Stereoselective Total Synthesis of Oxylipins: (6*S*,7*E*,9*R*,10*S*)-6,9,10-Trihydroxyoctadec-7-enoic Acid and (6*Z*,8*R*,9*R*,10*S*)-8,9,10-Trihydroxyoctadec-6-enoic Acid

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The stereoselective total syntheses of oxylipins **1b** and **1c** are described starting from readily accessible natural sugars *via* the *Grubbs* cross-metathesis, *Wittig* olefination, and Zn-mediated reductive elimination as key steps.

Introduction. – Oxylipins are saturated and unsaturated fatty acids that are widely distributed in nature as constituents of various complex lipids or as free carboxylic acids [1][2]. Plant oxylipins are polyunsaturated fatty acid derivatives, which are involved in plant defense responses to pest and pathogen attack. Indeed, some of these molecules show antimicrobial properties, and a few of them act as regulators of plant defense gene expression [3]. In particular, *Dracotium loretense*, a plant belonging to the Araceae family, is widely distributed in Peruvian Amazon and has been extensively used traditionally in Peruvian folk medicine to boost immune function [4–6]. Oxylipins **1a**–**1d**, isolated from the BuOH extract of the corms of *D. loretense*, are known to exhibit potent immunostimulatory effects at 10 μM concentration on human peripheral blood mononuclear cells (PBMCs) proliferation (*Fig.*) [7].

However, there are no reports on the total synthesis of **1c**, despite a recent report on oxylipin **1b** [8]. In continuation of our long-lasting interest on the total synthesis of bioactive natural products [9] by establishing novel synthetic routes, we herein report a

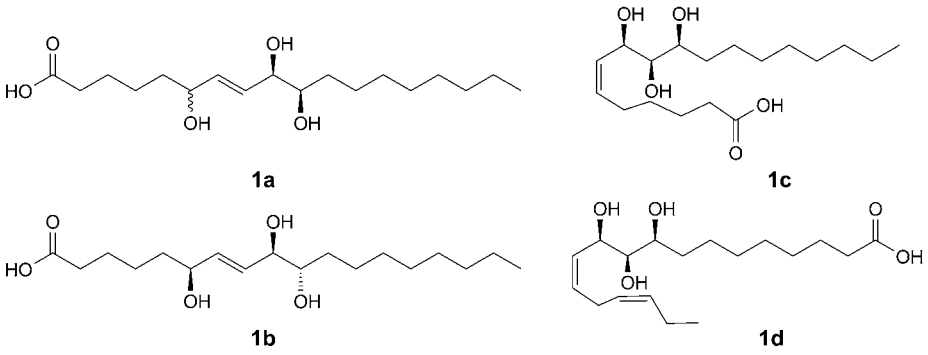

Figure. *Examples of oxylipins* (trihydroxy fatty acids)

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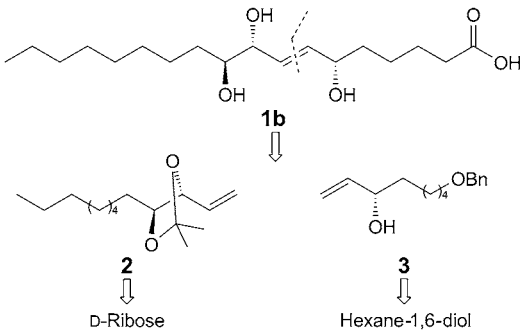
concise synthetic strategy for the most active oxylipins **1b** and **1c**, employing simple sugars as chiral starting materials. Our strategy involves mainly the retention of sugar stereogenic centers in the target molecules.

Results and Discussion. – *Synthesis of Oxylipin* **1b**. Retrosynthesis of **1b** is based on a convergent approach, wherein two fragments **2** and **3** could be coupled by olefin cross-metathesis in analogy to [8]. The fragment **2** was proposed to be obtained from D-ribose, while fragment **3** (chiral vinyl alcohol) could be prepared from hexane-1,6-diol (*Scheme 1*). The synthesis of fragment **2** started from D-ribose acetonide [10]. Treatment of 2,3-O-isopropylidene-D-ribose (**4**) with heptyltriphenylphosphonium bromide ($(Me(CH_2)_6)Ph_3P^+Br^-$) [11] in the presence of BuLi in THF at 0° [12] gave the olefin **5** as a (*E*)/(*Z*)-mixture (2:8) in 90% yield, which was inseparable by column chromatography. The (*E*)/(*Z*) ratio was determined by ^{1}H-NMR spectroscopy. Hydrogenation of **5** using Pd/C under H_2 in EtOH afforded the diol **6** in 98% yield. Treatment of **6** with MsCl in the presence of Et_3N in CH_2Cl_2 gave the bis(methanesulfonate) **7** in 89% yield. Reductive elimination of **7** using Zn powder in DMF [13] led to the olefin **2** in 95% yield (*Scheme 2*).

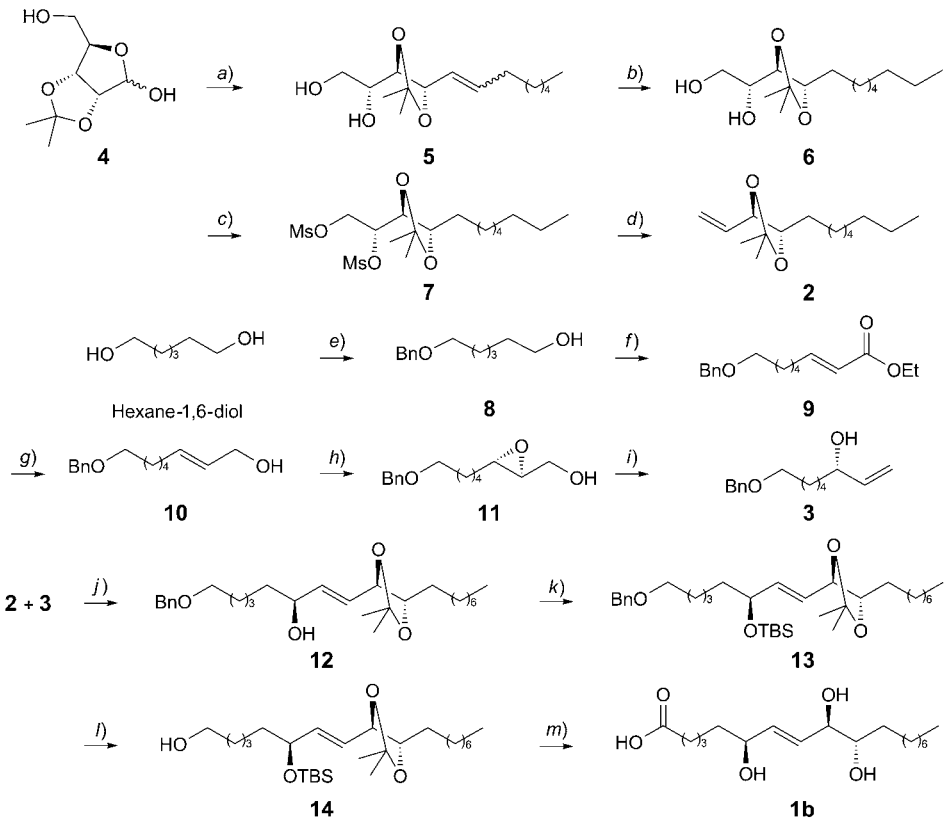
The second fragment **3** was prepared from the commercially available hexane-1,6-diol as outlined in *Scheme 2*. Oxidation of the benzyloxy alcohol **8** [14] under *Swern* conditions afforded the aldehyde, which was then subjected to *Wittig* olefination with ethyl 2-(triphenylphosphoranylidene)acetate ($Ph_3P{=}CHCOOEt$) to give the α,β-unsaturated ester **9** [15] in 92% yield over two steps. Reduction of the ester **9** with DIBAL-H gave the allylic alcohol **10** [16], which was then subjected to *Sharpless* asymmetric epoxidation [17] employing (+)-DET, $Ti(O^iPr)_4$, and ^{t}BuOOH to afford the chiral epoxy alcohol **11** in 88% yield. Treatment of **11** with I_2 in the presence of Ph_3P in THF gave the epoxy iodide, which was then subjected to Zn-mediated reductive elimination [18] to give the chiral allylic alcohol **3** [19] in 96% yield (*Scheme 2*).

The cross-coupling of fragments **2** and **3** was achieved using *Grubbs* 2nd-generation catalyst in CH_2Cl_2 [8]. In this cross-metathesis, the *trans*-isomer **12** was formed exclusively in 70% yield [20]. Protection of the OH group of **12** with TBSOTf in the presence of 2,6-lutidine afforded the silyl ether **13** in 80% yield. Removal of the Bn group in **13** with DDQ gave the primary alcohol **14** in 70% yield, which was then

Scheme 1. *Retrosynthetic Analysis of Oxylipin* **1b**



Scheme 2

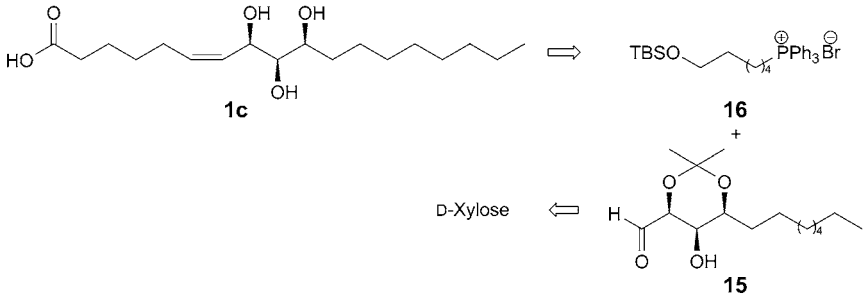


a) BuLi, THF, $(Me(CH_2)_6)Ph_3P^+Br^-$, $-40°$ to r.t.; 90%. *b*) H_2, 10% Pd/C, EtOH, 2 h; 98%. *c*) MsCl, Et_3N, CH_2Cl_2, r.t., 1 h; 89%. *d*) Zn, DMF, reflux, 7 h; 95%. *e*) NaH, BnBr, dry THF, r.t., 4 h; 95%. *f*) 1) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, $-78°$. 2) $Ph_3P{=}CHCO_2Et$, benzene, reflux, 8 h; overall yield for two steps, 92%. *g*) Diisobutylaluminium hydride (DIBAL-H), CH_2Cl_2, 0°, 4 h; 95%. *h*) (2*R*,3*R*)-Diethyl tartrate ((+)-DET), $Ti(O^iPr)_4$, ^{t}BuOOH (TBHP), CH_2Cl_2, 4-Å molecular sieves, 16 h, $-25°$; 88%. *i*) 1) I_2, Ph_3P, 1*H*-imidazole, toluene, 1 h. 2) Zn/EtOH, reflux, 6 h; overall yield for two steps 96%. *j*) *Grubbs*-II catalyst, CH_2Cl_2, r.t., 30 min; 70%. *k*) (*tert*-Butyl)(dimethyl)silyl trifluoromethanesulfonate (TBSOTf), 2,6-lutidine, CH_2Cl_2, 10 min; 80%. *l*) 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), CH_2Cl_2/H_2O 19:1, 4 h, r.t.; 70%. *m*) (Diacetoxyiodo)benzene, 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO), $MeCN/H_2O$ 4:1, 4 h, r.t., then, 3N HCl, THF, 60°, 10 h; 50%.

converted to the carboxylic acid using TEMPO/(diacetoxyiodo)benzene in $MeCN/H_2O$ (4:1) [21]. Global deprotection of TBS and acetonide groups with 3N HCl in THF under reflux conditions furnished the target molecule **1b** in 50% yield (*Scheme* 2). The spectroscopic data for **1b** were in agreement with those reported in the literature [8].

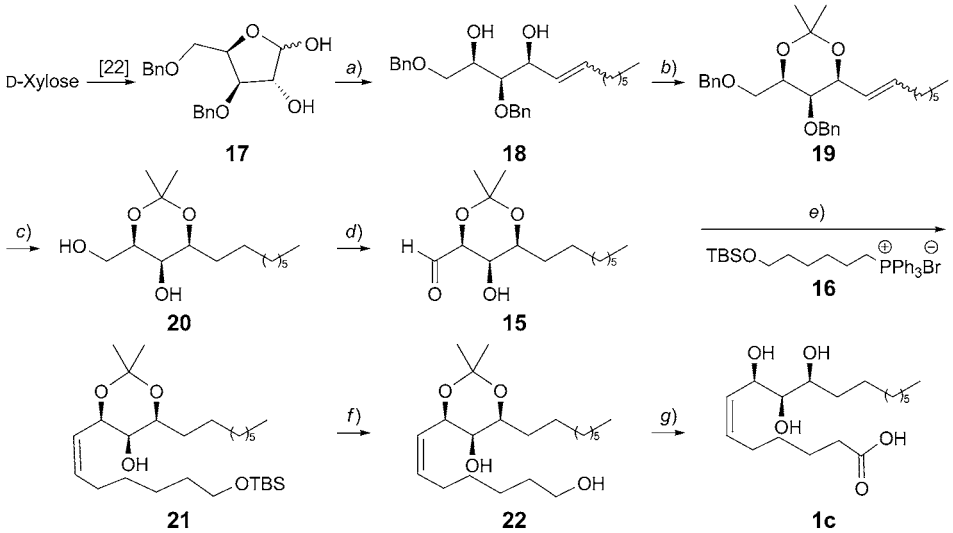
Synthesis of Oxylipin **1c**. Our retrosynthetic analysis of **1c** is depicted in *Scheme 3*. The internal (*Z*)-C=C bond was assumed to be attained through *Wittig* olefination, and the three stereogenic centers of **15** could be obtained from D-xylose. The (^{t}Bu)Me_2Si (TBS)-protected *Wittig* salt **16** could be prepared from 6-bromohexan-1-ol.

Scheme 3. *Retrosynthetic Analysis of Oxylipin* **1c**



The synthesis of aldehyde **15** was initiated from D-xylose. Compound **17** was prepared in four steps as described in [22]. *Wittig* olefination of **17** with $(Me(CH_2)_6)Ph_3P^+Br^-$ in presence of BuLi at 0° afforded the ene-diol **18** in 90% yield with a 9:1 (*E*)/(*Z*) ratio. Protection of **18** (92%) as acetonide, followed by hydrogenation, gave compound **20** in 95% yield. Selective oxidation of **20** with TEMPO/(diacetoxyiodo)benzene in CH_2Cl_2 afforded the aldehyde **15** in 70% yield (*Scheme 4*) [23]. The *Wittig* salt **16** was prepared as described in [24]. The coupling of fragments **15** and **16** through *Wittig* reaction using NaHMDS in THF at −78° gave the en-ol **21** in 70% yield with high diastereoselectivity ((*E*)/(*Z*) 1:9) favoring the (*Z*)-isomer, which

Scheme 4



a) BuLi, dry THF, $(Me(CH_2)_6)Ph_3P^+Br^-$, −40° to r.t.; 90%. *b*) 2,2-Dimethoxypropane/PPTS (cat.), CH_2Cl_2, 30 min, r.t.; 92%. *c*) H_2, 10% Pd/C, EtOH, 3 h; 95%. *d*) (Diacetoxyiodo)benzene, TEMPO, CH_2Cl_2, r.t., 2 h; 70%. *e*) Sodium bis(trimethylsilyl)amide (NaHMDS), dry THF, compound **16**, −78°, 3 h; 70%. *f*) Bu_4NF, THF, 30 min, r.t.; 80%. *g*) (Diacetoxyiodo)benzene, TEMPO, MeCN/H_2O 4:1, r.t., 2 h then 3N HCl, THF, 60°, 6 h; 60%.

was separated by column chromatography. Deprotection of **21** with Bu_4NF in THF gave the diol **22** in 80% yield. Compound **22** was then converted to the acid using TEMPO/(diacetoxyiodo)benzene [25] in MeCN/H_2O 4 : 1, followed by deprotection of the acetonide with 3N HCl in THF under reflux conditions to give the target molecule **1c** in 60% yield (*Scheme 4*). The spectroscopic data and optical rotation of the synthetic compound were identical to those reported for the natural product [7].

Conclusions. – We have reported an efficient and cost-effective synthetic procedure for the total synthesis of oxylipins **1b** and **1c** starting from D-ribose and D-xylose, respectively. The key steps involved were *Grubbs* cross-metathesis, *Wittig* olefination, Zn-mediated elimination, and selective oxidation.

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Experimental Part

General. Solvents were dried over standard drying agents and freshly distilled prior to use. The reagents were purchased from *Aldrich* and *Acros*, and were used without further purification unless otherwise stated. All moisture-sensitive reactions were carried out under N_2. Org. solns. were dried (Na_2SO_4) and concentrated *in vacuo* below 40°. Column chromatography (CC): silica gel (*Acme*'s, 60–120 mesh and 100–200 mesh). Optical rotations: *Horiba* high-sensitive polarimeter *SEPA-300* at 25°. IR Spectra: *PerkinElmer IR-683* spectrophotometer with NaCl optics; $\tilde{\nu}$ in cm^{-1}. ^{1}H- (300 MHz) and ^{13}C-NMR (75 MHz) spectra: *Bruker Avance 300* instrument; δ in ppm rel. to Me_4Si as internal standard, *J* in Hz. MS: *Agilent Technologies 1100 Series* (*Agilent* ChemStation software); in *m*/*z*.

*(1*R*)-1-[(4*R,5S*)-2,2-Dimethyl-5-[(*E/Z*)-oct-1-en-1-yl]-1,3-dioxolan-4-yl]ethane-1,2-diol* (**5**). To a pre-cooled (0°) soln. of the *Wittig* salt ($Me(CH_2)_6)Ph_3P^+Br^-$ (23.15 g, 52.64 mmol) in anh. THF (300 ml) was added BuLi (1.6M in hexane, 24.29 ml, 39.48 mmol) slowly under N_2. The orange-red soln. was stirred under the above conditions for 30 min, and then a soln. of **4** (5 g, 26.32 mmol) in dry THF (50 ml) was added dropwise under N_2. The mixture was stirred at this temp. for another 30 min and then allowed to warm to r.t. The reaction was monitored by TLC (petroleum ether/AcOEt 3 : 1), until all starting materials disappeared. The reaction was then quenched with sat. aq. NH_4Cl (50 ml), and the mixture was extracted with AcOEt (3 × 250 ml). The combined org. phase was dried (Na_2SO_4) and concentrated. Purification of the residue by CC gave **5** (6.44 g, 90%). Syrup. R_f (30% AcOEt/hexane) 0.40. IR (KBr): 3451, 2952, 2921, 2836, 1458, 1376. ^{1}H-NMR (300 MHz, $CDCl_3$): 6.01–5.72 (*m*, 1 H); 5.66–5.52 (*m*, 1 H); 4.15–4.03 (*m*, 1 H); 3.86–3.67 (*m*, 4 H); 2.22–2.02 (*m*, 2 H); 1.47 (*s*, 3 H); 1.36 (*s*, 3 H); 1.33–1.21 (*m*, 8 H); 0.88 (*t*, *J* = 6.7, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 136.6; 136.2; 124.9; 124.6; 108.6; 78.4; 78.1; 69.9; 64.2; 32.3; 31.5; 28.9; 28.8; 27.7; 25.1; 22.5; 14.0. ESI-MS: 295 ($[M+Na]^+$). HR-ESI-MS: 295.22437 ($C_{15}H_{28}NaO_4^+$; calc. 295.22473).

*(1*R*)-1-[(4*R,5S*)-2,2-Dimethyl-5-octyl-1,3-dioxolan-4-yl]ethane-1,2-diol* (**6**). To a soln. of **5** (3.0 g, 11.02 mmol) in MeOH (30 ml) was added 10% Pd/C (100 mg), and the mixture was stirred for 4 h under H_2 with 55 psi pressure. After filtering the catalyst, the solvent was removed and the resulting residue was purified by CC to afford **6** (2.96 g, 98%). Colorless oil. R_f (30% AcOEt/hexane) 0.5. $[\alpha]_D^{30} = -15.2$ (*c* = 1.5, $CHCl_3$). IR ($CHCl_3$): 3445, 2932, 2844, 1642, 1205, 1076. ^{1}H-NMR (300 MHz, $CDCl_3$): 4.27–4.10 (*m*, 1 H); 4.04–3.92 (*m*, 1 H); 3.89–3.70 (*m*, 3 H); 1.79–1.51 (*m*, 4 H); 1.49–1.18 (*m*, 18 H); 0.88 (*t*, *J* = 6.7, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 107.9; 77.9; 77.6; 69.6; 64.6; 31.8; 29.6; 29.5; 29.3; 29.2; 28.0; 26.5; 25.5; 22.6; 14.0. ESI-MS: 297 ($[M+Na]^+$). HR-ESI-MS: 297.20363 ($C_{15}H_{30}NaO_4^+$; calc. 297.20373).

*(1*R*)-1-[(4*S,5S*)-2,2-Dimethyl-5-octyl-1,3-dioxolan-4-yl]-2-[(methylsulfonyl)oxy]ethyl Methanesulfonate* (**7**). To a soln. of **6** (2.0 g, 7.30 mmol) in dry CH_2Cl_2 (50 ml) was added Et_3N (2.16 ml, 21.89 mmol); and the mixture was stirred at 0° under N_2. After 10 min, MsCl (1.75 ml, 15.84 mmol) was added, and the mixture was stirred at r.t. for 4 h. The reaction was quenched with H_2O, and the mixture

extracted with CH_2Cl_2 (2 × 25 ml). The org. extract was washed with H_2O (10 ml), followed by brine (5 ml). The org. layer was dried (Na_2SO_4) and concentrated *in vacuo* to give the crude product, which was purified by CC (10% AcOEt/hexane) to provide **7** (2.78 g, 89%). Colorless oil. R_f (10% AcOEt/hexane) 0.6. $[\alpha]_D^{25} = -21.0$ ($c = 0.5$, $CHCl_3$). IR (KBr) : 2928, 2857, 1443, 1372, 1218, 772. ^{1}H-NMR (300 MHz, $CDCl_3$): 4.87 (*td*, *J* = 2.2, 5.2, 1 H); 4.61 (*dd*, *J* = 2.2, 12.0, 1 H); 4.44 (*dd*, *J* = 5.2, 12.0, 1 H); 4.31 – 4.19 (*m*, 2 H); 3.13 (*s*, 3 H); 3.09 (*s*, 3 H); 1.71 – 1.50 (*m*, 4 H); 1.43 (*s*, 3 H); 1.34 (*s*, 3 H); 1.31 – 1.23 (*m*, 10 H); 0.87 (*t*, *J* = 7.5, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 108.6; 77.0; 76.7; 75.4; 68.2; 39.3; 37.6; 31.7; 29.3; 29.3; 29.1; 28.1; 27.2; 26.7; 24.9; 22.6; 14.0. ESI-MS: 453 ($[M + Na]^+$). HR-ESI-MS: 453.15873 ($C_{17}H_{34}NaO_8S_2^+$; calc. 453.15895).

*(4*R*,5*S*)-4-Ethenyl-2,2-dimethyl-5-octyl-1,3-dioxolane* (**2**). A mixture of **7** (2 g, 4.65 mmol), NaI (4.2 g, 28.02 mmol), and Zn dust (1.82 g, 28.95 mmol) in DMF (20 ml) was heated at 90° for 8 h (TLC). The mixture was brought to r.t., then poured into H_2O (30 ml), and extracted with Et_2O (3 × 15 ml). The combined org. extracts were washed successively with 10% aq. $Na_2S_2O_3$ (1 × 10 ml) soln., H_2O (3 × 10 ml), and brine (1 × 10 ml), and dried (Na_2SO_4). The org. layer was concentrated *in vacuo* to give a crude product, which was purified by CC to provide **2**. (1.06 g, 95%) Colorless oil. R_f (10% AcOEt/hexane) 0.5. $[\alpha]_D^{25} = -5.4$ ($c = 0.8$, $CHCl_3$). IR (KBr): 2981, 2949, 2942, 2837, 1632, 1212, 1055. ^{1}H-NMR (300 MHz, $CDCl_3$): 5.86 – 5.77 (*m*, 1 H); 5.29 (*dd*, *J* = 1.0, 16.8, 1 H); 5.22 (*dd*, *J* = 1.0, 9.8, 1 H); 4.47 (*t*, *J* = 6.9, 1 H); 4.16 – 4.10 (*m*, 1 H); 1.48 (*s*, 3 H); 1.36 (*s*, 3 H); 1.33 – 1.21 (*m*, 14 H); 0.88 (*t*, *J* = 6.9, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 134.5; 117.9; 107.9; 79.8; 78.2; 31.7; 30.2; 29.5; 29.4; 28.6; 28.1; 26.0; 25.5; 22.6; 14.0. ESI-MS: 263 ($[M + Na]^+$). HR-ESI-MS: 263.07910 ($C_{15}H_{28}NaO_2^+$; calc. 263.07912).

6-(Benzyloxy)hexan-1-ol (**8**) [14]. To a stirred suspension of NaH (2.03 g, 84.74 mmol, 60% (*w*/*v*) dispersion in mineral oil) in THF (100 ml) was added a soln. of hexane-1,6-diol (5 g, 42.37 mmol) in THF (20 ml) at 0°. After stirring for 30 min at r.t. Bu_4NF (0.5 g) and BnBr (5.5 ml, 46.60 mmol) were added subsequently, and stirring was continued overnight at r.t. The reaction was then quenched with H_2O (8 ml) at 0°, and the mixture was extracted with AcOEt (2 × 50 ml). The combined org. layers were washed with H_2O (50 ml) and brine (50 ml), and dried (Na_2SO_4). The solvent was removed *in vacuo*, and the residue was purified by CC to afford **8** (8.37 g, 95% yield). Colorless liquid. R_f (10% AcOEt/hexane) 0.2.

*Ethyl (2*E*)-8-(Benzyloxy)oct-2-enoate* (**9**) [15]. To a soln. of Ph_3P=CHCOOEt (3.9 g, 11.52 mmol) in benzene (50 ml), was added the aldehyde (2.0 g, 9.6 mmol) derived from **8** at reflux temp., and the mixture was stirred for another 30 min at the same temp. The solvent was evaporated under reduced pressure, and the product was purified by CC to afford **9** (2.44 g, 92%). Colorless oil. R_f (20% AcOEt/hexane) 0.40.

*(2*E*)-8-(Benzyloxy)oct-2-en-1-ol* (**10**) [16]. To a soln. of **9** (2.0 g, 7.25 mmol) in THF (20 ml) was added DIBAL-H (6.17 ml, 10.8 mmol, 25% in toluene) at −10°, and the resulting soln. was stirred for 30 min at 0°. The soln. was diluted with sodium potassium tartarate and extracted with AcOEt (2 × 50 ml). The org. extracts were washed with H_2O (2 × 25 ml), followed by brine (25 ml), and dried (Na_2SO_4). Evaporation of the solvent, followed by purification, afforded **10** (1.61 g, 95%). Colorless oil. R_f (30% AcOEt/hexane) 0.5.

*{(2*R*,3*R*)-3-[5-(Benzyloxy)pentyl]oxiran-2-yl}methanol* (**11**). A mixture of $Ti(O^iPr)_4$ (0.22 ml, 0.76 mmol), (+)-diethyl D-tatrate ((+)-DET; 0.15 ml, 0.89 mmol) and 3.0 g of activated 4-Å molecular sieves was stirred in 20 ml of anh. CH_2Cl_2 at −30° for 30 min. To this mixture was added **10** (1.5 g, 6.41 mmol) in CH_2Cl_2 (5 ml), and the resulting mixture was stirred at −30° for another 30 min. It was then treated with ^{t}BuOOH (1.26 ml, 3.5M in toluene) and stirred for 4 h at the same temp. Upon completion of the reaction, the mixture was allowed to warm to 0° and poured into freshly prepared cold soln. of $FeSO_4$ and tartaric acid (1.2 g and 0.4 g resp.) in deionized H_2O (1.5 ml). The resulting mixture was stirred for 30 min, and the aq. phase was separated and then extracted with Et_2O. The combined org. layers were treated with 30% aq. NaOH soln. The mixture was then stirred for 1 h at r.t., and the aq. layer was separated and extracted with Et_2O. The combined org. extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The resulting crude product was purified by CC to give **11** (1.41 g, 88%). Colorless liquid. R_f (30% AcOEt/hexane) 0.30. $[\alpha]_D^{25} = -44.8$ ($c = 0.8$, $CHCl_3$). IR (KBr): 3413, 2920, 2867, 1455, 1295, 1124. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.34 – 7.26 (*m*, 5 H); 5.22 – 5.08 (*m*, 2 H); 4.40 (*d*, *J* = 6.7, 2 H); 3.61 (*t*, *J* = 6.7, 1 H); 3.44 (*t*, *J* = 6.7, 1 H); 3.03 – 3.01 (*m*, 2 H); 1.67 – 1.49 (*m*, 2 H); 1.46 –

1.24 (*m*, 6 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 138.3; 128.2; 127.5; 127.3; 72.7; 70.0; 61.6; 58.4; 55.8; 31.3; 29.4; 25.8; 25.6. ESI-MS: 273 ($[M+Na]^+$). HR-ESI-MS: 273.14612 ($C_{15}H_{22}NaO_3^+$; calc. 273.14582).

*(3*R*)-8-(Benzyloxy)oct-1-en-3-ol* (**3**) [19]. To a soln. of **11** (1.20 g, 4.8 mmol) in anh. THF (20 ml) were added 1*H*-imidazole (0.39 g, 5.76 mmol), Ph_3P (1.38 g, 5.28 mmol), and I_2 (0.67 g, 5.28 mmol) at 0°. After 5 min, the cooling bath was removed, and the mixture was stirred for 1 h at r.t. During this period, the color was changed from brown to bright yellow and the mixture became highly viscous. The reaction was then quenched with sat. $Na_2S_2O_3$ soln. (10 ml), and the mixture was extracted with Et_2O (3 × 10 ml). The combined org. layers were washed with brine (10 ml), dried (Na_2SO_4), and concentrated under reduced pressure. Purification of the crude product by CC afforded the iodo compound, which was simultaneously treated with Zn (1.44 g, 24.0 mmol) in refluxing MeOH (20 ml) for 6 h. The mixture was filtered through *Celite* pad and washed with MeOH. The combined MeOH layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by CC to give **3** (1.07 g, 96%). Colorless syrup. R_f (10% AcOEt/hexane) 0.2.

*(1*E*,3*S*)-8-(Benzyloxy)-1-[(4*R*,5*S*)-2,2-dimethyl-5-octyl-1,3-dioxolan-4-yl]oct-1-en-3-ol* (**12**). Compounds **2** (1g, 4.1 mmol) and **3** (1.07g, 4.5 mmol) were mixed in anh. CH_2Cl_2 (2 ml) under N_2. It was then treated with *Grubbs* 2nd-generation catalyst (22 mg, 0.82 mmol) at r.t. After consumption of the starting materials, the reaction was quenched and the solvent was removed under reduced pressure to give a brown residue, which was then purified by CC to afford pure **12** (1.08 g, 70%). Colorless syrup. R_f (20% AcOEt/hexane) 0.5. $[\alpha]_D^{25} = +0.9$ ($c = 0.9$, $CHCl_3$). IR (KBr): 3428, 2928, 2902, 1654, 1476, 1079, 1012. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.43 – 7.28 (*m*, 5 H); 5.73 (*dd*, *J* = 6.0, 15.4, 1 H); 5.62 (*dd*, *J* = 7.5, 15.4, 1 H); 4.58 – 4.44 (*m*, 3 H); 4.20 – 4.07 (*m*, 2 H); 3.46 (*t*, *J* = 6.4, 2 H); 1.69 – 1.56 (*m*, 2 H); 1.48 (*s*, 3 H); 1.36 (*s*, 3 H); 1.32 – 1.19 (*m*, 20 H); 0.87 (*t*, *J* = 6.0, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 138.5; 137.1; 128.3; 127.5; 127.4; 127.0; 108.0; 78.9; 78.3; 72.8; 72.3; 70.2; 36.9; 31.8; 30.3; 29.6; 29.5; 29.2; 28.2; 26.1; 26.1; 25.8; 25.6; 25.2; 22.6; 14.0. ESI-MS: 469 ($[M+Na]^+$). HR-ESI-MS: 469.32883 ($C_{28}H_{46}NaO_4^+$; calc. 469.32897).

*({(1*E*,3*S*)-8-(Benzyloxy)-1-[(4*R*,5*S*)-2,2-dimethyl-5-octyl-1,3-dioxolan-4-yl]oct-1-en-3-yl}oxy)(*tert*-butyl)(dimethyl)silane* (**13**). To a soln. of **12** (0.5 g, 1.12 mmol) in dry CH_2Cl_2 (10 ml) was added EtN^iPr_2 (0.38 ml, 2.24 mmol), and the mixture was stirred at 0° under N_2. After 5 min, (*tert*-butyl)(dimethyl)silyl trifluoromethanesulfonate (TBDMSOTf; 0.28 ml, 1.12 mmol) was added and the mixture was stirred at the same temp. for 10 min. Then, sat. aq. $NaHCO_3$ soln. (10 ml) was added, and the mixture was extracted with CH_2Cl_2 (3 × 12 ml). The org. extract was washed with H_2O and brine, and the org. layer was dried (Na_2SO_4) and concentrated under reduced pressure to give a crude product, which was then purified by CC to provide **13**. (0.5 g, 80%). Colorless oil. R_f (10% AcOEt/hexane) 0.8. $[\alpha]_D^{25} = -0.8$ ($c = 0.45$, $CHCl_3$). IR (KBr): 2942, 2867, 1454, 1361, 1255, 1019. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.39 – 7.29 (*m*, 5 H); 5.67 (*dd*, *J* = 5.4, 15.4, 1 H); 5.56 (*dd*, *J* = 7.5, 15.4, 1 H); 4.53 – 4.43 (*m*, 3 H); 4.16 4.05 (*m*, 2 H); 3.46 (*t*, *J* = 6.6, 2 H); 1.69 – 1.54 (*m*, 2 H); 1.47 (*s*, 3 H); 1.35 (*s*, 3 H); 1.32 – 1.21 (*m*, 20 H); 0.96 – 0.83 (*m*, 12 H); 0.04 (*s*, 3 H); 0.03 (*s*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 137.4; 128.3; 127.5; 127.4; 125.5; 123.7; 101.9; 79.1; 78.4; 72.8; 72.5; 70.3; 38.1; 31.8; 30.5; 29.7; 29.4; 29.2; 28.3; 26.17; 26.16; 25.8; 25.7; 25.0; 24.8; 22.0; 18.1; 14.0; −4.3; −4.8. ESI-MS: 583 ($[M+Na]^+$). HR-ESI-MS: 583.32414 ($C_{34}H_{60}NaO_4Si^+$; calc. 583.32414).

*(6*S*,7*E*)-6-{[(*tert*-Butyl)(dimethyl)silyl]oxy}-8-[(4*R*,5*S*)-2,2-dimethyl-5-octyl-1,3-dioxolan-4-yl]oct-7-en-1-ol* (**14**). To a stirred soln. of **13** (0.5g, 0.89 mmol), in CH_2Cl_2/H_2O 19 : 1 (5 ml) was added DDQ (0.24 g, 0.97 mmol) and the mixture was stirred for 4 h. The reaction was then quenched with solid $NaHCO_3$, and the mixture was extracted with CH_2Cl_2 (3 × 10 ml). The org. extract was washed with H_2O and brine, and the org. layer was dried (Na_2SO_4) and concentrated *in vacuo* to give a crude product, which was then purified by CC to afford **14** (0.32 g, 70%). Colorless oil. R_f (20% AcOEt/hexane) 0.5. $[\alpha]_D^{25} = -5.0$ ($c = 0.05$, $CHCl_3$). IR (KBr): 3467, 2983, 2959, 2932, 2873, 1642, 1217, 1065. ^{1}H-NMR (300 MHz, $CDCl_3$): 5.68 (*dd*, *J* = 5.4, 15.4, 1 H); 5.57 (*dd*, *J* = 7.5, 15.4, 1 H); 4.52 – 4.44 (*m*, 1 H); 4.17 – 4.05 (*m*, 2 H); 3.63 (*t*, *J* = 6.4, 2 H); 1.64 – 1.51 (*m*, 4 H); 1.47 (*s*, 3 H); 1.36 (*s*, 3 H); 1.31 – 1.19 (*m*, 18 H); 0.95 – 0.81 (*m*, 12 H); 0.05 (*s*, 3 H); 0.03 (*s*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 137.3; 125.5; 107.8; 79.1; 78.4; 72.4; 62.9; 38.1; 32.7; 31.8; 30.5; 29.6; 29.4; 29.2; 28.3; 26.1; 25.8; 25.7; 25.7; 24.8; 22.6; 18.2; 14.1; −4.3; −4.8. ESI-MS: 493 ($[M+Na]^+$). HR-ESI-MS: 493.36836 ($C_{27}H_{54}NaO_4Si^+$; calc. 493.36889).

*(6*S*,7*E*,9*R*,10*S*)-6,9,10-Trihydroxyoctadec-7-enoic Acid* (**1b**) [8]. To a stirred soln. of **22** (0.1g, 0.21 mmol) in MeCN/H_2O 4 : 1 (5 ml) were added (diacetoxyiodo)benzene (0.14 g, 0.46 mmol) and TEMPO (0.006 g, 0.04 mmol) at 0°, and stirring was continued at r.t. for 4 h. After completion of the

reaction, the solvent was removed under reduced pressure, and the crude mixture was dissolved in AcOEt, and sat. aq. $Na_2S_2O_3$ soln. (3 ml) was added. The combined org. layers were washed with H_2O (5 ml), followed by brine (3 ml), and dried (Na_2SO_4). The crude residue was dissolved in THF (5 ml), and aq. 3N HCl (0.5 ml) was added at r.t. The resulting mixture was heated at 60° for 10 h. Upon completion, the mixture was neutralized with aq. $NaHCO_3$ soln., and then extracted with $CHCl_3$. The org. layer was washed with H_2O (5 ml), followed by brine (3 ml), and then dried (Na_2SO_4). Removal of the solvent, followed by CC, gave **1b** (0.035g, 50% overall yield). White solid. R_f (5% MeOH/$CHCl_3$) 0.2. $[\alpha]_D^{25} = +6.0$ ($c = 0.25$, MeOH) ($[\alpha]_D^{24} = +6.3$ ($c = 0.980$, MeOH [8]). ^{1}H-NMR (300 MHz, CD_3OD): 5.70 (*dd*, $J = 14.9$, 4.0, 1 H); 5.57 (*dd*, $J = 14.9$, 5.9, 1 H); 4.08 (*q*, $J = 5.9$, 1 H); 3.99 (*dd*, $J = 6.9$, 3.0, 1 H); 3.54–3.52 (*m*, 1 H); 2.30 (*t*, 6.9 Hz, 2 H); 1.68–1.59 (*m*, 2 H); 1.46–1.41 (*m*, 6 H); 1.34–1.20 (*m*, 12 H); 0.88 (*t*, 6 H). ^{13}C-NMR (75 MHz, CD_3OD): 177.3; 137.0; 130.8; 76.5; 75.0; 73.1; 37.7; 34.2; 33.7; 31.2; 30.8; 30.7; 30.4; 28.3; 27.0; 26.4; 23.8; 14.2. ESI-MS: 353 ($[M + Na]^+$). HR-ESI-MS: 353.22985 ($C_{18}H_{34}NaO_5^+$; calc. 353.22937).

*(2*R*,3*R*,4*S*,5*E/Z*)-1,3-Bis(benzyloxy)dodec-5-ene-2,4-diol* (**18**). To a pre-cooled (0°) soln. of the *Wittig* salt ($Me(CH_2)_6)Ph_3P^+Br^-$ (10.66 g, 24.24 mmol) in anh. THF (100 ml) was slowly added BuLi (1.6M in hexane, 11.18 ml, 18.18 mmol) under N_2. The orange red soln. was stirred for 30 min, and then a soln. of **17** (336 mg, 1.12 mmol) in dry THF (15 ml) was added dropwise under N_2. The mixture was stirred at the same temp. for another 30 min and then allowed to warm to r.t. The reaction was monitored by TLC until all starting materials disappeared. The reaction was then quenched by sat. aq. NH_4Cl (50 ml), and the mixture was extracted with AcOEt (3 × 100 ml). The combined org. phases were dried (Na_2SO_4) and concentrated. Purification of the residue by CC gave **18** (4.49 g, 90%). Syrup. IR (KBr): 3405, 2955, 2932, 1655, 1455, 1365. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.39–7.28 (*m*, 10 H); 4.76–4.46 (*m*, 5 H); 3.98–3.85 (*m*, 3 H); 3.62–3.46 (*m*, 3 H); 2.24–1.98 (*m*, 2 H); 1.43–1.19 (*m*, 8 H); 0.87 (*d*, $J = 6.9$, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 137.8; 137.7; 134.6; 134.2; 128.9; 128.47; 128.40; 128.3; 128.0; 127.9; 127.86; 127.80; 82.0; 81.7; 75.3; 75.1; 73.4; 73.0; 71.2; 71.0; 70.4; 70.1; 68.2; 31.6; 29.4; 28.9; 27.8; 25.5; 14.0. ESI-MS: 435 ($[M + Na]^+$).

*(4*R*,5*R*,6*S*)-5-(Benzyloxy)-4-[(benzyloxy)methyl]-2,2-dimethyl-6-[(*E/Z*)-oct-1-en-1-yl]-1,3-dioxane* (**19**). To a stirred soln. of **18** (4.0 g, 9.71 mmol) in dry CH_2Cl_2 (50 ml) at 0° was added 2,2-dimethoxypropane (2.37 ml, 19.42 mmol), followed by catalytic amount of pyridinium *p*-toluenesulfonate (PPTS). After stirring at r.t. for 4 h, the reaction was quenched with solid $NaHCO_3$. The mixture was diluted with H_2O and extracted with CH_2Cl_2 (3 × 50 ml). The combined org. layers were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by CC to afford **19** (4.03 g, 92%). Colourless liquid. R_f (10% AcOEt/hexane) 0.6. IR (KBr): 2932, 2850, 1452, 1372, 1208. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.76–7.65 (*m*, 5 H); 7.53–7.40 (*m*, 5 H); 5.91–5.67 (*m*, 2 H); 5.62–5.48 (*m*, 2 H); 5.02–4.93 (*m*, 0.5 H); 4.61 (*t*, $J = 6.7$, 1.5 H); 4.05–3.95 (*m*, 2 H); 3.80–3.58 (*m*, 3 H); 2.17–2.01 (*m*, 2 H); 1.44 (*s*, 3 H); 1.42–1.24 (*m*, 11 H); 0.9 (*t*, $J = 6.2$, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 138.2; 137.2; 133.4; 128.3; 128.1; 127.7; 127.5; 127.2; 126.8; 98.7; 74.6; 73.4; 72.6; 71.2; 69.4; 68.7; 31.6; 29.7; 29.4; 28.9; 28.0; 22.5; 19.1; 14.0. ESI-MS: 475 ($[M + Na]^+$).

*(4*R*,5*R*,6*S*)-4-(Hydroxymethyl)-2,2-dimethyl-6-octyl-1,3-dioxan-5-ol* (**20**). To a soln. of **19** (4.0 g, 8.85 mmol) in EtOH (20 ml) was added 10% Pd/C (100 mg), and the mixture was stirred for 4 h under H_2 at 55 psi pressure. After filtering the catalyst, the solvent was evaporated, and the resulting residue was purified by CC to afford **20** (2.30 g, 95%). White solid. R_f (40% AcOEt/hexane) 0.5. $[\alpha]_D^{25} = -5.4$ ($c = 0.9$, $CHCl_3$). IR (KBr): 3442, 2986, 2952, 13751, 1220, 1056. ^{1}H-NMR (300 MHz, $CDCl_3$): 4.16–4.07 (*m*, 1 H); 3.91 (*td*, $J = 1.5$, 6.0, 1 H); 3.85–3.69 (*m*, 3 H); 1.61–1.50 (*m*, 2 H); 1.46 (*s*, 3 H); 1.43 (*s*, 3 H); 1.32–1.22 (*m*, 12 H); 0.87 (*t*, $J = 7.5$, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 99.3; 73.2; 72.8; 65.6; 63.7; 31.8; 30.8; 29.7; 29.4; 29.4; 29.2; 24.8; 22.6; 19.0; 14.0. ESI-MS: 297 ($[M + Na]^+$). HR-ESI-MS: 297.20363 ($C_{15}H_{30}NaO_4^+$; calc. 297.20373).

*(4*S*,5*R*,6*S*)-5-Hydroxy-2,2-dimethyl-6-octyl-1,3-dioxane-4-carbaldehyde* (**15**). To a soln. of **20** (2.0 g, 7.30 mmol) in dry CH_2Cl_2 (30 ml), (diacetoxyiodo)benzene (2.82 g, 8.76 mmol) and TEMPO (0.22, 1.46 mmol) were added at 0° under N_2 and stirred for 2 h at r.t. Then, the reaction was quenched by sat. aq. $Na_2S_2O_3$ soln. (10 ml). The combined org. layers were washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. The crude residue was purified by CC to give **15** (1.4 g, 70%). Colorless liquid. R_f (20% AcOEt/hexane) 0.6. $[\alpha]_D^{25} = -2.1$ ($c = 0.5$, $CHCl_3$). IR (KBr): 3405, 2955, 2932, 1720, 1695,

1365. ^{1}H-NMR (300 MHz, $CDCl_3$): 8.97 (*s*, 1 H); 4.20–4.12 (*m*, 1 H); 3.95–4.01 (*m*, 1 H); 3.85–3.72 (*m*, 1 H); 1.60–1.49 (*m*, 2 H); 1.48 (*s*, 3 H); 1.45 (*s*, 3 H); 1.35–1.22 (*m*, 12 H); 0.90 (*t*, *J* = 7.2, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 200.5; 99.7; 74.1; 73.5; 69.5; 32.1; 30.7; 30.4; 29.9; 29.5; 29.5; 29.1; 23.4; 19.8; 14.2. ESI-MS: 295 ($[M + Na]^+$).

*(4*R*,5*R*,6*S*)-4-[(1*Z*)-7-{[(*tert-*Butyl)(dimethyl)silyl]oxy}hept-1-en-1-yl]-2,2-dimethyl-6-octyl-1,3-dioxan-5-ol* (**21**). To a pre-cooled soln. of **16** (4.05 g, 7.30 mmol) in anh. THF (50 ml) was added NaHMDS (7.29 ml, 1M in hexane, 7.30 mmol) slowly under N_2. The orange red soln. was stirred for *ca.* 30 min at the same temp., and then a soln. of **15** (1 g, 3.65 mmol) in dry THF (10 ml) at $-78°$ was added dropwise under N_2. The resulting mixture was stirred at this temp. for another 30 min and then allowed to warm to r.t. The reaction was monitored by TLC until all starting materials disappeared. It was then quenched with sat. aq. NH_4Cl (20 ml), and the mixture was extracted with AcOEt (3 × 20 ml). The combined org. phases were dried (Na_2SO_4) and concentrated. Purification of the residue by CC gave **21** (1.2 g, 70%; (*Z*)/(*E*) 9:1, determined by ^{1}H-NMR). Colorless syrup. R_f (20% AcOEt/hexane) 0.5. $[\alpha]_D^{25} = -24.5$ (*c* = 1.0, $CHCl_3$). IR (neat): 3455, 2986, 2935, 1365, 1221, 1155, 1056. ^{1}H-NMR (300 MHz, $CDCl_3$): 5.67–5.62 (*m*, 2 H); 4.61 (*dd*, *J* = 5.5, 14.5, 1 H); 3.81 (*td*, *J* = 1.1, 6.6, 1 H); 3.78–3.71 (*m*, 1 H); 3.60 (*t*, *J* = 6.6, 2 H); 2.17–2.02 (*m*, 2 H); 1.88–182 (*m*, 2 H); 1.51 (*s*, 3 H); 1.44 (*s*, 3 H); 1.40–1.22 (*m*, 18 H); 0.91–0.85 (*m*, 12 H); 0.05 (*s*, 6 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 134.3; 126.3; 91.1; 72.9; 69.4; 67.7; 63.0; 32.6; 31.8; 31.2; 29.9; 29.5; 29.2; 28.0; 25.9; 25.5; 25.4; 24.9; 22.6; 19.0; 18.3; 14.0; −5.2. ESI-MS: 493 ($[M + Na]^+$). HR-ESI-MS: 493.36836 ($C_{27}H_{54}NaO_4Si^+$; calc. 493.36889).

*(4*R*,5*R*,6*S*)-4-[(Z)-7-Hydroxyhept-1-en-1-yl]-2,2-dimethyl-6-octyl-1,3-dioxan-5-ol* (**22**). To a stirred soln. of **21** (0.5 g, 1.06 mmol) in dry THF (5 ml) at 0° was added Bu_4NF (0.27 ml, 1.06 mmol). After stirring at r.t. for 2 h, the mixture was diluted with H_2O (5 ml) and extracted with AcOEt (3 × 10 ml). The combined org. layers were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The crude residue was purified by CC to afford **22** (0.3 g, 80%). Colorless oil. R_f (20% AcOEt/hexane) 0.6. $[\alpha]_D^{25} = -15.6$ (*c* = 0.5, $CHCl_3$). IR (neat): 3446, 2972, 2951, 1368, 1219, 1165, 1054. ^{1}H-NMR (300 MHz, $CDCl_3$): 5.69–5.60 (*m*, 2 H); 4.61 (*dd*, *J* = 5.4, 12.0, 1 H); 3.81 (*td*, *J* = 1.0, 7.6, 1 H); 3.67–3.62 (*m*, 3 H); 2.18–2.06 (*m*, 2 H); 1.64–1.54 (*m*, 4 H); 1.51 (*s*, 3 H); 1.44 (*s*, 3 H); 1.37–1.24 (*m*, 16 H); 0.88 (*t*, *J* = 6.5, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 134.1; 126.4; 99.2; 72.9; 69.5; 67.6; 62.8; 32.4; 31.8; 31.2; 29.9; 29.6; 29.5; 29.2; 27.9; 27.1; 25.3; 24.9; 22.6; 19.0; 14.0. ESI-MS: 379 ($[M + Na]^+$). HR-ESI-MS: 379.24550 ($C_{21}H_{40}NaO_4^+$; calc. 379.24607).

(*6*Z*,8*R*,9*R*,10*S*)-8,9,10-Trihydroxyoctadec-6-enoic Acid* (**1c**) [7]. To a stirred soln. of **22** (0.2 g, 10.56 mmol) in MeCN/H_2O 4:1 (10 ml) were added (diacetoxyiodo)benzene (0.39 g, 1.2 mmol) and TEMPO (0.017 g, 0.11 mmol) at 0° and the stirring was continued for 4 h at r.t. After completion of the reaction, the solvent was removed under reduced pressure, and the crude mixture was dissolved in AcOEt, and sat. aq. $Na_2S_2O_3$ soln. (3 ml) was added. The combined org. layers were washed with H_2O (5 ml), brine (5 ml) and dried (Na_2SO_4), and concentrated *in vacuo*. The crude residue was dissolved in THF and treated with aq. 3N HCl (0.5 ml), and the mixture was heated at 60° for 10 h. The mixture was then neutralized with sat. aq. $NaHCO_3$ and extracted with $CHCl_3$. The org. layer was washed with H_2O (5 ml), brine (5 ml) and dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by CC to provide **1c** (0.11 g, 60%). White solid. R_f (5% MeOH/$CHCl_3$) 0.2. $[\alpha]_D^{25} = -16.8$ (*c* = 0.9, MeOH); [7]: $[\alpha]_D^{24} = -17.4$ (*c* = 0.2, MeOH). ^{1}H-NMR (300 MHz, $CDCl_3$): 5.61 (*dt*, *J* = 10.9, 6.7, 1 H); 5.49 (*ddt*, *J* = 10.9, 9.8, 1.3, 1 H); 4.50 (*dd*, *J* = 7.1, 6.7, 1 H); 3.75 (*m*, 1 H); 3.30 (*dd*, *J* = 6.7, 1.5, 1 H); 2.27 (*t*, *J* = 8.3, 2 H); 1.73–1.50 (*m*, 6 H); 1.49–1.19 (*m*, 14 H); 0.94 (*t*, *J* = 6.6, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 178.3; 135.1; 131.0; 76.8; 71.7; 69.0; 35.0; 34.7; 33.0; 30.3; 30.2; 29.9; 29.7; 28.5; 26.3; 25.8; 23.7; 14.3. ESI-MS: 353 ($[M + Na]^+$). HR-ESI-MS: 353.22985 ($C_{18}H_{34}NaO_5^+$; calc. 353.22912).

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