁷

In conclusion the total synthesis described here for the synthesis of the δ -lactone **1** will help to prepare it and other similar molecules in sufficient quantities to be used as standards during the mechanistic studies of the biosynthesis of polyketides.

Experimental Section

General Procedures. All reactions were carried out in oven or flame-dried glassware with magnetic stirring under nitrogen atmosphere using dry, freshly distilled solvents, unless otherwise noted. Reactions were monitored by thin layer chromatography (TLC) carried out on 0.25 mm silica gel plates with UV light, I_2 , 7% ethanolic phosphomolybdic acid-heat and 2.5% ethanolic anisaldehyde (with 1% AcOH and 3.3% conc. H_2SO_4)-heat as developing agents. Silica gel finer than 200 mesh was used for flash column chromatography. Yields refer to chromatographically and spectroscopically homogeneous materials unless otherwise stated. IR spectra were recorded as neat liquids or KBr pellets. NMR spectra were recorded on 200, 300 and 400 MHz spectrometers at room temperature of $\sim 21^\circ\text{C}$ in CDCl_3 using tetramethylsilane as internal standard or the solvent signal as secondary standard and the chemical shifts are shown in δ scales. Multiplicities of NMR signals are designated as s (singlet), d (doublet), t (triplet), q (quartet), br (broad), m (multiplet, for unresolved lines), etc. ^{13}C NMR spectra were recorded with complete proton decoupling. Mass spectra were obtained under electron impact (EI), electron spray ionisation (ESI) and liquid secondary ion mass spectrometric (LSIMS) techniques.

Synthesis of 5. To a stirred solution of oxalyl chloride (5.2 mL, 59.1 mmol) in dry CH_2Cl_2 (220 mL) at -78°C , DMSO (9 mL, 126.1 mmol) was added drop-wise with stirring under N_2 atmosphere. After 15 min, 3-benzyloxy-2-methyl-(2*R*)-propan-1-ol **4** (7.1 g, 39.4 mmol) in dry CH_2Cl_2 (20 mL) was added to the reaction mixture. After 30 min of stirring at -78°C , Et_3N (27.5 mL, 197 mmol) was added and stirred at the same temperature for another 30 min. Reaction mixture was quenched with saturated aqueous NH_4Cl solution and extracted with CH_2Cl_2 . The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated in *vacuo*. The crude aldehyde was used in the next step with further purification.

To the stirred solution of the crude aldehyde in CH_2Cl_2 (150 mL), $\text{Ph}_3\text{P}=\text{C}(\text{CH}_3)\text{CO}_2\text{Et}$ (21.3 g, 59.1 mmol) was added at room temperature under nitrogen atmosphere. After 12 h the reaction mixture was concentrated and chromatographed (SiO_2 , 4-6% EtOAc in petroleum ether eluant) to give the α,β -unsaturated ester intermediate that was used directly in the next step.

The α,β -unsaturated ester was taken in dry ether (150 mL), cooled to 0°C and LiAlH_4 (748 mg, 19.7 mmol) was added portion wise with stirring and the reaction mixture was then stirred at that temperature for 5 min. The reaction was quenched with saturated aqueous Na_2SO_4 (50 mL) at 0°C

and stirred for another 15 min. The precipitated solid was filtered through a short pad of celite and the filter cake was washed with ether. The filtrate and washings were combined and washed with brine, dried (Na_2SO_4), filtered and concentrated in *vacuo*. Column chromatography (SiO_2 , 35-40% EtOAc in petroleum ether eluant) of the residue provided the pure allylic alcohol **5** (6.93 g, 80%) as colorless liquid. Data for **5**: $R_f = 0.3$ (silica gel, 50% EtOAc in Petroleum ether); $[\alpha]_D^{22} = -16.7$ (c 0.77, CHCl_3); IR (neat): ν_{max} 3400, 3050, 2850, 2000, 1690, 1470, 1370, 1225, 1050, 900, 730, 690 cm^{-1} ; ^1H NMR (200 MHz, CDCl_3 , atom numbering starting from right): δ 7.28 (m, 5H, aromatic protons), 5.2 (d, $J = 8.92$ Hz, 1H, $\text{C}_3 - \text{H}$), 4.47 (s, 2H, benzylic protons), 3.94 (s, 2H, $\text{C}_1 - \text{H}_2$), 3.29 and 3.23 (two dd, $J = 6.69, 8.92$ Hz, 2H, $\text{C}_5 - \text{H}_2$), 2.72 (m, 1H, $\text{C}_4 - \text{H}$), 1.68 (s, 3H, $\text{C}_2 - \text{CH}_3$), 0.99 (d, $J = 6.69$ Hz, 3H, $\text{C}_4 - \text{CH}_3$); ^{13}C NMR (75 MHz, CDCl_3): δ 138.43, 135.33, 128.44, 128.24, 127.45, 75.08, 72.82, 68.47, 32.56, 17.49, 13.81; Mass (EI): m/z 220 $[\text{M}]^+$.

Synthesis of 6. To a stirred solution of oxalyl chloride (3.6 mL, 40.9 mmol) in dry CH_2Cl_2 (130 mL) at -78 °C, DMSO (6.2 mL, 87.3 mmol) was added drop-wise with stirring under N_2 atmosphere. After 15 min, allylic alcohol **5** (6 g, 27.3 mmol) in dry CH_2Cl_2 (25 mL) was added to the reaction mixture. After 30 min of stirring at -78 °C, Et_3N (19 mL, 136.5 mmol) was added and stirred at the same temperature for another 30 min. Reaction mixture was quenched with saturated aqueous NH_4Cl solution and extracted with CH_2Cl_2 . The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated in *vacuo*. The crude aldehyde was used in the next step with further purification.

To the stirred solution of crude aldehyde in Et_2O (100 mL), at 0 °C, EtMgBr (21 mL, 2M in THF, 41 mmol) was added drop-wise under N_2 atmosphere. After stirring at the same temperature for 1 h, the reaction mixture was quenched with saturated aqueous NH_4Cl solution, and extracted with ether. The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated in *vacuo*. Column chromatography (SiO_2 , 8-12% EtOAc in petroleum ether eluant) of the residue provided the pure secondary allylic alcohol **6** (4.1g, 60%) as colorless liquid. Data for **6**: $R_f = 0.45$ (silica gel, 20% EtOAc in Petroleum ether); $[\alpha]_D^{22} = -21.04$ (c 0.48, CHCl_3); IR (neat): ν_{max} 3450, 2850, 2000, 1460, 1360, 1325, 1225, 1090, 1000, 875 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3 , atom numbering starting from right): δ 7.28 (m, 5H, aromatic protons), 5.17 (d, $J = 9.44$ Hz, 1H, $\text{C}_5 - \text{H}$), 4.46 (s, 2H, benzylic protons), 3.86 (t, $J = 6.8$ Hz, 1H, $\text{C}_3 - \text{H}$), 3.27 (dd, $J = 6.6, 7.9$ Hz, 1H, $\text{C}_7 - \text{H}$), 3.23 (dd, $J = 6.6, 9.0$ Hz, 1H, $\text{C}_7 - \text{H}'$), 2.72 (m, 1H, $\text{C}_6 - \text{H}$), 1.53 (m, 2H, $\text{C}_2 - \text{H}_2$), 1.25 (s, 3H, $\text{C}_4 - \text{CH}_3$), 1.0 (d, $J = 6.8$ Hz, 3H, $\text{C}_6 - \text{CH}_3$), 0.84 (t, $J = 7.55$ Hz, 3H, $\text{C}_1 - \text{H}_3$); ^{13}C NMR (75 MHz, CDCl_3): δ 138.57, 137.36, 129.41, 128.21, 127.41, 79.13, 75.16, 72.86, 32.58, 27.47, 17.54, 11.24, 9.93; Mass (ESI): m/z 271 $[\text{M} + \text{Na}]^+$, 231 $[\text{M} - \text{H}_2\text{O} + \text{H}]^+$.

Synthesis of 3. Activated powdered 4Å molecular sieve (800 mg, 20 wt%) in CH_2Cl_2 (60 mL) were taken in a flame dried 25 mL round bottom flask under nitrogen atmosphere. After cooling to -23 °C, a solution of (–)-DET (3.3 mL, 19.3 mmol) in CH_2Cl_2 (1 mL) and a solution of $\text{Ti}(\text{O}^i\text{Pr})_4$ (4.8 mL, 16.1 mmol) in CH_2Cl_2 (1 mL), each separately stirred, prior to the addition, with 4Å molecular sieve (5 mg) for 15 min, were cannulated sequentially into the reaction flask

with stirring. After 20 min, a solution of allylic alcohol **6** (4 g, 16.1 mmol) in CH₂Cl₂ (15 mL) was added, followed after 30 min by the addition of TBHP (4.4 mL, 3.64 M in Toluene, 16.1 mmol) at the same temperature. The stirring was continued for another 2 h and was quenched with H₂O (140 mL) and the temperature was allowed to rise to 0 °C. An aqueous solution of NaOH (20 mL, 30%) saturated with NaCl was added to the reaction mixture and stirred for 30 min. CH₂Cl₂ was evaporated under reduced pressure and the aqueous phase was extracted with Et₂O and the combined organic extracts were washed with brine, dried (Na₂SO₄), filtered and concentrated in *vacuo*. Purification by column chromatography (SiO₂, 13-20% EtOAc in Petroleum ether eluant) afforded pure epoxy alcohol **3** (3 g, 70%) as colorless oil. Data for **3**: R_f = 0.45 (silica gel, 25% EtOAc in Petroleum ether); $[\alpha]_D^{22} = +16.9$ (*c* 0.42, CHCl₃); IR (neat): ν_{\max} 3450, 3050, 2850, 2000, 1450, 1350, 1225, 1190, 1010, 900, 725 cm⁻¹; ¹H NMR (200 MHz, CDCl₃, atom numbering starting from right): δ 7.25 (m, 5H, aromatic protons), 4.45 (s, 2H, benzylic protons), 3.49-3.26 (m, 3H, C₃-H and C₇-H₂), 2.76 (d, *J* = 9.66 Hz, 1H, C₅-H), 1.99 (bs, 1H, OH), 1.81 (m, 1H, C₆-H), 1.53 (m, 2H, C₂-H₂), 1.25 (s, 3H, C₄-CH₃), 1.0 (d, *J* = 6.69 Hz, 3H, C₆-CH₃), 0.95 (t, *J* = 7.43 Hz, 3H, C₁-H₃); ¹³C NMR (75 MHz, CDCl₃): δ 138.08, 128.22, 127.50, 74.00, 73.23, 72.92, 63.69, 63.10, 33.05, 25.42, 15.12, 14.55, 9.90; Mass (LSIMS): *m/z* 265 [M + H]⁺.

Synthesis of 7. Freshly activated and dried Zn powder (5 g, 76 mmol) was added at room temperature under nitrogen atmosphere to a vigorously stirred solution of cp₂TiCl₂ (9.4 g, 38 mmol) in dry THF (120 mL). The mixture was stirred for 45 min at room temperature while the color of the solution turned from red to green. It was cooled to -18 °C and a solution of epoxy alcohol **3** (2 g, 7.6 mmol) in dry THF (20 mL) was slowly added. The reaction mixture was allowed to attain the room temperature over a period of 2 h and the stirring was continued for an additional 4 h. Reaction mixture was then re-cooled to 0 °C and quenched by adding 1N HCl (30 mL) and stirred at 0 °C for 1h. THF was evaporated under reduced pressure and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with 1N HCl, H₂O, 10% NaHCO₃ solution, brine, dried (Na₂SO₄), filtered and concentrated in *vacuo*. Purification by column chromatography (SiO₂, 25-30% EtOAc in Petroleum ether eluant) afforded the pure olefinic diol **7** (1.4 g, 70%) as colorless oil. Data for **7**: R_f = 0.3 (silica gel, 40% EtOAc in Petroleum ether); $[\alpha]_D^{22} = +18.4$ (*c* 1.45, CHCl₃); IR (neat): ν_{\max} 3450, 1770, 1690, 1650, 1500, 1400, 1250, 1125, 1050, 1025, 795, 750 cm⁻¹; ¹H NMR (200 MHz, CDCl₃, atom numbering starting from right): δ 7.28 (m, 5H, aromatic protons), 5.13 (s, 1H, olefinic proton), 5.07 (s, 1H, olefinic proton), 4.49 (s, 2H, benzylic protons), 4.35 (d, *J* = 3.72 Hz, 1H, C₅-H), 3.96 (t, *J* = 6.69 Hz, 1H, C₃-H), 3.5 (d, *J* = 5.2 Hz, 2H, C₇-H₂), 2.8 (bs, 1H, OH), 2.36 (bs, 1H, OH), 2.0 (m, 1H, C₆-H), 1.64 (m, 2H, C₂-H₂), 0.98 (d, *J* = 6.69 Hz, 3H, C₆-CH₃), 0.91 (t, *J* = 7.43 Hz, 3H, C₁-H₃); ¹³C NMR (75 MHz, CDCl₃): δ 151.95, 138.39, 128.85, 128.14, 128.02, 111.26, 75.35, 74.94, 74.76, 73.79, 37.69, 29.31, 11.37, 10.60; Mass (ESI): *m/z* 287 [M + Na + H]⁺, 265 [M + H]⁺, 247 [M - H₂O + H]⁺.

Synthesis of 8. The olefinic diol intermediate **7** (1.3 g, 4.9 mmol) was dissolved in EtOAc (10 mL) containing 0.05 mL of *n*-BuNH₂. To that solution, 10% Pd-C (50 mg) was added with stirring

and subjected to hydrogenation under atmospheric pressure using a hydrogen-filled balloon. After 3 h, the reaction mixture was filtered through a short Celite pad and the filter cake was washed with EtOAc. The filtrate and the washings were combined and concentrated in *vacuo*. Purification by column chromatography (SiO₂, 25-27% EtOAc in petroleum ether eluant) provided the saturated diol intermediate as colorless liquid that was used in the next step directly.

2,2-dimethoxy propane (2.4 mL, 19.6 mmol) and CSA (58 mg, 0.25 mmol) were added to a stirred solution of the intermediate from the previous step in CH₂Cl₂ (10 mL) at 0 °C. Temperature was allowed to rise to room temperature and stirring continued for another 2 h. It was then quenched with saturated aqueous NaHCO₃ solution and extracted with CH₂Cl₂. The organic extracts were washed with brine, dried (Na₂SO₄), filtered and concentrated in *vacuo*. The residue was chromatographed (SiO₂, 5% EtOAc in petroleum ether eluant) to give the acetonide intermediate that was used in the next step directly.

To the acetonide prepared above and dissolved in EtOAc (10 mL), 10% Pd-C (50 mg) was added with stirring and subjected to hydrogenation under atmospheric pressure using a hydrogen-filled balloon. After 1 h, the reaction mixture was filtered through a short Celite pad and the filter cake was washed with EtOAc. The filtrate and the washings were combined and concentrated in *vacuo*. Column chromatography (SiO₂, 20-25% EtOAc in petroleum ether eluant) of the residue provided pure primary alcohol **8** (317 mg, 30%) as colorless liquid. Data for **8**: $R_f = 0.3$ (silica gel, 40% EtOAc in Petroleum ether); $[\alpha]_D^{22} = -5.45$ (*c* 0.22, CHCl₃); IR (neat): ν_{\max} 3450, 1500, 1400, 1240, 1200, 1125, 1050, 1020, 800, 750 cm⁻¹; ¹H NMR (300 MHz, CDCl₃, atom numbering starting from left): δ 3.65-3.59 (m, 3H, C₁ - H₂ and C₅ - H), 3.48 (dd, *J* = 7.55, 3.02 Hz, 1H, C₃ - H), 2.19 (bs, 1H, OH), 1.88-1.77 (m, 2H, C₂ - H and C₄ - H), 1.49-1.35 (m, 2H, C₆ - H₂), 1.33 (s, 3H, acetonide methyl), 1.3 (s, 3H, acetonide methyl), 0.97 (d, *J* = 6.8 Hz, 3H, C₂ - CH₃), 0.92 (t, *J* = 7.55 Hz, 3H, C₇ - H₃), 0.82 (d, *J* = 6.8 Hz, 3H, C₄ - CH₃); ¹³C NMR (75 MHz, CDCl₃): δ 100.39, 77.42, 71.21, 67.07, 37.39, 35.64, 25.04, 23.67, 23.54, 12.11, 10.64, 10.46; Mass (ESI): *m/z* 217 [M + H]⁺, 199 [M - H₂O + H]⁺.

Synthesis of 9. To a mixture of CH₃CN (1 mL), CCl₄ (1 mL), and H₂O (1.5 mL) at room temperature, NaIO₄ (385 mg, 1.8 mmol) was added followed by RuCl₃.H₂O (0.02 mg, 0.6 × 10⁻⁴ mmol) at the room temperature with stirring. After being stirred at room temperature for 30 min, the reagent mixture was added to the alcohol **8** (120 mg, 0.6 mmol) in CH₃CN (2 mL) with stirring at 0 °C. After 30 min at 0 °C, the reaction mixture was taken in a separating funnel with ethyl acetate. The organic layer was washed with water, brine, dried (Na₂SO₄), filtered and concentrated in *vacuo*. The crude acid was used in the next step without further purification.

The crude acid, dissolved in 4 mL of ether, was cooled to 0 °C and an ethereal solution of CH₂N₂ was added till yellow color persisted. After 5 min at 0 °C, solvent was evaporated and the residue was chromatographed (SiO₂, 4% EtOAc in petroleum ether eluant) to afford compound **9** (59 mg, 40%) as colorless oil. Data for **9**: $R_f = 0.4$ (silica gel, 10%EtOAc in Petroleum ether); $[\alpha]_D^{22} = -9.02$ (*c* 0.20, CHCl₃); IR (neat): ν_{\max} 1725, 1500, 1400, 1230, 1200, 1180, 1050, 1020, 925 cm⁻¹; ¹H NMR (200 MHz, CDCl₃, atom numbering starting from left): δ 3.68 (s, 3H, methoxy), 3.65-3.55 (m, 2H, C₃ - H and C₅ - H), 2.52 (dq, *J* = 6.69, 5.2 Hz 1H, C₂ - H), 1.81

(m, 1H, C₄ - H), 1.43 (m, 2H, C₆ - H₂), 1.28 (s, 6H, acetonide methyls), 1.18 (d, *J* = 6.69 Hz, 3H, C₂ - CH₃), 0.91 (t, *J* = 7.43 Hz, 3H, C₇ - H₃), 0.81 (d, *J* = 7.43 Hz, 3H, C₄ - CH₃); ¹³C NMR (75 MHz, CDCl₃): δ 174.92, 100.53, 75.41, 70.91, 51.62, 42.97, 36.55, 24.89, 23.64, 23.55, 11.87, 11.44, 10.49; Mass (ESI): *m/z* 245 [M + H]⁺.

Synthesis of 1. Ester **9** (30 mg, 0.12 mmol) was treated with 5 mL of AcOH-H₂O (4:1) mixture at 0 °C and stirred at room temperature for 9 h. Acetic acid and water were evaporated under reduced pressure and column chromatography (SiO₂, 50-70% EtOAc in petroleum ether eluant) of the residue afforded the desired lactone **1** (14.4 mg, 70%) as colorless liquid. Data for **1**: *R*_f = 0.3 (silica, 50% EtOAc in petroleum ether); [*α*]_D²² = +108° (*c* 0.21, CHCl₃); IR (neat): ν_{max} 3444, 2973, 2926, 2884, 1730, 1714, 1462, 1360, 1292, 1221, 1111, 1056, 1024, 982, 848, 813, 787, 718, 675, 666, 618, 576 cm⁻¹; ¹H NMR (300 MHz, CDCl₃, atom numbering starting clockwise from pyran oxygen): δ 4.09 (ddd, *J* = 7.93, 6.04, 2.27 Hz, 1H, C₆ - H), 3.76 (dd, *J* = 10.39, 4.34 Hz, 1H, C₄ - H), 2.41 (dq, *J* = 10.58, 7.18 Hz, 1H, C₃ - H), 2.19 (bs, 1H, OH), 2.12 (ddq, *J* = 7.18, 4.53, 2.67 Hz, 1H, C₅ - H), 1.89-1.74 (m, 1H, C₇ - H), 1.62-1.48 (m, 1H, C₇ - H'), 1.37 (d, *J* = 6.8 Hz, 3H, C₃ - CH₃), 1.02 (t, *J* = 7.55 Hz, 3H, C₇ - H₃), 0.95 (d, *J* = 7.18 Hz, 3H, C₅ - CH₃); ¹³C NMR (75 MHz, CDCl₃): δ 173.78, 81.46, 73.90, 39.93, 36.81, 25.26, 14.29, 9.78, 4.33; Mass (LSIMS): *m/z* 173 [M + H]⁺.

[Supplementary information](#)

The ¹³C NMR spectra of compounds **1**, **3**, **5-9** are provided.

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References and Notes

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 18. All the new compounds were characterized by ^1H NMR, ^{13}C NMR, IR, mass spectroscopic analysis.