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Stereoselective total synthesis of polyketide lactone, (3*R*,4*S*,5*S*,9*S*)-3,5,9-trihydroxy-4-methylundecanoic acid δ-lactone

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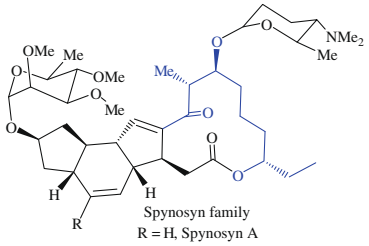
ABSTRACT

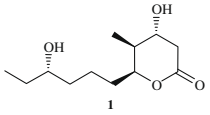
The total synthesis of lactone **1** has been described. The convergent asymmetric synthesis relies on the use of an Evans' *syn*-aldol, chain extension with lithio *tert*-butyl acetate, and the stereoselective reduction of a ketone as the key reactions.

1. Introduction

During the studies of the biosynthesis of spinosyns, a family of new insect control agents,[1] a truncated version of the spinosyn polyketide synthase was expressed in the heterologous host *Saccharopolyspora erythraea* JC2.[2] This resulted in the formation of a novel pentaketide lactone, which was identified as (3*R*,4*S*,5*S*,9*S*)-3,5,9-trihydroxy-4-methyl undecanoic acid δ-lactone **1**. The discovery of this molecule helped in understanding the crucial steps of spinosyn biosynthesis,[2] which supported the widely accepted hypothesis of the step by step functionalization of the growing polyketide chain in the biosynthesis of macrolides.[3] However, to date, only two syntheses[4,5] of lactone **1** have been described. An efficient and enantioselective synthesis of lactone **1** is essential for providing further material for biological and mechanistic studies. As part of our ongoing project on the synthesis of bio-active lactones,[6] compound **1** attracted our interest because of its structure. Herein, we report a shorter and facile total synthesis of lactone **1** featuring the use of reactions such as an aldol, *t*-butyl acetate addition, and a stereoselective reduction.

Retrosynthetic analysis reveals that the important key intermediate **2** could be achieved through Evans' *syn*-aldol condensation. The required fragment **5** could be obtained by three routes (see Scheme 1).





1

2. Results and discussion

The synthesis of **1** began with the preparation of **5** by three different approaches.

In route 1 (Scheme 2), the known epoxy chloride **9** was converted to alkyne diol **10** and further treated with benzyl bromide to afford benzyl ether **11** as reported earlier.[7] The secondary hydroxyl group was protected as an MOM ether **6** and deprotection of the THP, tosylation followed by lithium aluminum hydride reduction furnished the corresponding substituted alkyne **14**.

Reduction of the triple bond and removal of the benzyl ether were achieved using Pd/C, followed by oxidation of the primary hydroxyl group to the aldehyde furnished fragment **5**.

In route 2 (Scheme 3), 5-hexyne-1-ol was protected as its benzyl ether **16**, which was converted to chiral allylic alcohol **17** as reported.[8] Protection of the hydroxyl group as an MOM ether afforded **18**, which upon reduction with Pd/C gave saturated compound **15** simultaneously removing the benzyl group. Oxidation of **15** as shown in Scheme 2 afforded the required aldehyde **5**.

In route 3 (Scheme 4), 5-hexene-1-ol **19** was protected as benzyl ether **20** and subjected to epoxidation using anhydrous *m*-CPBA and sodium bicarbonate in anhydrous CH_2Cl_2 followed by quenching with saturated Na_2SO_3 to afford epoxide **21** in 96% yield. The epoxide was subjected to hydrolytic kinetic resolution (HKR)[9] using chiral Jacobsen's salen cobalt(III) acetate catalyst [(*R*,*R*)-(−)-*N*,*N*′-bis-3,5-di *tert*-butylic salicylidene)-1,2-cyclohexanediaminocobalt(III) acetate] to afford the enantioenriched (>96% ee) epoxide **8** and terminal diol in 47% yield.

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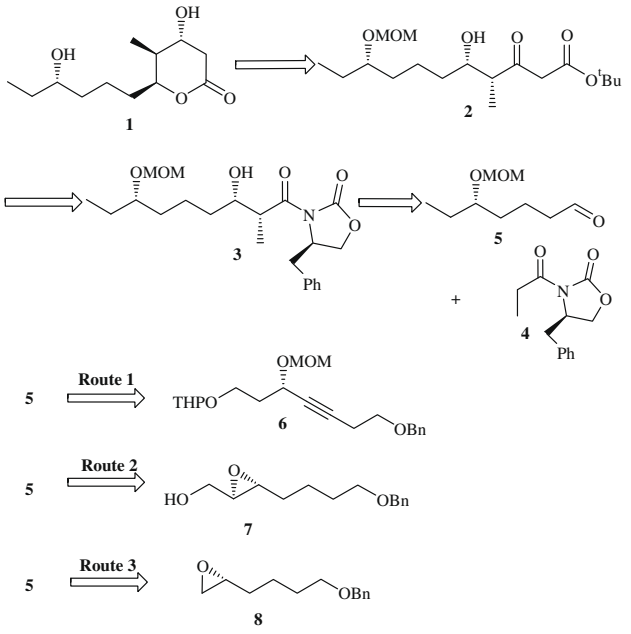
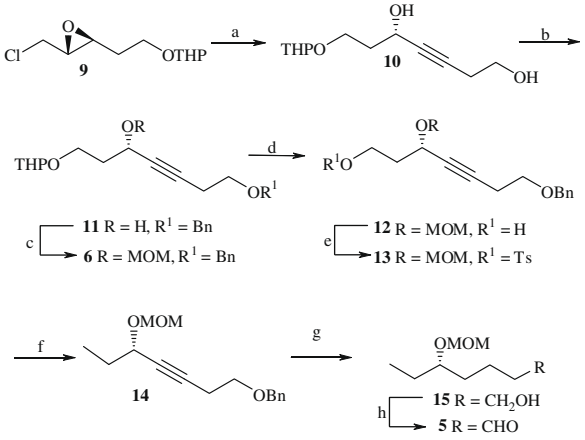
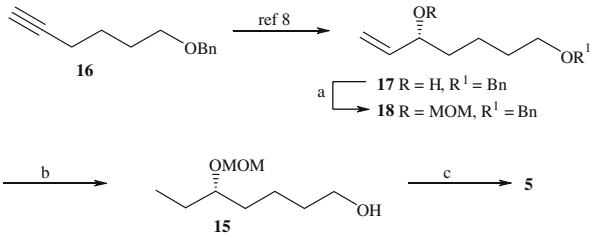


Scheme 1. Retrosynthesis.

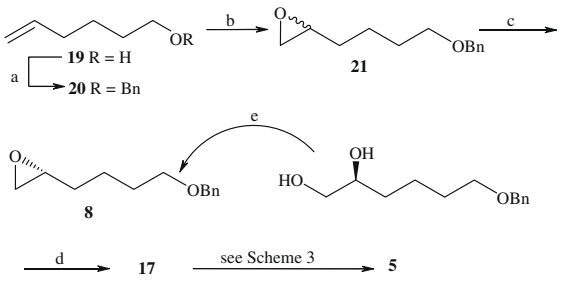


Scheme 2. Reagents and conditions: (a) Li/Liq NH_3, $Fe(NO_3)_3$, anhydrous THF, −33 °C, 2 h, then $BF_3{\cdot}Et_2O$, ethylene oxide, 6 h, 78%; (b) BnBr, NaH, anhydrous DMF, 6 h, 69%; (c) MOMCl, anhydrous CH_2Cl_2, iPr$_2$NEt, rt, 4 h, 90%; (d) PPTS, MeOH, rt, 12 h, 82%; (e) TsCl, Et_3N, anhydrous CH_2Cl_2, 0 °C–rt, 30 min, 92%; (f) LAH, anhydrous THF, 0 °C–rt, 30 min, 88%; (g) Pd/C, H_2, rt, 4 h, 97%; (h) IBX, DMSO, anhydrous CH_2Cl_2, 0 °C–rt, 2 h, 92%.



Scheme 3. Reagents and conditions: (a) MOMCl anhydrous CH_2Cl_2, iPr$_2$NEt, 0 °C–rt, 4 h, 95%; (b) Pd/C, H_2, rt, 4 h, 97%; (c) IBX, DMSO, CH_2Cl_2, 0 °C–rt, 2 h, 92%.

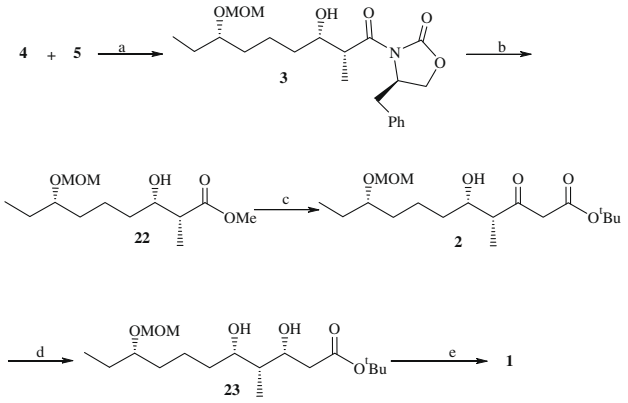
Epoxide **8** was then converted to the one carbon homologated allylic alcohol **17** by reaction with dimethyl sulfonium methylide.[10] Protection of the hydroxyl group as an MOM ether afforded



Scheme 4. Reagents and conditions: (a) BnBr, anhydrous THF, NaH, 0 °C–rt, 2 h, 93%; (b) *m*-CPBA, anhydrous CH_2Cl_2, $NaHCO_3$, 0 °C–rt, 2 h, 92%; (c) (*R*,*R*)-(−)-*N*,*N*′-Bis(3,5-di-*tert*-butylsalcylidene)-1,2cyclohexanediaminocobalt(II), 0 °C–rt, 16 h, 42%; (d) $(CH_3)_3SI$, BuLi, anhydrous THF, −10 °C–rt, 2.5 h, 84%; (e) (i) TBSCl, anhydrous CH_2Cl_2, 0 °C–rt, 2 h, 96%; (ii) TsCl, DMAP, anhydrous CH_2Cl_2, 0 °C–rt, 1 h, 91%; (iii) TBAF, anhydrous THF, 0 °C–rt, 6 h, 85%.

18. The required aldehyde **5** was prepared from **17** as discussed in Scheme 3. The spectroscopic analysis of the aldehyde **5** prepared from the three routes matched perfectly. Among the three different asymmetric routes described for **5**, the latter (route 3) was found to be the more efficient one in terms of yields and the fewer number of steps involved.

Aldehyde **5** was subjected to an Evans *syn* aldol[11] reaction with the enolate of chiral *N*-propionyl oxazolidinone **4** to give the aldol adduct **3** in higher conversion and diastereoselectivity (78%, de 98%), after chromatographic purification (Scheme 5). Replacement of the chiral auxiliary with methoxy group was carried out using a Grignard reagent.[11] Having accessed ester **22**, the subsequent reaction with lithium *tert*-butyl acetate[12] at −78 °C proceeded smoothly to provide 5-hydroxy-3-oxoester **2** in 82% yield. The reduction of the hydroxyketoester **2** with $Et_2BOMe/NaBH_4$ gave *syn* dihydroxyester **23**[13] with high diastereoselectivity (*syn:anti* = 95:5) in 78% yield.



Scheme 5. Reagents and conditions: (a) Bu_2BOTf, Et_3N, anhydrous CH_2Cl_2, −80–0 °C, 1 h, 78%; (b) EtMgBr, anhydrous THF, anhydrous MeOH–CH_2Cl_2 (1:1), 10 min., 0 °C–rt, 87%; (c) *n*-BuLi, iPr$_2$NH, anhydrous THF, *t*-BuOAc, −78 to −15 °C, 1.45 h, 82%; (d) Et_2BOMe, $NaBH_4$, anhydrous THF–MeOH (1:4), −78 °C, 6 h, 78%; (e) THF, H_2O, HCl, rt, 48 h, 75%.

Finally lactonization was accomplished by treatment of ester **23** with HCl/THF/H_2O[14] at room temperature for 48 h to give the target molecule **1** in 75% yield. The spectroscopic and physical data (^{1}H and ^{13}C NMR, IR, $[\alpha]_D^{25}$, R_f) for **1** were identical in all respects to the published data.

3. Conclusions

A facile and effective synthesis of undecanoic acid δ-lactone **1** had been achieved. A notable feature of the synthesis was the

use of reactions such as the *syn* aldol addition, *tert*-butyl acetate reaction, and ring cyclization, which represents one of the shortest asymmetric syntheses of this undecanoic acid δ-lactone.

4. Experimental

4.1. General

Reactions were carried out under N_2 in anhydrous solvents such as CH_2Cl_2, THF, and EtOAc. All reactions were monitored by TLC (silica-coated plates and visualized under UV light). Light petroleum ether (bp 60–80 °C) was used. Yields refer to chromographically and spectroscopically (^1H, ^{13}C NMR) homogeneous materials. Air-sensitive reagents were transferred by syringe or double-ended needle. Evaporation of solvents was performed at reduced pressure on a Buchi rotary evaporator. ^1H and ^{13}C NMR spectra of samples in $CDCl_3$ were recorded on Varian FT-200 MHz (Gemini) and Bruker UXNMR FT-300 MHz (Avance) spectrometers. Chemical shifts (δ) are reported relative to TMS ($\delta = 0.0$) as an internal standard. Mass spectra were recorded using E1 conditions at 70 eV on LC-MSD (Agilent technologies) spectrometers. All high resolution spectra were recorded on QSTAR XL hybrid ms/ms system (Applied Biosystems/MDS sciex, foster city, USA), equipped with an ESI source (IICT, Hyderabad). Column chromatography was performed on silica gel (60–120 mesh) supplied by Acme Chemical Co., India. TLC was performed on Merck 60 F-254 silica gel plates. Optical rotations were measured with JASCO DIP-370 Polarimeter at 25 °C.

4.1.1. (5*S*)-7-(Tetrahydro-2*H*-2-pyranyloxy)-3-heptyne-1,5-diol 10

To freshly distilled ammonia (100 mL) in a 500-mL two-necked round-bottomed flask fitted with a cold finger condenser was added a catalytic amount of $Fe(NO_3)_3$, followed by the piece-wise addition of lithium metal (3.92 g, 560.0 mmol) at −33 °C and the resulting gray colored suspension was stirred for 30 min. To this suspension chloro compound **14** (15.4 g, 70.0 mmol) in dry THF (100 mL) was added over 20 min. The reaction mixture was stirred for 2 h at −33 °C. After 2 h, the addition of catalytic amount of $BF_3{\cdot}Et_2O$ followed by ethylene oxide was carried out successively, stirred for 6 h at the same temperature, and quenched by the addition of solid NH_4Cl (20 g) and the ammonia was then allowed to evaporate. The reaction mixture was diluted with water (10 mL) and EtOAc (100 mL) and filtered on a small pad of Celite. The filtrate was extracted with EtOAc (3 × 80 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography (100% EtOAc) to afford **10** as a pale yellow-colored viscous liquid (12.44 g, 78%). $[\alpha]_D^{25} = +5.1$ (*c* 1.05, $CHCl_3$), $R_f = 0.3$ (EtOAc/hexane; 4:1); IR (neat): ν_{max} 3484, 2942, 1121, 1028, 984; ^1H NMR (300 MHz, $CDCl_3$) δ 4.60 (m, 1H, CH), 4.55 (m, 1H, CH), 3.97–3.78 (m, 2H, C*H*$_2$–O–THP), 3.69 (t, *J* = 6.0 Hz, 2H, C*H*$_2$–OH), 3.61–3.46 (m, 2H, CH_2 of THP), 2.46 (dt, *J* = 1.5, 6.0 Hz, 2H, propargylic CH_2), 1.96 (m, 2H, CH_2), 1.90–1.38 (m, 6H, 3 × CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 98.7, 82.1, 81.9, 63.9, 62.2, 61.9, 60.4, 37.2, 30.2, 25.0, 22.6, 19.2; HRMS (ESI): $[M+Na]^+$ *m/z* calcd for $C_{12}H_{20}O_4Na$: 251.1259, found: 251.1269 (+3.8663 ppm error).

4.1.2. (3*S*)-7-(Benzyloxy)-1-(tetrahydro-2*H*-2-pyranyloxy)-4-heptyn-3-ol 11

To a suspension of NaH (7.55 g, 188.81 mmol) in dry DMF (50 mL) at 0 °C was added diol **10** (12.3 g, 53.94 mmol) in DMF (20 mL) in a dropwise manner. The reaction mixture was stirred at room temperature for 30 min and again the mixture was cooled to 0 °C. After the addition of BnBr (7.0 mL, 59.34 mmol), the reaction mixture was brought to room temperature and stirred for 6 h, cooled to 0 °C, and quenched carefully with saturated NH_4Cl solution (120 mL). Then EtOAc (200 mL) was added, the organic layer was separated, washed with H_2O (3 × 50 mL) brine solution (50 mL), and dried in vacuo. Column chromatography (EtOAc/hexane 1:4) of the crude product afforded **11** (11.83 g, 69%) along with 16% recovered starting material **10**. Compound **11** was colorless oil. $R_f = 0.3$ (EtOAc/hexane, 2:3); $[\alpha]_D = -40.3$ (*c* 0.9, $CHCl_3$); IR (neat): ν_{max} 3433, 2923, 2854, 1727, 1603, 1445, 1349, 1062, 1029, 738, 697 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.45–7.22 (m, 5H, ArH), 4.83–4.41 (m, 3H, Ph–C*H*$_2$, CH of THP), 4.2 (m, 1H, CH), 3.94–3.63 (m, 2H, C*H*$_2$–O–THP), 3.69 (t, *J* = 5.87 Hz, 2H, C*H*$_2$–OBn), 3.59–3.38 (m, 2H, CH_2 of THP), 2.51 (dt, *J* = 2.2, 6.6 Hz, 2H, propargylic CH_2), 1.98 (m, 2H, CH_2), 1.86–1.38 (m, 6H, 3 × CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.9, 128.2, 127.9, 127.6, 98.9, 83.2, 80.6, 70.5, 66.2, 63.5, 62.2, 61.0, 36.1, 30.5, 25.3, 23.1, 19.4; HRMS (ESI): $[M+Na]^+$ *m/z* calcd for $C_{19}H_{26}O_4Na$: 341.1728, found: 341.1736 (+2.1124 ppm error).

4.1.3. 2-[(3*S*)-7-(Benzyloxy)-3-(methoxymethoxy)-4-heptynyl]oxytetrahydro-2*H*-pyran 6

To a solution of alcohol **11** (11.5 g, 36.16 mmol) in anhydrous CH_2Cl_2 (60 mL) at 0 °C were added iPr$_2$NEt (9.44 mL, 54.24 mmol), catalytic DMAP (10 mg), and MOMCl (3.76 mL, 47.01 mmol) successively and the mixture was stirred for 4 h at room temperature, quenched by adding water (20 mL), and extracted with CH_2Cl_2 (3 × 20 mL). The organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4 (2 g), and concentrated in vacuo. The crude residue was purified by column chromatography (EtOAc/hexane 1:19) to afford the MOM ether **6** (11.9 g, 90%) as a light yellow oil. $R_f = 0.3$ (EtOAc/hexane, 1:9); $[\alpha]_D = -36.9$ (*c* 1.0, $CHCl_3$); IR (neat): ν_{max} 3447, 2929, 1456, 1359, 1099, 1030, 755 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35–7.23 (m, 5H, ArH), 4.89 (dd, *J* = 2.6, 6.6 Hz, 1H, C*H*$_a$H$_b$–O–CH_3), 4.60–4.40 (m, 3H, CH_aH_b–O–CH_3, propargylic CH, CH of THP), 4.52 (s, 2H, Ph–C*H*$_2$), 3.90–3.76 (m, 2H, C*H*$_2$–O–THP), 3,55 (t, *J* = 7.1 Hz, 2H, C*H*$_2$–OBn), 3.5–3.41 (m, 2H, CH_2 of THP), 3.3 (s, 3H, CH_2–O–C*H*$_3$), 2.51 (dt, *J* = 1.8, 7.1 Hz, 2H, propargylic CH_2), 1.96 (m, 2H, CH_2), 1.87–1.48 (m, 6H, 3 × CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.4, 128.3, 127.9, 127.5, 98.7, 96.3, 93.9, 83.0, 79.7, 70.3, 66.0, 63.4, 62.0, 58.2, 36.2, 30.5, 25.4, 20.2, 19.3; HRMS (ESI): $[M+Na]^+$ *m/z* calcd for $C_{21}H_{30}O_5Na$: 385.1990, found: 385.1995 (+1.0537 ppm error).

4.1.4. (3*S*)-7-(Benzyloxy)-3-(methoxymethoxy)-4-heptyn-1-ol 12

To a stirred solution of compound **6** (12.5 g, 34.53 mmol) in MeOH (40 mL) was added a catalytic amount of pyridinium *p*-toluenesulfonate under a nitrogen atmosphere. After stirring for 12 h at room temperature, the reaction mixture was quenched with solid $NaHCO_3$ (1 g) and filtered off, the solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:3) to afford **12** (7.87 g, 82% yield) as a yellow liquid. $R_f = 0.3$ (EtOAc/hexane, 2:3); $[\alpha]_D = -88.1$ (*c* 1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.4–7.28$ (m, 5H, ArH), 4.96 (d, *J* = 6.6 Hz, 0.5H, C*H*$_2$–O–CH_3), 4.82 (d, *J* = 11.7 Hz, 0.5H, C*H*$_2$–O–CH_3), 4.67 (s, 1H, Ph–C*H*$_a$H$_b$), 4.58 (d, *J* = 6.6 Hz, 0.5H, CH_2–O–CH_3), 4.55 (s, 1H, Ph–CH_aH_b), 4.49 (d, *J* = 11.7 Hz, 0.5H, C*H*$_2$–O–CH_3), 4.33 (m, 1H, CH), 3.93–3.73 (m, 2H, C*H*$_2$–OH), 3.68 (t, *J* = 6.6 Hz, 1H, C*H*$_a$H$_b$–OBn), 3.58 (t, *J* = 6.6 Hz, 1H, CH_aH_b–OBn), 3.38 (s, 3H, CH_2–O–C*H*$_3$), 2.56 (m, 2H, propargylic CH_2), 2.0 (m, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 128.2$, 127.8, 127.6, 127.5, 93.8, 72.8, 70.4, 68.1, 67.5, 65.8, 64.1, 59.6, 38.1, 20.1; HRMS (ESI): $[M+Na]^+$ *m/z* calcd for $C_{16}H_{22}O_4Na$: 301.1415, found: 301.1427 (+3.720 ppm error).

4.1.5. (3*S*)-7-(Benzyloxy)-3-(methoxymethoxy)-4-heptynyl 4-methyl-1-benzenesulfonate 13

To a stirred solution of **12** (2.4 g, 8.63 mmol) and Et_3N (2.4 mL, 17.26 mmol) in anhydrous CH_2Cl_2 (20 mL) at 0 °C was added *p*-toluenesulfony1 chloride (2.46 g, 12.94 mmol). The mixture was stirred at room temperature for 2 h and extracted with EtOAc. The extract was washed with water and brine, dried over anhydrous Na_2SO_4, and evaporated. Purification of the residual oil was carried out by column chromatography to provide tosylate **13** as a colorless oil (3.31 g, 89%). R_f = 0.5 (EtOAc/hexane, 1:4); $[\alpha]_D = -47.4$ (*c* 1.35, $CHCl_3$); IR (neat): ν_{max} 2927, 1359, 1177, 1098, 1030, 918, 750; ^{1}H NMR (300 MHz, $CDCl_3$):^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.77 (d, *J* = 8.3 Hz, 2H, ArH), 7.31 (d, *J* = 8.3 Hz, 2H, ArH), 7.29 (m, 5H, ArH), 4.83 (d, *J* = 6.7 Hz, 1H, CH_aH$_b$–O–CH$_3$), 4.5 (s, 2H, Ph–CH_2), 4.6 (d, *J* = 6.7 Hz, 1H, CH$_a$$H_b$–O–CH$_3$), 4.38 (t, *J* = 6.7 Hz, 1H, CH), 4.17 (m, 2H, CH$_2$), 3.51 (t, *J* = 6.7 Hz, 2H, CH$_2$), 3.29 (s, 3H, CH$_3$), 2.49–2.42 (m, 2H, CH$_2$), 2.45 (s, 3H, CH$_3$), 2.02 (m, 2H, CH$_2$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.7, 137.6, 132.9, 129.7, 128.3, 127.8, 127.7, 127.6, 93.8, 72.9, 70.5, 68.1, 66.8, 65.8, 65.1, 62.0, 35.2, 21.5, 20.0; HRMS (ESI): [M+Na]$^+$ *m/z* calcd for $C_{23}H_{28}O_6SNa$: 455.1504, found: 455.1504 (−0.0669 ppm error).

4.1.6. (5*S*)-1-(Benzyloxy)-5-(methoxymethoxy)-3-heptyne 14

To a magnetically stirred suspension of $LiAlH_4$ (1.74 g, 45.83 mmol) in anhydrous THF (30 mL) at 0 °C was added compound **13** (9.9 g, 22.91 mmol) in anhydrous THF (10 mL) and the mixture was allowed to stir at room temperature for 30 min. The reaction mixture was cooled to 0 °C and quenched with ice-cooled water (2 mL), saturated Na_2SO_4 solution (8 mL). The mixture was filtered over a small pad of *Celite* and dried over anhydrous Na_2SO_4. Evaporation of the solvent and purification of the residue by column chromatography (EtOAc/hexane, 1:24) furnished **14** (5.3 g, 88%) as a colorless liquid. $[\alpha]_D^{25} = -99.3$ (*c* 1.0, $CHCl_3$) R_f = 0.4 (EtOAc/hexane; 1:19); IR (neat): ν_{max} 2933, 2880, 1456, 1358, 1102, 1032, 921, 738, 698 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35–7.20 (m, 5H, ArH), 4.88 (d, *J* = 6.61, 1H, CH_aH$_b$–O–CH$_3$), 4.58–4.45 (m, 1H, CH$_a$$H_b$–O–CH$_3$), 4.52 (s, 2H, Ph–C$H_2$), 4.20 (t, *J* = 6.2 Hz, 1H, CH), 3.55 (t, *J* = 7.1 Hz, 2H, CH_2–O–Bn), 3.33 (s, 3H, CH$_2$–O–CH_3), 2.51 (dt, *J* = 1.3, 6.9 Hz, 2H, propargylic CH$_2$), 1.70 (m, 2H, CH$_2$), 1.0 (t, *J* = 7.5, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.1, 128.2, 127.8, 127.4, 93.8, 72.8, 70.1, 68.4, 66.9, 66.0, 55.3, 28.9, 20.1, 9.6; HRMS (ESI): [M+Na]$^+$ *m/z* calcd for $C_{16}H_{22}O_3Na$: 285.1466, found: 285.1466 (−0.2261 ppm error).

4.1.7. (3*R*)-7-(Benzyloxy)-1-hepten-3-ol (17) (route 2)

A stirred solution of **24**[8] (4 g, 11.56 mmol) and zinc (7.5 g, 115.6 mmol) in anhydrous EtOH (35 mL) was refluxed for 30 min. The reaction mixture was filtered on a *Celite* pad and concentrated under reduced pressure. The crude product was purified by column chromatography (EtOAc/hexane, 1:3) which furnished **17** (2.41 g, 95%) $[\alpha]_D^{25} = -6.0$ (*c* 1.0, $CHCl_3$); R_f = 0.4 (EtOAc/hexane; 2:3); IR (neat): ν_{max} 3413, 2934, 2859, 1453, 1363, 1097, 991, 921, 741, 697 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35–7.18 (m, 5H, ArH), 5.89–5.77 (m, 1H), 5.19 (d, *J* = 17.3 Hz, 1H), 5.07 (d. *J* = 9.8 Hz, 1H), 4.47 (s, 2H, Ph–CH_2), 4.14–4.03 (m, 1H, CH), 3.44 (t, *J* = 6.0 Hz, 2H, CH_2–OBn), 1.80–1.35 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.0, 138.5, 128.3, 127.6, 127.5, 114.7, 73.2, 72.9, 70.2, 36.7, 29.5, 22.0; HRMS (ESI): [M+Na]$^+$ *m/z* calcd for $C_{14}H_{20}O_2Na$: 243.1360, found: 243.1370 (+3.7025 ppm error).

4.1.8. (3*R*)-7-(Benzyloxy)-1-hepten-3-ol 17 (route 3)

Trimethylsulfonium iodide (17.26 g, 84.61 mmol) was suspended in anhydrous THF (100 mL) and cooled to −10 °C. *n*-BuLi (33 mL, 2.5 M in THF, 82.5 mmol) was added dropwise and the reaction was allowed to warm slowly to 0 °C. The solution was cooled to −10 °C and the epoxide **8** (4.4 g, 21.15 mmol) in anhydrous THF (15 mL) was added dropwise producing a milky suspension. The reaction mixture was allowed to warm to 0 °C over about 30 min and then to room temperature and stirred for 2 h. Water was added at 0 °C and the organic layer separated; the aqueous layer was extracted with Et_2O (2 × 50 mL) and the combined organic layers dried over anhydrous Na_2SO_4 (1 g). The crude compound was purified by using column chromatography (EtOAc/hexane, 1:3) to afford **17** (3.90 g, 84%) $[\alpha]_D^{25} = -5.6$ (*c* 1.0, $CHCl_3$); NMR (^{1}H and ^{13}C), IR, and HRMS data were identical to **17** which was prepared from 5-hexyne1-ol.

4.1.9. (3*R*)-7-(Benzyloxy)-3-(methoxymethoxy)-1-heptene 18

To a solution of alcohol **17** (2.5 g, 11.36 mmol) in anhydrous CH_2Cl_2 (30 mL) at 0 °C were added *i*Pr_2NEt (3 mL, 17.04 mmol), catalytic DMAP (5 mg), and MOMCl (1.18 mL, 14.77 mmol) successively and the mixture was stirred for 4 h at room temperature, quenched by adding water (10 mL), and extracted with CH_2Cl_2 (3 × 10 mL). The organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4 (1 g), and concentrated in vacuo. The crude residue was purified by column chromatography (EtOAc/hexane 1:24) to afford the MOM ether **18** (2.85 g, 95%) as a yellow oil. $[\alpha]_D^{25} = +26.0$ (*c* 0.5, $CHCl_3$); R_f = 0.4 (EtOAc/hexane; 1:19); IR (neat): ν_{max} 2937, 2859, 1454, 1361, 1151, 1099, 1035, 920, 737; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31–7.26 (m, 5H, ArH), 5.69–5.56 (m, 1H), 5.21–5.13 (m, 2H), 4.64 (d 1H, *J* = 6.61 Hz, CH_aH$_b$–O–CH$_3$), 4.47 (s, 2H, Ph–CH_2), 4.45 (d, *J* = 6.23 Hz, 1H, CH$_a$$H_b$–O–CH$_3$), 3.94 (m, 1H, CH), 3.43 (t, *J* = 6.42 Hz, 2H, CH_2–O–Bn), 3.33 (s, 3H, CH$_2$–O–CH_3), 1.68–1.36 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.6, 138.3, 128.3, 127.6, 127.4, 117.2, 93.7, 77.2, 72.8, 70.2, 55.4, 35.2, 29.6, 22.0; HRMS (ESI): [M+Na]$^+$ *m/z* calcd for $C_{16}H_{24}O_3Na$: 287.1623, found: 287.1616 (−2.4884 ppm error).

4.1.10. (5*S*)-5-(Methoxymethoxy)heptan-1-ol 15

A stirred solution of **14** or **18** (5.2 g 19.84 mmol) and 10% Pd/C (100 mg) in anhydrous EtOAc (75 mL) was hydrogenated at 1 atm and room temperature for 4 h. The reaction mixture was filtered through *Celite* pad and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (EtOAc/hexane, 1:4) and gave **15** (3.40 g, 97%) as a colorless liquid. $[\alpha]_D^{25} = +4.9$ (*c* 1.1, $CHCl_3$); R_f = 0.3 (EtOAc/hexane; 3:7); IR (neat): ν_{max} 3419, 2936, 2880, 1461, 1378, 1039 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.61 (m, 2H, CH_2–O–CH$_3$), 3.62 (t, *J* = 6.0 Hz, 2H, CH_2–OH), 3.46 (m, 1H, CH), 3.35 (s, 3H, CH$_2$–O–CH_3), 1.65–1.22 (m, 8H, 4 × CH$_2$), 0.90 (t, *J* = 7.5 Hz, 3H, CH$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 95.2, 78.5, 62.3, 55.3, 33.3, 32.6, 26.7, 21.3, 9.3; HRMS (ESI): [M+Na]$^+$ *m/z* calcd for $C_9H_{20}O_3Na$: 199.1334, found: 199.1331 (−1.6053 ppm error).

4.1.11. 7-(Benzyloxy)-2-heptyn-1-ol 16a

To a suspension of Mg (1.0 g, 41.66 mmol) in anhydrous THF (50 mL) ethyl bromide (4.43 g, 40.69 mmol) was added dropwise under nitrogen atmosphere at 0 °C. It was allowed to stir for half an hour at room temperature. To this Grignard reagent, compound **16** (5.1 g, 27.12 mmol) in anhydrous THF (75 mL) was added at 0 °C. After stirring for 2 h at room temperature, paraformaldehyde (3.0 g) was added to the reaction mixture. The reaction mixture was stirred for another 5 h. The reaction mixture was quenched with saturated NH_4Cl solution and filtered over *Celite*. The filtrate was washed with water, brine, and dried over Na_2SO_4. The organic layer was concentrated. The crude material was purified by column chromatography (EtOAc/hexane, 3:7) to provide the pure product **16a** (5.02 g, 85%) as a liquid. IR (neat): ν_{max} 3410, 2937, 2862, 1495, 1454, 1363, 1105, 1018, 793, 699 cm^{-1}; ^{1}H NMR ($CDCl_3$ 300 MHz) δ 7.28 (m, 5H, ArH), 4.47 (s, 2H, Ar-CH$_2$), 4.17 (m, 2H, CH$_2$–OH), 3.46 (t, *J* = 6.2 Hz, 2H, CH$_2$–OBn), 2.23 (tt, *J* = 2.2, 6.9 Hz, 2H, propargylic CH$_2$), 1.76–

1.56 (m, 4H, 2 × CH_2); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.1, 128.2, 127.5, 127.4, 85.4, 78.7, 72.6, 69.5, 50.7, 28.6, 25.1, 18.3; MASS (ESIMS) *m/z* 236 $[M+NH_4]^+$.

4.1.12. (*E*)-7-(Benzyloxy)-2-hepten-1-ol 16b

To a stirred suspension of $LiAlH_4$ (1.20 g, 31.65 mmol) in anhydrous THF (20 mL) at 0 °C was added dropwise a solution of **16a** (4.6 g, 21.10 mmol) in anhydrous THF (50 mL). The reaction mixture was allowed to attain room temperature and refluxed for 4 h. The reaction was quenched at 0 °C with dropwise addition of saturated aqueous Na_2SO_4 solution (10 mL). The solid material was filtered and washed with hot EtOAc several times. The organic layers were combined, washed once with water, brine solution, and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by column chromatography (EtOAc/hexane, 4:7) to afford **16b** as a colorless liquid (4.17 g, 90%). IR (neat): ν_{max} 2933, 2858, 1496, 1454, 1364, 1097, 971, 739 cm^{-1}; ^1H NMR ($CDCl_3$ 300 MHz) δ 7.28 (m, 5H, ArH), 5.62 (m, 2H), 4.46 (s, 2H, Ar-CH_2), 4.03 (m, 2H, CH_2–OH), 3.43 (t, *J* = 6.2 Hz, 2H, CH_2–OBn), 2.06 (m, 2H, allylic CH_2), 1.61 (m, 2H, CH_2), 1.48 (m, 2H, CH_2); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.3, 132.5, 129.1, 128.2, 127.5, 127.4, 72.7, 70.0, 63.3, 31.8, 29.0, 25.5; MASS (ESIMS): *m/z* 238 $[M+NH_4]^+$.

4.1.13. (2*R*,3*R*)-3-[4-(benzyloxy)butyl]oxiran-2-ylmethanol 7

Anhydrous CH_2Cl_2 (20 mL) was added to 4 Å activated molecular sieves powder and the suspension was cooled to −24 °C, L (−)-DET (0.75 g, 3.63 mmol) in anhydrous CH_2Cl_2 (5 mL) and $Ti(O^iPr)_4$ (1.03 g, 3.63 mmol) were added subsequently with stirring and the resulting mixture was stirred for 30 min at −24 °C, compound **16b** (4.0 g, 18.18 mmol) in anhydrous CH_2Cl_2 (20 mL) was then added, and the reaction mixture was stirred for another 30 min at −24 °C. TBHP (3.3 M in toluene, 8.26 mL, and 27.27 mmol) was then added and the resulting mixture was stirred at the same temperature for 4 h. The reaction mixture was warmed to 0 °C, quenched with 6 mL of water, and then stirred for 1 h at room temperature. A 30% aqueous NaOH solution saturated with NaCl (10 mL) was then added and the reaction mixture stirred vigorously for another 30 min at room temperature. The resulting mixture was washed well with CH_2Cl_2. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2. Combined organic layers were washed with brine solution and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and purified by silica gel column chromatography (EtOAc/hexane, 1:2) to afford **7** as a viscous liquid (3.43 g, 80%). $[\alpha]_D^{25} = +19.6$ (*c* 1.0, $CHCl_3$); IR (neat): ν_{max} 3424, 2936, 2861, 1496, 1454, 1364, 1099, 740, 699 cm^{-1}; ^1H NMR ($CDCl_3$ 300 MHz) δ 7.28 (m, 5H, ArH), 4.46 (s, 2H, Ar-CH_2), 3.84 (m, 1H, C$H_a$$H_b$–OH), 3.57 (m, 1H, CH_aH_b–OH), 3.44 (t, *J* = 6.0 Hz, 2H, CH_2–OBn), 2.90 (m, 1H), 2.84 (m, 1H), 1.79 (br, s, 1H, OH), 1.70–1.48 (m, 6H, 3 × CH_2); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.1, 128.1, 127.4, 127.3, 72.6, 69.7, 61.6, 58.4, 55.7, 31.0, 29.1, 22.4; HRMS (ESI) calcd for $C_{14}H_{20}O_3Na$ $[M+Na]^+$ 259.1310, found 259.1306.

4.1.14. (2*R*,3*S*)-2-[4-(Benzyloxy)butyl]-3-(iodomethyl)oxirane 24

To a stirred solution of **7** (3.2 g, 13.55 mmol) in a mixture of 27 mL of anhydrous ether and 9 mL of anhydrous CH_3CN were added TPP (4.26 g, 16.27 mmol), imidazole (2.30 g, 33.89 mmol), and iodine (2.23 g, 8.81 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 20 min. Solids were filtered and washed with ether. The filtrate was extracted with ether, washed with 10% aqueous $Na_2S_2O_3$ solution, water, brine solution, and dried over anhydrous Na_2SO_4. The residue was concentrated under reduced pressure and purified by silica gel column chromatography (EtOAc/hexane, 1:49) to afford **24** as a colorless liquid (4.26 g, 91%). $[\alpha]_D^{25} = -6.9$ (*c* 1.0, $CHCl_3$); IR (neat): ν_{max} 2935, 2858, 1495, 1454, 1362, 1170, 1101, 895, 738, 698 cm^{-1}; ^1H NMR ($CDCl_3$ 300 MHz) δ 7.28 (m, 5H, ArH), 4.47 (s, 2H, Ar-CH_2), 3.44 (t, *J* = 6.0 Hz, 2H, CH_2–OBn), 3.26 (m, 1H), 2.94 (m, 2H), 2.73 (m, 1H), 1.73–1.50 (m, 6H, 3 × CH_2); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.3, 128.1, 127.4, 127.3, 72.6, 69.7, 62.2, 58.0, 31.2, 29.2, 22.4, 5.1; HRMS (ESI): calcd for $C_{14}H_{19}O_2NaI$ $[M+Na]^+$ 369.0327, found 369.0311.

4.1.15. (4*R*)-4-Benzyl-3-[(2*R*,3*S*,7*S*)-3-hydroxy-7-(methoxymethoxy)-2-methylnonanoyl]-1,3-oxazolan-2-one 3

To an ice-cooled solution of 2-(iodooxy)benzoic acid (7.36 g, 27.27 mmol) in anhydrous DMSO (7.8 ml, 109.0 mmol) was added a solution of alcohol **15** (3.2 g, 18.18 mmol) in anhydrous CH_2Cl_2 (20 mL). The mixture was stirred at room temperature for 2 h and then filtered through a *Celite* pad and washed with Et_2O (2 × 10 mL). The combined organic filtrates were washed with H_2O (2 × 5 mL) and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by silica gel column chromatography using (EtOAc/hexane, 1:9) to afford aldehyde **5** (2.91 g, 92%) as a yellow liquid. The unstable aldehyde **5** was immediately used for the aldol reaction.

To a solution of 4-benzyl-3-propionyl-1,3-oxazolidin-2-one **4** (4.22 g, 18.13 mmol) in anhydrous CH_2Cl_2 (36 mL) was added di-*n*-butylboryl triflate (1 M in CH_2Cl_2, 18.13 mL, 18.13 mmol) at 0 °C. The resulting brown solution was stirred for 10 min, then Et_3N (3.15 mL, 22.67 mmol) was added, resulting in a color change from red to light yellow. The mixture was stirred for 1 h at 0 °C and cooled to −80 °C. A solution of the above aldehyde **5** (2.63 g, 15.11 mmol) in anhydrous CH_2Cl_2 (8 mL) was then added and stirring was continued for 1 h at −80 °C. The reaction mixture was allowed to warm to 0 °C and stirred for 30 min at this temperature. The reaction was quenched with pH 7 phosphate buffer (15 mL), MeOH (50 mL), finally treated with a mixture of MeOH/H_2O_2 (2:1, 35 mL), allowed to warm to room temperature, and stirred for 1 h. Most of the organic solvents was removed by rotary evaporation and the aqueous layer was extracted with Et_2O (2 × 50 mL). The combined extracts were washed with saturated $NaHCO_3$ solution, saturated NaCl solution, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by column chromatography (EtOAc/hexane, 5:13) to afford the aldol product **3** (4.78 g, 78%) as a light yellow gummy oil. $[\alpha]_D^{25} = -38.4$ (*c* 1.4, $CHCl_3$) R_f = 0.2 (EtOAc/hexane; 2:3); IR (neat): ν_{max} 3471, 2935, 1780, 1695, 1384, 1211, 1105, 1036 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36–7.14 (m, 5H, ArH), 4.71–4.54 (m, 1H, CH), 4.61 (m, 2H, CH_2–O–CH_3), 4.25–4.13 (m, 2H, lactone CH_2), 3.91 (m, 1H, OH), 3.71 (m, 1H, CH), 3.45 (m, 1H, CH), 3.35 (s, 3H, CH_2–O–CH_3), 3.28 (m, 1H, CH), 2.73 (m, 2H, Ph–CH_2), 1.68–1.28 (m, 8H, 4 × CH_2), 1.24 (d, *J* = 6.7 Hz, 3H, CH_3), 0.90 (t, *J* = 6.7 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.2, 153.0, 134.9, 129.3, 128.8, 127.3, 95.3, 78.4, 71.3, 66.0, 55.3, 55.0, 42.1, 37.6, 33.9, 33.5, 26.7, 21.6, 10.4, 9.4; HRMS (ESI): $[M+Na]^+$ *m/z* calcd for $C_{22}H_{33}NO_6Na$: 430.2331, found: 430.2345 (+3.1751 ppm error).

4.1.16. Methyl (2*R*,3*S*,7*S*)-3-hydroxy-7-(methoxymethoxy)-2-methylnonanoate 22

To a solution of aldol product **3** (3.7 g, 9.11 mmol) in anhydrous CH_2Cl_2-MeOH (57 mL; 1:1) at 0 °C was added dropwise EtMgBr (13.66 mL, 1 M in THF, 13.66 mmol) which was diluted to 0.768 M by adding anhydrous MeOH (18.7 mL). The reaction mixture was allowed to stir at room temperature for 10 min. Next a 1-M $NaHSO_3$ (10 mL) solution was added to quench the reaction. The organic solvents were removed under reduced pressure. The residue was extracted with CH_2Cl_2 (2 × 30 mL) and the organic layer

was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (EtOAc/hexane, 3:14) to afford **22** (2.07 g, 87%). $[\alpha]_D^{25} = -10.2$ (*c* 1.2, $CHCl_3$), $R_f = 0.5$ (EtOAc/hexane, 1:4); IR (neat): ν_{max} 3469, 2937, 1735, 1459, 1372, 1255, 1038 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.2 (m, 2H, CH_2–O–CH_3), 3.84 (m, 1H, CH), 3.7 (s, 3H, O=C–OCH_3), 3.45 (m, 1H, CH), 3.35 (s, 3H, CH_2–O–CH_3), 2.49 (dq, J = 3.0, 6.7 Hz, 1H, CH), 1.65–1.23 (m, 8H, 4 × CH_2), 1.17 (d, J = 7.5 Hz, 3H, CH_3), 0.90 (t, J = 7.5 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.4, 95.3, 78.5, 71.6, 55.4, 51.7, 44.3, 33.9, 33.5, 26.7, 21.6, 10.7, 9.4; HRMS (ESI): $[M+Na]^+$ *m/z* calcd for $C_{13}H_{26}O_5Na$: 285.1677, found: 285.1688 (+3.5279 ppm error).

4.1.17. *tert*-Butyl (4*R*,5*S*,9*S*)-5-hydroxy-9-(methoxymethoxy)-4-methyl-3-oxoundecanoate 2

To a solution of LDA, prepared from diisopropylamine (1.88 mL. 13.35 mmol) in anhydrous THF (20 mL) and *n*-butyllithium (2.3 mL, 2.5 M in THF), *tert*-butyl acetate (1.32 g, 11.45 mmol) in anhydrous THF (5 mL) was added at −78 °C. Then, the hydroxyester **22** (1 g, 3.81 mmol) in anhydrous THF (5 mL) was added dropwise at −78 °C. The mixture was stirred at −50 °C for 1.5 h, and, then, at −15 °C for 15 min. Ice-water (20 mL) was added to quench the reaction, and the aqueous layer was extracted with ether (2 × 25 mL). The combined organic layer was washed with saturated $NaHC0_3$ (20 mL) and water (2 × 15 mL), and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (EtOAc/hexane, 4:21) to afford **2** (1.08 g, 82%). $[\alpha]_D^{25} = -5.0$ (*c* 1.1, $CHCl_3$), $R_f = 0.5$ (EtOAc/hexane, 1:4); IR (neat): ν_{max} 3451, 2933, 1735, 1708, 1639, 1459, 1369, 1317, 1253, 1149, 1037 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.60 (m, 2H, CH_2–OCH_3), 3.93 (m, 1H, CH), 3.50–3.37 (m, 3H, O=C–CH_2–C=O, CH), 3.35 (s, 3H, CH_2–O–CH_3), 2.68 (dq, J = 3.0, 7.5 Hz, 1H, CH), 1.58–1.41 (m, 8H, 4 × CH_2), 1.47 (s, 9H, ^{t}Bu), 1.14 (d, J = 7.5 Hz, 3H, CH_3), 0.90 (t, J = 7.5 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.8, 166.5, 95.3, 82.1, 78.5, 70.8, 55.4, 50.9, 49.5, 34.0, 33.5, 27.9, 26.7, 21.6, 9.5, 9.4; HRMS (ESI): $[M+Na]^+$ *m/z* calcd for $C_{18}H_{34}O_6Na$: 369.2253, found: 369.2259 (+1.6009 ppm error).

4.1.18. *tert*-Butyl (3*R*,4*R*,5*S*,9*S*)-3,5-dihydroxy-9-(methoxymethoxy)-4-methylundecanoate 23

A solution of diethylmethoxyborane (2.6 mL, 1 M in THF) and **2** (0.75 g, 2.16 mmol) in anhydrous THF–MeOH (20 mL; 4:1) was stirred for 2 h at room temperature under nitrogen. Then, the solution was cooled to −78 °C and solid $NaBH_4$ (98.8 mg, 2.6 mmol) was added in one portion. The mixture was stirred for 6 h at −78 °C, and a mixture of 30% H_2O_2 (10 mL), phosphate buffer (pH 7, 20 mL), and methanol (20 mL) was added. Almost all of the organic solvent was removed under reduced pressure, and the residual aqueous solution was extracted with CH_2C1_2 (2 × 50 mL). The extract was dried over anhydrous Na_2SO_4 and concentrated. To the residue was added glacial AcOH (1 mL) in EtOAc (20 mL) and stirred for 2 h to completely decompose the boric acid ester of diols. Then the reaction was quenched by saturated $NaHCO_3$ (5 mL). The organic layer was separated, the aqueous layer was again extracted with EtOAc (2 × 30 mL) and dried over anhydrous Na_2SO_4, the solvent was removed under reduced pressure, the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:5) to afford **23** (0.588 g, 1.68 mmol, 78%). $[\alpha]_D^{25} = +3.0$ (*c* 1.0, $CHCl_3$), $R_f = 0.3$ (EtOAc/hexane, 1:4); IR (neat): ν_{max} 3447, 2933, 1726, 1636, 1460, 1369, 1154, 1037, 760 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.6 (m, 2H, CH_2–OCH_3), 4.20 (dt, J = 2.2, 9.8 Hz, 1H, CH), 3.85(m, 1H, CH), 3.45 (m, 1H, CH), 3.35 (s, 3H, CH_2–O–CH_3), 2.50 (dd, J = 6.0, 15.8 Hz, 1H O=C–CH_aH_b), 2.25 (dd, J = 3.0, 16.6 Hz, 1H, O=C–CH_aH_b), 1.57–1.27 (m, 9H, 4 × CH_2, CH), 1.46 (s, 9H, ^{t}Bu), 0.91 (d, J = 6.0 Hz, 3H, CH_3), 0.90 (t, J = 6.7 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4, 95.3, 81.3, 78.6, 75.9, 72.9, 55.4, 40.5, 35.0, 33.6, 29.6, 28.0, 26.7, 21.6, 9.4, 5.0; HRMS (ESI): $[M+Na]^+$ *m/z* calcd for $C_{18}H_{36}O_6Na$: 371.2409, found: 371.2415 (+1.4573 ppm error).

4.1.19. (4*R*,5*S*,6*S*)-4-Hydroxy-6-[(4*S*)-4-hydroxyhexyl]-5-methyltetrahydro-2*H*-2-pyranone 1

To a solution of ester **23** (0.43 g, 1.23 mmol) in 10 mL of THF was added 1.8 mL of water. To the resulting solution 0.9 mL of concentrated HCl was added dropwise after which the mixture was stirred at room temperature for 48 h. The reaction mixture was quenched by adding $NaHCO_3$ (1 g) then concentrated in vacuo, and purified by silica gel column chromatography (EtOAc/hexanes, 1:1) to give **1** (0.214 g, 0.093 mmol, 75%) as light yellow liquid. $[\alpha]_D^{25} = -39.5$ (*c* 0.27, $CHCl_3$), $R_f = 0.3$ (MeOH/$CHCl_3$, 2:23); IR (neat): ν_{max} 3445, 2929, 1712, 1459, 1382, 1253 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.71 (ddd, J = 2.5, 4.7, 8.1 Hz, 1H, CH), 4.06 (ddd, J = 3.2, 3.4, 5.6 Hz, 1H, CH), 3.55 (m, 1H, CH), 2.81 (dd, J = 5.5, 18.5 Hz, 1H, O=CCH_aH_b), 2.53 (ddd, J = 0.9, 3.2, 18.1 Hz, 1H, O=CCH_aH_b), 1.95 (m, 1H, CH), 1.74 (m, 1H, CH_aH_b), 1.65 (m, 2H, CH_2), 1.50 (m, 3H, CH_aH_b and CH_2), 1.42 (m, 2H, CH_2), 0.95 (d, J = 7.2 Hz, 3H, CH_3), 0.94 (t, J = 7.3 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3, 78.0, 73.0, 68.6, 37.4, 36.4, 35.8, 31.7, 30.3, 21.6, 10.2, 9.8; HRMS (ESI): $[M+Na]^+$ *m/z* calcd for $C_{12}H_{22}O_4Na$: 253.1415, found: 253.1425 (+3.6377 ppm error).

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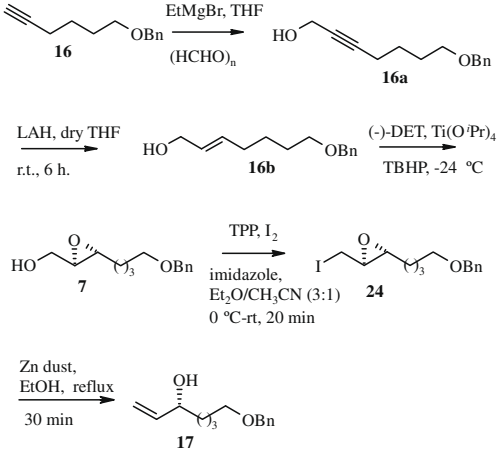

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