FULL PAPER

An Efficient Stereoselective Synthesis of Key Fragments of Elaiophylin

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The stereoselective synthesis of key fragments **3** and **7** of elaiophylin has been accomplished from readily available epichlorohydrin as the starting material. The key reactions involved are *Jacobsen*'s kinetic resolution, *Prins* cyclization, pyridinium chlorochromate-mediated oxidative cleavage, *Grignard* reaction, and cross-metathesis reaction.

Keywords: Macrolide, Elaiophylin, *Prins* cyclization, *Jacobsen*'s kinetic resolution, Cross-metathesis reaction.

Introduction

Elaiophylin (**1**), first isolated in 1959 from cultures of *Streptomyces melanosporus* [1] and shortly thereafter from a related microorganism (*Fig.*) [2]. Elaiophylin is a 16-membered macrolide which displays antimicrobial activity against several strains of Gram-positive bacteria [3][4]. Elaiophylin also has anthelmintic activity against *Trichonomonas vaginalis* [5 – 10], as well as inhibitory activity against K^+-dependent adenosine triphosphatases [11].

As a result of its structural complexity and potent biological activity, elaiophylin has been a target of considerable synthetic interest. The first synthesis of elaiophylin was accomplished by *Kinoshita et al.* [12][13]. Several other studies directed toward the synthesis of the elaiophylin framework have also been published [14 – 25]. As part of our continuous interest in the total synthesis of macrolides [26 – 31], we herein report an efficient stereoselective synthesis of key fragments of elaiophylin.

Results and Discussion

We devised an strategy to synthesize elaiophylin (**1**) (*Scheme 1*). We planned to prepare the OH ester **2**, dimerize it by conventional lactonization strategy. The retrosynthetic analysis suggested that OH ester **2** could be further simplified by disconnecting the C_{10}–C_{11} bond, leading to a fragment **3** and lactone fragment **7**.

The fragment **3** could be prepared from functionalized pyran **4** by a sequence of protection, functional group interconversions, and deprotection reactions. The pyran **4** could in turn be prepared by *Prins* cyclization of homoallylic alcohol **5** and (*S*)-3-(benzyloxy)-2-methylpropanal (**6**). The lactone **7** could easily accessed from **8** which in turn could be prepared *via Prins* cyclization of dihydroxy *trans*-olefin **9** and acetaldehyde **10**.

Synthesis of Lactone Fragment (**7**)

The synthesis of lactone fragment **7** (*Scheme 2*) began with known dihydroxy *trans*-olefin **9** prepared from epichlorohydrin [31].

To carry out the crucial *Prins* cyclization reaction [32], a mixture of **9** and acetaldehyde **10** in CH_2Cl_2 was treated with trifluoroacetic acid (TFA) to afford trifluoroacetate **11**. Hydrolysis of the trifluoroacetate **11** with K_2CO_3 in MeOH, resulted in tetrasubstituted tetrahydropyran **8** in 60% yield (over two steps). Then, selective protection of the primary OH group **8** as a benzyl ether in the presence of NaH and BnBr in THF afforded **12** in 70% yield. The alcohol **12** was protected as a methoxymethyl (MOM) ether [33] **13** in 90% yield using methoxymethyl chloride (MOMCl) in the presence of diisopropylethylamine (DIPEA) and a catalytic amount of 4-dimethylaminopyridine (DMAP). Cleavage of benzyl ether **13** with Li in liquid NH_3 resulted **14** in 90% yield [34]. Next objective was pyridinium chlorochromate (PCC)-mediated oxidative cleavage [35][36] of OH group in **14**. Thus, upon treatment of **14** with PCC in refluxing benzene afford the desired lactone **7** in 60% yield.

Synthesis of Fragment (**3**)

The synthesis of the other fragment **3** was initiated with dihydroxy *trans*-olefin **5** prepared from epichlorhydrin using known procedure [37]. *Prins* cyclization of homoallylic alcohol **5** with (*S*)-3-(benzyloxy)-2-methylpropanal

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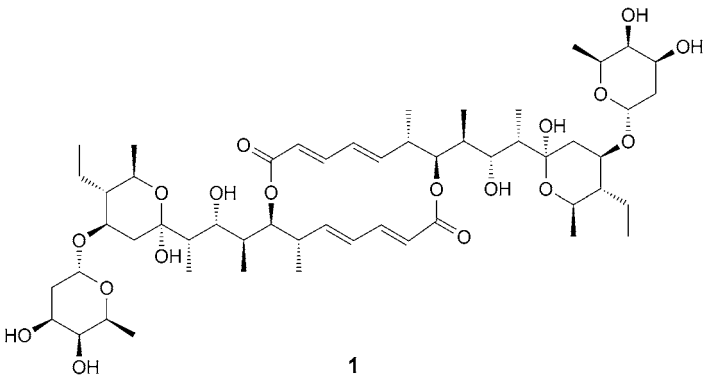
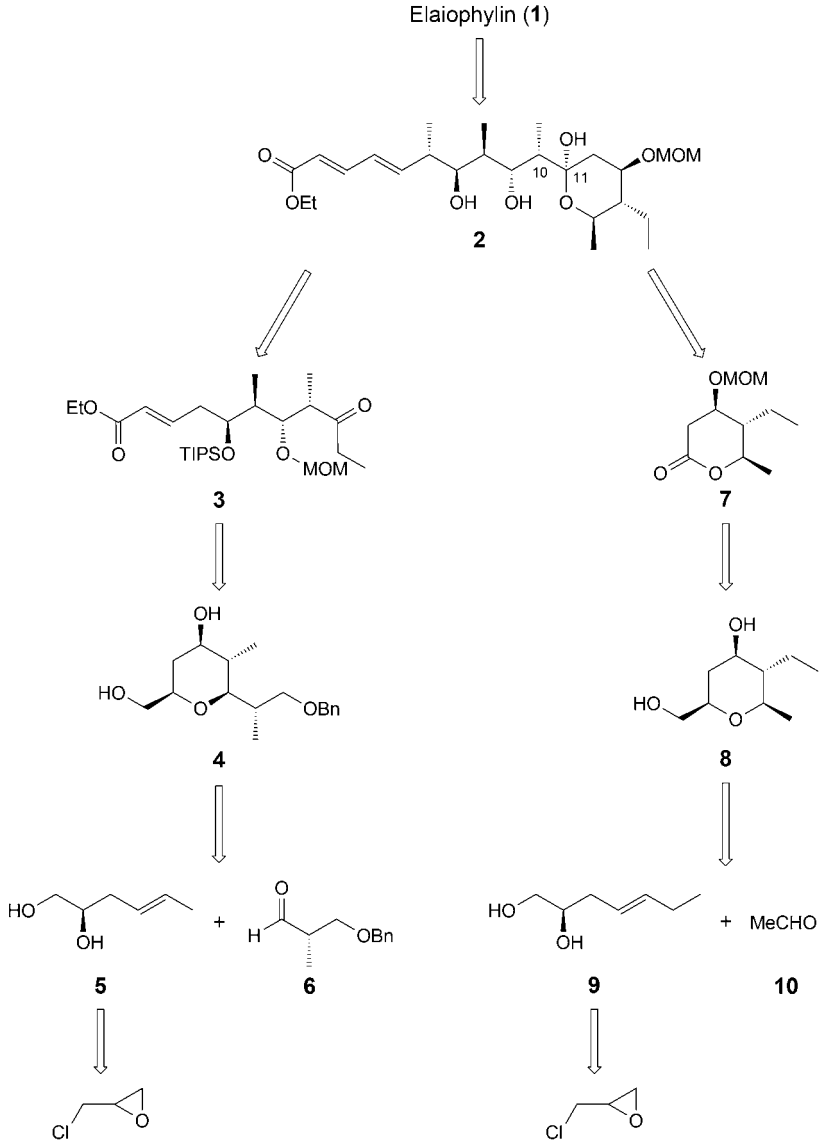


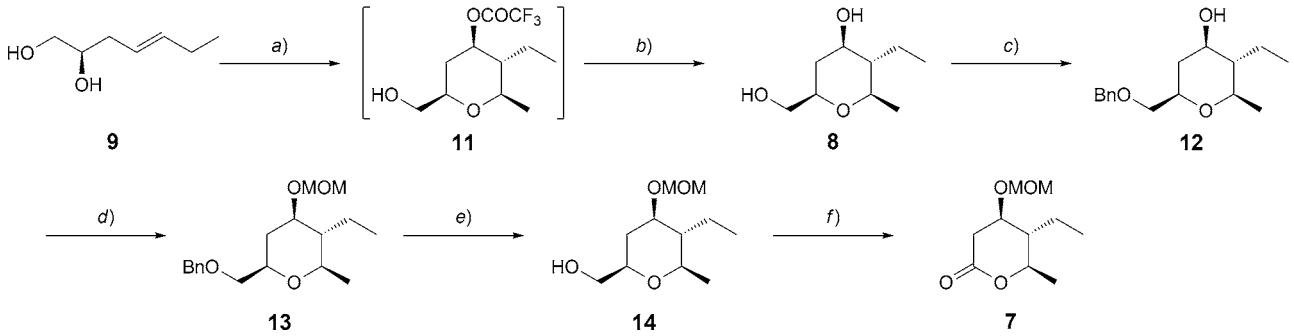
Figure. Structure of elaiophylin.

Scheme 1. Retrosynthetic Analysis of elaiophylin (**1**).



(**6**) [38] in the presence of TFA in CH_2Cl_2 resulted trifluoroacetate **15** which without purification but after workup was subjected to hydrolysis using K_2CO_3 in MeOH to yield **4**. The primary OH group in **4** was selectively tosylated to compound **16** using tosyl chloride, TEA in CH_2Cl_2 at 0 °C in 85% yield. The alcohol in compound

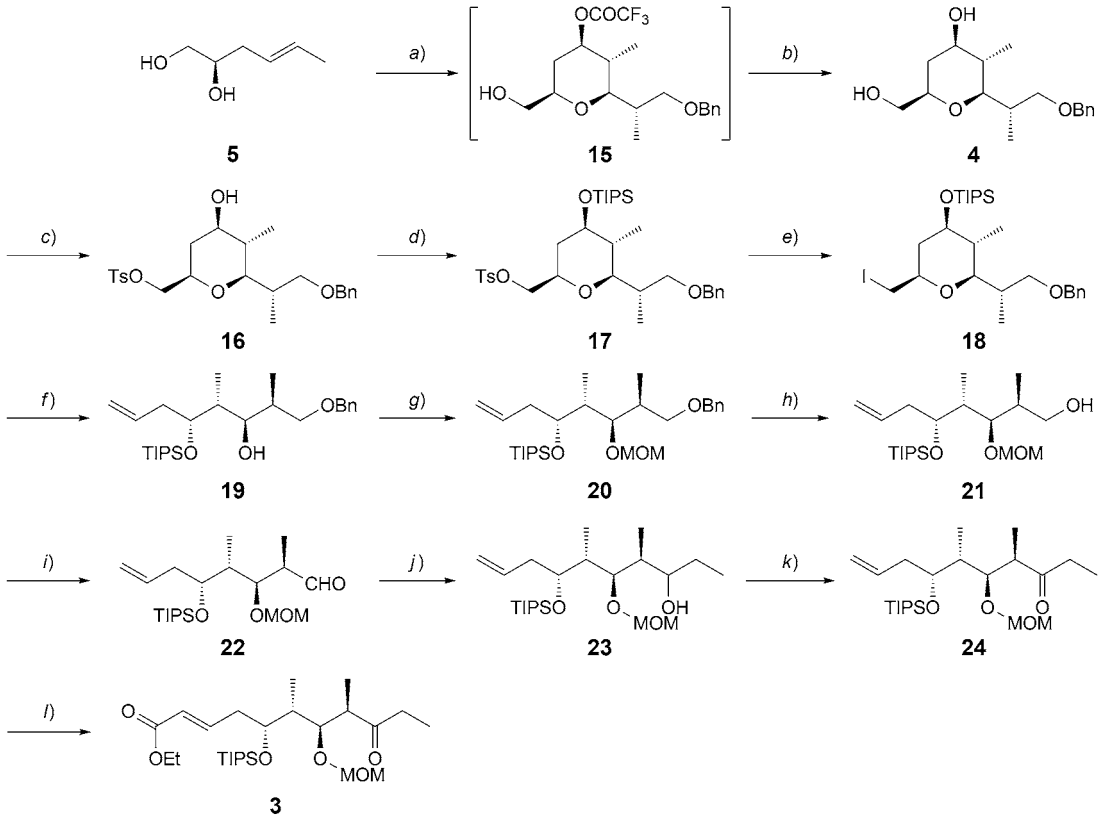
Scheme 2. Synthesis of fragment (**7**).



a) Acetaldehyde **10**, TFA, CH_2Cl_2, r.t., 3 h. *b*) K_2CO_3, MeOH, r.t., 0.5 h; 60% (over two steps). *c*) NaH, BnBr, TBAI, THF, 0 °C to r.t., 8 h; 70%. *d*) MOMCl, DIPEA, DMAP, CH_2Cl_2, 0 °C to r.t., 3 h; 90%. *e*) Li, liq. NH_3, THF, −33 °C, 5 min; 90%. *f*) Pyridinium chlorochromate (PCC), benzene, reflux, 6 h; 60%.

16 was protected as a TIPS ether **17** using triisopropylsilyl triflouoromethanesulphonate and 2,6-lutidine in CH_2Cl_2 at 0 °C for 1 h in 90% yield. Treatment of **17** with NaI in refluxing acetone furnished iodomethyl pyran **18**. Treatment of iodomethyl pyran **18** with Zn dust in refluxing EtOH resulted alcohol **19** in 80% yield [39 – 45]. The secondary alcohol of **19** was protected as its MOM ether **20** in the presence of MOMCl, DMAP, and DIPEA as base in CH_2Cl_2. Treatment of **20** with Li in liquid NH_3 resulted in benzyl ether cleavage to furnish primary alcohol **21** in 90% yield. Alcohol **21** was subjected to oxidation with *Dess–Martin* periodinane [46][47] in dry CH_2Cl_2

Scheme 3. Synthesis of fragment (**3**).



a) (*S*)-3-(Benzyloxy)-2-methylpropanal (**6**), TFA, CH_2Cl_2, r.t., 3 h. *b*) K_2CO_3, MeOH, r.t., 0.5 h; 60% (over two steps). *c*) TsCl, TEA, CH_2Cl_2, r.t., 0 °C to r.t., 5 h; 85%. *d*) TIPS-OTf, 2,6-lutidine, dry CH_2Cl_2, 0 °C to r.t., 1 h; 90%. *e*) NaI, acetone, reflux, 24 h; 95%. *f*) Zinc powder, EtOH, reflux, 1 h; 80%. *g*) Methoxymethyl chloride (MOMCl), DIPEA, DMAP, CH_2Cl_2, 0 °C to r.t., 3 h; 90%. *h*) Li, liq. NH_3, THF, −33 °C, 5 min; 90%. *i*) *Dess–Martin* periodinane (DMP), $NaHCO_3$, CH_2Cl_2, 0 °C to r.t., 1 h; 80%. *j*) Ethylmagnesium bromide, dry THF, 0 °C, 2 h; 90%. *k*) DMP, $NaHCO_3$, CH_2Cl_2, 0 °C to r.t., 1 h; 85%. *l*) Ethyl acrylate, *Grubbs*' second-generation catalyst, CH_2Cl_2, r.t., 1 h; 90%.

at 0 °C to room temperature for 1 h to furnish aldehyde **22** in 80% yield. The alcohol **23** could be easily obtained by *Grignard* reaction of aldehyde **22** with EtMgBr in THF at room temperature in 90% yield. The resultant alcohol **23** was oxidized to ketone **24** in 90% yield using *Dess–Martin* periodinane. Treatment of keto compound **24** with ethyl acrylate in the presence of 10 mol-% *Grubbs*' second-generation catalyst under nitrogen atmosphere in CH_2Cl_2 at room temperature afforded **3** in 90% yield (*Scheme 3*).

Conclusions

In conclusion, we have developed an efficient stereoselective synthetic pathway for the synthesis of key fragments **7** and **3** of elaiophylin. To date, over 100 mg quantities of key fragments **7** and **3** has been synthesized using this route and efforts towards the coupling of both fragments and total synthesis of elaiophylin is presently under investigation in our laboratory.

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Experimental Part

General

All reagents were reagent grade and used without further purification unless specified otherwise. Solvents were distilled before use: THF, toluene, and Et_2O were distilled from Na, benzophenone ketyl; MeOH from Mg and I_2; and CH_2Cl_2 from CaH_2. All air- or moisture-sensitive reactions were conducted under N_2 or Ar in flame-dried or oven-dried glassware with magnetic stirring. Column chromatography (CC): silica gel (SiO_2, 60 – 120 mesh or 100 – 200 mesh) packed in glass columns. Technical grade AcOEt and petroleum ether used for CC were distilled before use. Optical rotations: *JASCO DIP 300* digital polarimeter using a 1 ml cell with a 1 dm path length. IR Spectra: *PerkinElmer IR-683* spectrophotometer (*PerkinElmer*, Waltham, MA, USA); KBr pellets and $CHCl_3$; neat (as mentioned); $\tilde{\nu}$ in cm^{-1}. ^{1}H- and ^{13}C-NMR spectra: *Varian Gemini FT-200, Bruker Avance 300*, and *Bruker Avance 500* spectrometers (*Bruker*, Beijing, P. R. China) at 200, 300, or 500 MHz, resp., in $CDCl_3$ or C_6D_6; δ in ppm rel. to Me_4Si as internal standard, J in Hz. ESI-MS: *CEC-21-11013* or *Finnigan Mat 1210* double-focusing mass spectrometers operating at a direct inlet system or LC/MSD Trap SL (*Agilent Technologies*, Santa Clara, CA, USA); in m/z.

(6*R*)-2,6-Anhydro-3,5-dideoxy-5-ethyl-6-methyl-D-*xylo*-hexitol (**8**). Trifluoroacetic acid (30.5 ml) was added slowly to a soln. of the homoallylic alcohol **9** (2.48 g, 19.0 mmol) and acetaldehyde **10** (3.2 g, 57.2 mmol) in CH_2Cl_2 (15 ml) at r.t. under a N_2 atmosphere. The mixture was stirred for 3 h, then sat. aq. $NaHCO_3$ soln. (20 ml) was added, and pH was adjusted to > 7 by addition of Et_3N. The layers were separated and the aq. layer was extracted with CH_2Cl_2 (3 × 40 ml) and the org. layers were combined and the solvent was removed under reduced pressure. The residue was dissolved in MeOH (30 ml) and stirred with K_2CO_3 (1.95 g) for 0.5 h. The MeOH was then removed under reduced pressure and H_2O (15 ml) was added. The mixture was extracted with CH_2Cl_2 (3 × 20 ml) and the combined org. layers were dried (Na_2SO_4) and the solvent was removed under reduced pressure. CC of the crude afforded **8** (2 g, 60%) as a colorless oil. $[\alpha]_D^{25} = -4.5$ ($c = 0.02$, $CHCl_3$). IR (neat): 3399, 2933, 2876, 1727, 1376, 1113, 1062, 1013. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.91 (*t*, *J* = 7.5, 3 H); 1.23 (*d*, *J* = 6.2, 3 H); 1.39 – 1.93 (*m*, 5 H); 1.95 – 2.47 (br. *s*, 1 H); 3.23 – 3.37 (*m*, 1 H); 3.38 – 3.72 (*m*, 4 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 9.8; 19.3; 19.4; 37.0; 50.8; 65.9; 69.6; 74.7; 75.6. ESI-MS: 174 (M^+).

(6*R*)-2,6-Anhydro-1-*O*-benzyl-3,5-dideoxy-5-ethyl-6-methyl-D-*xylo*-hexitol (**12**). To a suspension of NaH (60%, 0.10 g, 4.48 mmol) in dry THF (20 ml) was added dropwise a soln. of alcohol **8** (0.65 g, 3.73 mmol) in THF (10 ml) at 0 °C. To this mixture, TBAI (0.02 g) and benzyl bromide (0.44 ml, 3.73 mmol) were added subsequently and stirring was continued for 2 h at same temp. and 6 h at r.t. The reaction was quenched by crushed ice flakes until a clear soln. (biphasic) formed. The mixture was extracted with AcOEt (2 × 30 ml). The org. extracts were washed with H_2O (1 × 20 ml), brine (1 × 20 ml), and dried (Na_2SO_4). Evaporation of the solvents followed by CC afforded the pure product **12** (0.7 g, 70% yield) as a colorless liquid. $[\alpha]_D^{25} = +5.6$ ($c = 0.65$, $CHCl_3$). IR (neat): 3437, 2964, 2930, 2875, 1108, 1025. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.90 (*t*, *J* = 7.5. 3 H); 1.26 (*d*, *J* = 6.0, 3 H); 1.36 – 1.83 (*m*, 4 H); 1.91 – 2.04 (*m*, 1 H); 3.23 – 3.46 (*m*, 2 H); 3.46 – 3.71 (*m*, 3 H); 4.57 (*d*, *J* = 6.0, 2 H); 7.22 – 7.43 (*m*, 5 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 9.7; 19.2; 19.4; 37.9; 50.7; 69.7; 73.0; 73.3; 74.4; 74.8; 127.5; 127.7; 128.3; 130.2. ESI-MS: 287 ($[M + Na]^+$).

(6*R*)-2,6-Anhydro-1-*O*-benzyl-3,5-dideoxy-5-ethyl-4-*O*-(methoxymethyl)-6-methyl-D-*xylo*-hexitol (**13**). To alcohol **12** (0.61 g, 2.3 mmol) in anh. CH_2Cl_2 (20 ml) at 0 °C were added diisopropylethyl amine (3.15 ml, 18.4 mmol), cat. DMAP, and MOMCl (0.69 g, 9.2 mmol) successively, and the mixture was stirred for 3 h at r.t. Then, the reactions was quenched by adding H_2O (6 ml) and extracted with CH_2Cl_2. The org. extracts were washed with brine (5 ml), dried (Na_2SO_4), and concentrated under vacuum to remove the solvent and the crude was purified by CC to afford the pure product **13** (0.65 g, 90%) as an oil. $[\alpha]_D^{25} = -25.7$ ($c = 1.95$, $CHCl_3$). IR (neat): 3449, 2933, 2884, 1100, 1037, 738. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.87 (*t*, *J* = 7.5, 3 H); 1.24 (*d*, *J* = 6.2, 3 H); 1.31 – 1.73 (*m*, 4 H); 1.99 – 2.14 (*m*, 1 H); 3.20 – 3.62 (*m*, 8 H); 4.41 – 4.64 (*m*, 3 H); 4.68 – 4.79 (*d*, *J* = 6.9, 1 H); 7.15 – 7.37 (*m*, 5 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 9.2; 19.0; 19.4; 34.8; 48.5;

55.4; 73.0; 73.2; 74.3; 74.8; 75.2; 94.8; 127.4; 127.6; 128.2; 138.1. ESI-MS: 331 ([M + Na]$^+$).

(6*R*)-2,6-Anhydro-3,5-dideoxy-5-ethyl-4-*O*-(methoxymethyl)-6-methyl-D-*xylo*-hexitol (**14**). To a soln. of Li (0.05 g, 8.0 mmol) in liquid NH_3 (20 ml) was added compound **13** (0.62 g, 2.01 mmol) in dry THF (2 ml). The mixture was stirred for 5 min, and then the reaction was quenched with solid NH_4Cl (350 mg). NH_3 was allowed to evaporate and the residual mixture was taken in Et_2O (10 ml) and washed with H_2O (10 ml), brine (3 ml), and dried (Na_2SO_4). Removal of the solvent and purification by CC of the crude product afforded alcohol **14** (0.4 g, 90%) as a colorless liquid. $[\alpha]_D^{25}$ = −43.2 (c = 1.15, $CHCl_3$). IR (neat): 3447, 2935, 2885, 1379, 1096, 1040, 915. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.88 (*t*, *J* = 7.5, 3 H); 1.25 (*d*, *J* = 6.0, 3 H); 1.40 – 1.76 (*m*, 4 H); 1.94 – 2.06 (*m*, 1 H); 3.30 – 3.68 (*m*, 8 H); 4.62 (*d*, *J* = 6.7, 1 H); 4.78 (*d*, *J* = 6.7, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 9.4; 19.1; 19.4; 34.0; 48.7; 55.5; 65.9; 74.9; 75.0; 75.5; 95.1. ESI-MS: 241 ([M + Na]$^+$).

(4*R*,5*R*,6*R*)-5-ethyltetrahydro-4-(methoxymethoxy)-6-methyl-2*H*-pyran-2-one (**7**). To the activated molecular sieves (3Å; 3 g) were added PCC (2.84 g, 13.2 mmol) and dry benzene (22 ml). To this mixture was added a soln. of **14** (0.36 g, 1.65 mmol) in benzene (20 ml) and stirred under reflux for 6 h. Et_2O (50 ml) was added and the mixture was filtered through a short pad of *Celite* and SiO_2. The filter cake was washed thoroughly with Et_2O (2 × 30 ml) and the filtrate was concentrated. The residue after flash chromatography afforded the lactone **7** (0.2 g, 60%) as a colorless liquid. $[\alpha]_D^{25}$ = +24.5 (c = 0.65, $CHCl_3$). IR (neat): 3449, 2927, 1747, 1036, 764. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.00 (*t*, *J* = 7.3. 3 H); 1.22 – 1.31 (*m*, 2 H); 1.42 (*d*, *J* = 6.2, 3 H); 1.50 – 1.67 (*m*, 1 H); 2.55 – 2.73 (*m*, 2 H); 3.36 (*s*, 3 H); 3.90 (*q*, *J* = 4.5, 1 H); 3.95 – 4.06 (*m*, 1 H); 4.62 (*q*, *J* = 7.1, 2 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 10.4; 19.8; 22.2; 35.5; 48.0; 55.6; 72.8; 76.6; 95.0; 174.9. HR-EI-MS: 203.1282 ([M + H]$^+$, $C_{10}H_{19}O_4^+$; calc. 203.1278).

(6*R*)-2,6-Anhydro-6-[(2*S*)-1-(benzyloxy)propan-2-yl]-3,5-dideoxy-5-methyl-D-*xylo*-hexitol (4). Trifluoroacetic acid (50.9 ml) was added slowly to a soln. of the homoallylic alcohol **5** (3.68 g, 31.7 mmol) and (*S*)-3-(benzyloxy)-2-methylpropanal (**6**; 16.9 g, 95.1 mmol) in CH_2Cl_2 (50 ml) at r.t. under a N_2 atmosphere. The mixture was stirred for 3 h and then sat. aq. $NaHCO_3$ soln. (40 ml) was added and pH was adjusted to > 7 by addition of Et_3N. The layers were separated and the aq. layer was extracted with CH_2Cl_2 (3 × 40 ml) and the org. layers were combined and the solvent was removed under reduced pressure. The residue was dissolved in MeOH (30 ml) and stirred with K_2CO_3 (1.95 g) for 0.5 h. The MeOH was then removed under reduced pressure and H_2O (15 ml) was added. The mixture was extracted with CH_2Cl_2 (3 × 20 ml) and the combined org. layers were dried ($MgSO_4$) and the solvent was removed under reduced pressure. CC of the crude afforded **4** (5.6 g, 60%) as a colorless oil. $[\alpha]_D^{25}$ = +8.7 (c = 1.8, $CHCl_3$). IR (neat): 3407, 2926, 2863, 1095, 744. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.85 (*d*, *J* = 6.9, 3 H); 0.95 (*d*, *J* = 6.2, 3 H), 1.30 – 1.60 (*m*, 2 H); 1.74 – 1.91 (*m*, 1 H); 1.93 – 2.24 (*m*, 1 H); 3.16 – 3.85 (*m*, 7 H); 4.45 (*d*, *J* = 4.1, 2 H); 7.16 – 7.36 (*m*, 5 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 9.5; 12.0; 34.1; 36.6; 40.3; 67.4; 70.4; 71.4; 73.0; 75.4; 79.4; 127.3; 127.4; 128.2; 138.5. ESI-MS: 317 ([M + Na]$^+$).

2,6-Anhydro-6-[(2*S*)-1-(benzyloxy)propan-2-yl]-3,5-dideoxy-5-methyl-1-*O*-[(4-methylphenyl)sulfonyl]-D-*xylo*-hexitol (**16**). To a soln. of diol **4** (3.28 g, 11.1 mmol) in dry CH_2Cl_2 (5 ml), Et_3N (6.2 ml, 44.6 mmol) was added at 78 °C followed by addition of tosyl chloride (2.53 g, 13.3 mmol) over 2 h. The mixture was allowed to warm to r.t. and to stir for 5 h. The reaction was treated with aq. 1N HCl (2 ml) and extracted with CH_2Cl_2 (3 × 10 ml). The org. layer was washed with sat. aq. $NaHCO_3$ (6 ml) and H_2O (6 ml). The combined org. phases were dried (Na_2SO_4) and concentrated under reduced pressure. Flash chromatography of the crude afforded tosylate **16** (4.25 g, 85%) as a gummy liquid. $[\alpha]_D^{25}$ = +10.3 (c = 0.7, $CHCl_3$). IR (neat): 3449, 2924, 2854, 1730, 1177, 769. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.74 (*d*, *J* = 7.3, 3 H); 0.90 (*d*, *J* = 6.5, 3 H); 1.07 – 1.52 (*m*, 2 H); 1.66 (br. *s*, 1 H); 1.79 – 2.19 (*m*, 2 H); 2.43 (*s*, 3 H); 3.03 – 3.43 (*m*, 4 H); 3.43 – 3.63 (*m*, 1 H); 3.75 – 4.18 (*m*, 2 H); 4.43 (*d*, *J* = 4.1, 2 H); 7.15 – 7.44 (*m*, 7 H); 7.72 (*d*, *J* = 8.2, 2 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 9.3; 11.9; 21.6; 34.0; 36.8; 40.1; 71.9; 72.4; 72.8; 73.0; 73.1; 79.4; 127.4; 127.5; 127.8; 128.3; 129.7; 132.8; 138.6; 144.7. ESI-MS: 471 ([M + Na]$^+$).

(6*R*)-2,6-Anhydro-6-[(2*S*)-1-(benzyloxy)propan-2-yl]-3,5-dideoxy-5-methyl-1-*O*-[(4-methylphenyl)sulfonyl]-4-*O*-[tri(propan-2-yl)silyl]-D-*xylo*-hexitol (**17**). To a stirred soln. of compound **16** (4.11 g, 9.17 mmol) in dry CH_2Cl_2 (25 ml) was added 2,6-lutidine (3.2 ml, 27.5 mmol) at 0 °C, then added triisopropylsilyl triflouoromethanesulphonate (2.9 ml, 11.0 mmol). The mixture was stirred for 1 h at 0 °C, the reaction was quenched with a sat. aq. NH_4Cl soln. (10 ml) and extracted with CH_2Cl_2. The org. layer was separated and aq. layer was extracted with CH_2Cl_2. Combined org. layer was washed with H_2O, brine, and dried (Na_2SO_4). Solvent was removed *in vacuo* and purified the residue by SiO_2 CC to afford **17** (5.0 g, 90% yield). $[\alpha]_D^{25}$ = −6.8 (c = 0.8, $CHCl_3$). IR (neat): 3448, 2927, 2862, 1364, 1178, 1092, 979, 670. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.74 (*d*, *J* = 6.9, 3 H); 0.90 (*d*, *J* = 6.6, 3 H); 1.05 (*s*, 18 H); 1.18 – 1.60 (*m*, 5 H); 1.75 – 1.88 (*dd*, *J* = 2.8, 12.2, 1 H); 1.92 – 2.09 (*m*, 1 H); 2.43 (*s*, 3 H); 3.08 – 3.28 (*m*, 2 H); 3.31 – 3.41 (*t*, *J* = 8.6, 1 H); 3.43 – 3.59 (*m*, 2 H); 3.81 – 3.99 (*m*, 2 H); 4.45 (*q*, *J* = 12.2, 2 H); 7.13 – 7.40 (*m*, 7 H); 7.65 – 7.85 (*m*, 2 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 9.3; 12.4; 12.7; 18.1; 21.6; 34.2; 37.6; 40.7; 72.1; 72.2; 73.0; 73.1; 74.1; 79.5; 127.4; 127.5; 127.8; 128.3; 129.7; 132.9; 138.7; 144.6. ESI-MS: 627 ([M + Na]$^+$).

(1*R*,5*R*)-1,5-Anhydro-1-[(2*S*)-1-(benzyloxy)propan-2-yl]-2,4-dideoxy-5-(iodomethyl)-2-methyl-3-*O*-[tri(propan-2-yl)silyl]-D-*threo*-pentitol (**18**). NaI (17.7 g, 118 mmol) was

added to a soln. of **17** (4.82 g, 7.9 mmol) in 10 ml of acetone and heated to reflux for 24 h. Acetone was removed under reduced pressure. To the residue was added H_2O (8 ml) and AcOEt (10 ml) and the org. layer was separated, dried (Na_2SO_4), concentrated, and chromatographed to afford **18** (4.25 g, 95%) as a liquid. $[\alpha]_D^{25} = -16.0$ (c = 1.05, $CHCl_3$). IR (neat): 3449, 2937, 2863, 1460, 1093, 677. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.85 (*d*, *J* = 6.7, 3 H); 0.93 (*d*, *J* = 6.4, 3 H); 1.07 (*s*, 18 H); 1.16 – 1.70 (*m*, 5 H); 1.94 – 2.23 (*m*, 2 H); 3.00 – 3.17 (*m*, 2 H); 3.18 – 3.26 (*dd*, *J* = 1.8, 10.1, 1 H); 3.26 – 3.40 (*m*, 2 H); 3.41 – 3.64 (*m*, 2 H); 4.51 (*s*, 2 H); 7.27 – 7.38 (*m*, 5 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 9.6; 11.9; 12.3; 12.7; 18.1; 34.4; 40.6; 41.5; 73.1; 73.2; 74.3; 74.5; 79.5; 127.4; 127.7; 128.2; 138.8. ESI-MS: 560 (M^+).

(2*S*,3*R*,4*R*,5*R*)-1-(Benzyloxy)-2,4-dimethyl-5-{[tri(propan-2-yl)silyl]oxy}oct-7-en-3-ol (**19**). To the iodide **18** (4.18 g, 7.46 mmol) in EtOH (25 ml), Zn dust (9.7 g, 149 mmol) was added. The mixture was refluxed for 1 h and then was cooled to 25 °C. Addition of solid NH_4Cl (0.5 g) and Et_2O (10 ml) followed by stirring for 5 min gave a gray suspension. The suspension was filtered through *Celite* and filtrate was concentrated under reduced pressure. Purification by flash chromatography gave **19** (2.6 g, 80%) as a colorless liquid. $[\alpha]_D^{25} = +4.7$ (c = 1.25, $CHCl_3$). IR (neat): 3488, 2938, 2864, 1459, 1090, 882, 675. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.76 (*d*, *J* = 6.7, 3 H), 0.89 (*d*, *J* = 6.7, 3 H); 1.08 (*s*, 18 H); 1.34 – 1.46 (*m*, 3 H); 1.72 – 1.96 (*m*, 2 H); 2.32 – 2.47 (*m*, 2 H); 3.37 – 3.58 (*m*, 2 H); 3.77 – 3.90 (*m*, 1 H); 4.10 – 4.22 (*m*, 1 H); 4.50 (*q*, *J* = 7.5, 2 H); 4.94 – 5.16 (*m*, 2 H); 5.66 – 5.90 (*m*, 1 H); 7.14 – 7.46 (*m*, 5 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 9.1; 12.1; 12.6; 18.1; 35.6; 38.0; 39.8; 73.2; 73.4; 74.6; 76.1; 116.9; 127.4; 127.5; 128.3; 135.6; 138.6. ESI-MS: 435 (M^+).

(5*R*,6*R*,7*R*)-5-[(2*S*)-1-(Benzyloxy)propan-2-yl]-6,10-dimethyl-9,9-di(propan-2-yl)-7-(prop-2-en-1-yl)-2,4,8-trioxa-9-silaundecane (**20**). The compound **20** (2.5 g, 90%) was prepared from **19** (2.5 g, 5.7 mmol) as a yellow liquid following the same procedure as described for the synthesis of **13**. $[\alpha]_D^{25} = +1.0$ (c = 1.15, $CHCl_3$). IR (neat): 3448, 2929, 2864, 1636, 1037, 763, 673. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.81 (*d*, *J* = 6.4, 6 H); 1.06 (*s*, 18 H); 1.19 – 1.40 (*m*, 3 H); 1.58 – 1.83 (*m*, 1 H); 1.90 – 2.16 (*m*, 1 H); 2.23 – 2.48 (*m*, 2 H); 3.23 – 3.48 (*m*, 5 H); 3.67 – 3.84 (*m*, 1 H); 4.05 – 4.28 (*m*, 1 H); 4.47 (*s*, 2 H); 4.63 (*d*, *J* = 2.6, 2 H); 4.92 – 5.14 (*m*, 2 H); 5.53 – 5.82 (*m*, 1 H); 7.16 – 7.39 (*m*, 5 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 9.1; 9.8; 13.1; 18.4; 34.9; 39.0; 40.3; 55.6; 71.4; 72.8; 73.5; 80.9; 98.6; 116.8; 127.3; 127.6; 128.2; 134.8; 138.6. ESI-MS: 501 ([M + Na]$^+$).

(2*S*,3*R*,4*R*,5*R*)-3-(Methoxymethoxy)-2,4-dimethyl-5-{[tri(propan-2-yl)silyl]oxy}oct-7-en-1-ol (**21**). The compound **21** (1.5 g, 90%) was prepared from **20** (2.0 g, 4.18 mmol) as a yellow liquid following the same procedure as described for the synthesis of **14**. $[\alpha]_D^{25} = +25.4$ (c = 0.45, $CHCl_3$). IR (neat): 3426, 2939, 2865, 1462, 1158, 1036, 915, 676. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.73 (*d*, *J* = 6.9, 3 H); 0.80 (*d*, *J* = 6.7, 3 H), 1.08 (*s*, 18 H); 1.22 – 1.31 (*m*, 3 H); 1.62 – 1.80 (*m*, 1 H); 1.81 – 2.00 (*m*, 1 H); 2.27 – 2.51 (*m*, 2 H); 3.43 (*s*, 3 H); 3.46 (*d*, *J* = 8.1, 2 H); 3.75 – 3.86 (*dd*, *J* = 1.7, 9.8, 1 H); 4.04 – 4.17 (*m*, 1 H); 4.64 (*d*, *J* = 6.4, 1 H); 4.83 (*d*, *J* = 6.6, 1 H); 4.96 – 5.14 (*m*, 2 H); 5.54 – 5.77 (*m*, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 8.8; 9.1; 13.3; 18.4; 36.6; 38.9; 40.0; 56.1; 64.9; 71.3; 80.4; 99.0; 117.1; 134.5. ESI-MS: 411 ([M + Na]$^+$).

(2*R*,3*S*,4*R*,5*R*)-3-(Methoxymethoxy)-2,4-dimethyl-5-{[tri(propan-2-yl)silyl]oxy}oct-7-enal (**22**). To a soln. of alcohol **21** (1.13 g, 2.9 mmol) in dry CH_2Cl_2 (20 ml), *Dess–Martin* periodinane (2.47 g, 5.8 mmol) and $NaHCO_3$ (0.48 g, 5.8 mmol) were added at 0 °C under N_2 atmosphere. The turbid soln. was allowed to warm to r.t. and stirred for 1 h. The reaction was diluted with CH_2Cl_2 (15 ml), quenched with sat. aq. $NaHCO_3$ (10 ml), and sat. aq. $Na_2S_2O_3$ (10 ml). The mixture was vigorously stirred until a clear soln. was formed. The org. layer was separated and the aq. layer was extracted with CH_2Cl_2 (2 × 20 ml). The combined org. extracts were washed with brine (1 × 50 ml), dried (Na_2SO_4), filtered and concentrated. CC separation over SiO_2 afforded aldehyde **22** (0.90 g, 80%) as a colorless oil. IR (neat): 3449, 2927, 2860, 1637, 1035, 761, 672. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.84 (*m*, 6 H); 1.08 (*s*, 18 H); 1.22 – 1.30 (*m*, 3 H); 1.69 – 1.84 (*m*, 1 H); 2.29 – 2.53 (*m*, 3 H); 3.20 (*s*, 3 H); 4.04 – 4.35 (*m*, 2 H); 4.57 (*d*, *J* = 6.7, 1 H); 4.72 (*d*, *J* = 6.9, 1 H); 4.93 – 5.20 (*m*, 2 H); 5.53 – 5.84 (*m*, 1 H); 9.70 (*s*, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 6.2; 8.8; 13.2; 18.4; 38.9; 40.2; 49.0; 55.5; 70.9; 80.2; 98.3; 117.2; 134.3; 203.9. ESI-MS: 409 ([M + Na]$^+$).

(4*S*,5*R*,6*R*,7*R*)-5-(Methoxymethoxy)-4,6-dimethyl-7-{[tri(propan-2-yl)silyl]oxy}dec-9-en-3-ol (**23**). Freshly prepared EtMgBr (prepared *in situ* from 0.15 g (6.37 mmol) of Mg and 0.69 g (6.37 mmol) of EtBr in 10 ml of dry THF) was added drop wise to a stirred soln. of aldehyde **22** (0.82 g, 2.12 mmol) in dry THF (10 ml) at 0 °C. After addition was completed, the mixture was allowed to stir at r.t. for 2 h and then quenched with sat. aq. NH_4Cl soln. The org. layer was separated and the compound from aq. layer was extracted with AcOEt (2 × 10 ml). The combined org. layers were washed with H_2O and brine, and dried (Na_2SO_4). Concentration under reduced pressure and purification by SiO_2 CC afforded **23** (0.80 g, 90%) as a viscous liquid. $[\alpha]_D^{25} = +8.0$ (c = 1.85, $CHCl_3$). IR (neat): 3449, 2927, 2863, 1460, 1035, 674. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.81 (*d*, *J* = 6.7, 3 H); 0.88 (*d*, *J* = 6.7, 3 H); 0.94 (*t*, *J* = 7.5, 3 H); 1.09 (*s*, 18 H); 1.22 – 1.33 (*m*, 2 H); 1.35 – 1.58 (*m*, 3 H); 1.59 – 1.81 (*m*, 2 H); 2.29 – 2.46 (*m*, 2 H); 2.88 – 3.11 (br. *s*, 1 H); 3.39 (*s*, 3 H); 3.51 – 3.70 (*m*, 2 H); 4.01 – 4.17 (*td*, *J* = 2.2, 3.7, 1 H); 4.69 (*d*, *J* = 6.0, 1 H); 4.74 (*d*, *J* = 6.0, 1 H); 4.98 – 5.13 (*m*, 2 H); 5.57 – 5.79 (*m*, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 6.4; 9.3; 10.5; 13.2; 18.4; 28.0; 38.7; 39.6; 40.1; 55.8; 71.5; 77.5; 86.9; 99.0; 117.1; 134.4. ESI-MS: 439 ([M + Na]$^+$).

(4*R*,5*S*,6*R*,7*R*)-5-(Methoxymethoxy)-4,6-dimethyl-7-{[tri(propan-2-yl)silyl]oxy}dec-9-en-3-one (**24**). The compound **24** (0.65 g, 85%) was prepared from **23** (0.76 g, 1.82 mmol) as a yellow liquid following the same procedure as described for the synthesis of **22**. $[\alpha]_D^{25} = -14.0$ (c = 0.95, $CHCl_3$). IR (neat): 3447, 2924, 2859, 1713, 1461, 1035, 770, 675. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.83 (*d*, *J* = 6.7, 3 H); 0.98 – 1.19 (*m*, 24 H); 1.20 – 1.50 (*m*, 3 H); 1.58 – 1.82 (*m*, 1 H); 2.24 – 2.47 (*m*, 3 H); 2.47 – 2.71 (*m*, 2 H); 3.20 (*s*, 3 H); 3.99 – 4.27 (*m*, 2 H); 4.44 (*d*, *J* = 6.6, 1 H); 4.56 (*d*, *J* = 6.6, 1 H); 4.95 – 5.17 (*m*, 2 H); 5.52 – 5.80 (*m*, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 7.9; 8.4; 9.1; 13.2; 18.4; 33.6; 39.5; 40.2; 48.5; 55.8; 71.0; 81.2; 98.1; 117.1; 134.4; 212.5. ESI-MS: 437 ([*M* + Na]$^+$).

Ethyl (2*E*,5*R*,6*R*,7*S*,8*R*)-7-(Methoxymethoxy)-6,8-dimethyl-9-oxo-5-{[tri(propan-2-yl)silyl]oxy}undec-2-enoate (**3**). To a stirred soln. of compound **24** (0.61 g, 1.47 mmol) in anh. CH_2Cl_2 (0.5 ml) under N_2 atmosphere were added ethyl acrylate and *Grubbs*' second-generation catalyst (0.12 g, 10 mol-%). The mixture was stirred at r.t. until consumption of all the starting material (1 h). The mixture was concentrated to dryness and applied to CC (SiO_2) to afford **3** in 90% yield (0.65 g). $[\alpha]_D^{25} = +1.1$ (c = 1.65, $CHCl_3$). IR (neat): 3431, 2941, 2867, 1720, 1166, 1035, 676. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.84 (*d*, *J* = 6.7, 3 H); 0.95 – 1.17 (*m*, 21 H); 1.19 – 1.36 (*m*, 6 H); 1.36 – 1.46 (*m*, 3 H); 1.49 – 1.66 (*m*, 1 H); 2.26 – 2.70 (*m*, 5 H); 3.22 (*s*, 3 H); 4.07 (*dd*, *J* = 1.5, 9.0, 1 H), 4.18 (*q*, *J* = 6.7, 2 H); 4.23 – 4.32 (*m*, 1 H); 4.47 (*d*, *J* = 6.0, 1 H); 4.55 (*d*, *J* = 6.0, 1 H); 5.83 (*d*, *J* = 15.8, 1 H); 6.70 – 6.88 (*m*, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 7.8; 8.7; 9.3; 13.0; 14.2; 18.3; 33.6; 38.7; 40.3; 48.3; 55.8; 60.2; 70.4; 80.9; 98.0; 123.4; 144.3; 166.2; 212.4. HR-EI-MS: 487.3448 ([*M* + H]$^+$, $C_{26}H_{51}O_6Si^+$; calc. 487.3449).

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