

# **Synthetic Variants of Mycolactone Bind and Activate Wiskott-Aldrich Syndrome Proteins – supporting information**

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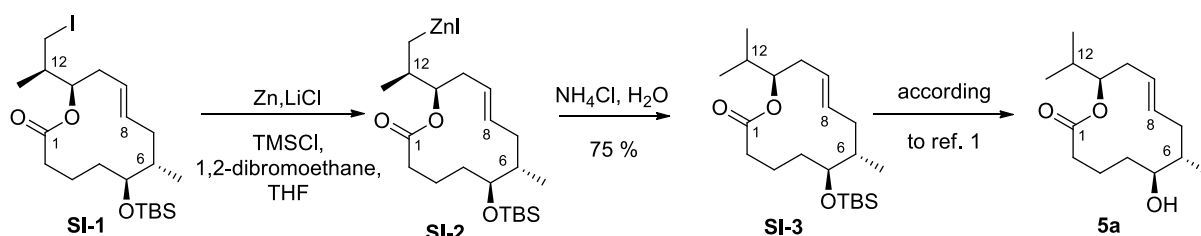
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## 1. Material and methods

NMR spectra were recorded on Bruker AV 300 or AV 400 spectrometer and calibrated using undeuterated solvent as internal reference, unless otherwise indicated. Coupling constants ( $J$ ) were reported in Hertz. Attached proton tests (APT) were performed to distinguish between different carbons in the  $^{13}\text{C}$  NMR spectra. The following abbreviations were used to explain multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and b = broad. Optical rotations were recorded on a Perkin Elmer polarimeter (model 341LC) and are expressed in  $\text{deg}\cdot\text{cm}^2\cdot\text{g}^{-1}$  units. High-resolution mass spectra (HRMS) were recorded on an Agilent Q-TOF (ESI) coupled with a 1100 series HPLC. Melting points were recorded on a Büchi 510 melting point apparatus. All reactions were carried out in oven-dried glassware under an argon atmosphere using dry solvents, unless otherwise noted. Tetrahydrofuran (THF) was distilled under argon from sodium-benzophenone, toluene was dried using the Dry Solvent Station GT S100 developed by GlassTechnology and dichloromethane was distilled over  $\text{CaH}_2$ . All other anhydrous solvents were purchased from Sigma-Aldrich. Reagents were purchased from Aldrich, Acros or Alfa Aesar and used without further purification, unless otherwise noted. Yields refer to chromatographically and spectroscopically ( $^1\text{H}$  NMR) homogenous materials, unless otherwise noted. Reactions were monitored by thin-layer chromatography (TLC) carried out on Merck TLC silica gel 60 F254 glass-coated plates, using UV light, iodine vapor, potassium permanganate as visualizing agents. All separations were performed by flash chromatography on Merck silica gel 60 (40–63  $\mu\text{m}$ ) unless otherwise specified. Ozone was generated by passing 100% oxygen through an Argentox ozone generator GLX2. Microwave reactions were performed in a CEM Intelligent Explorer (Model 541416) microwave.

## 2. Syntheses of the southern fragments of mycolactone analogues



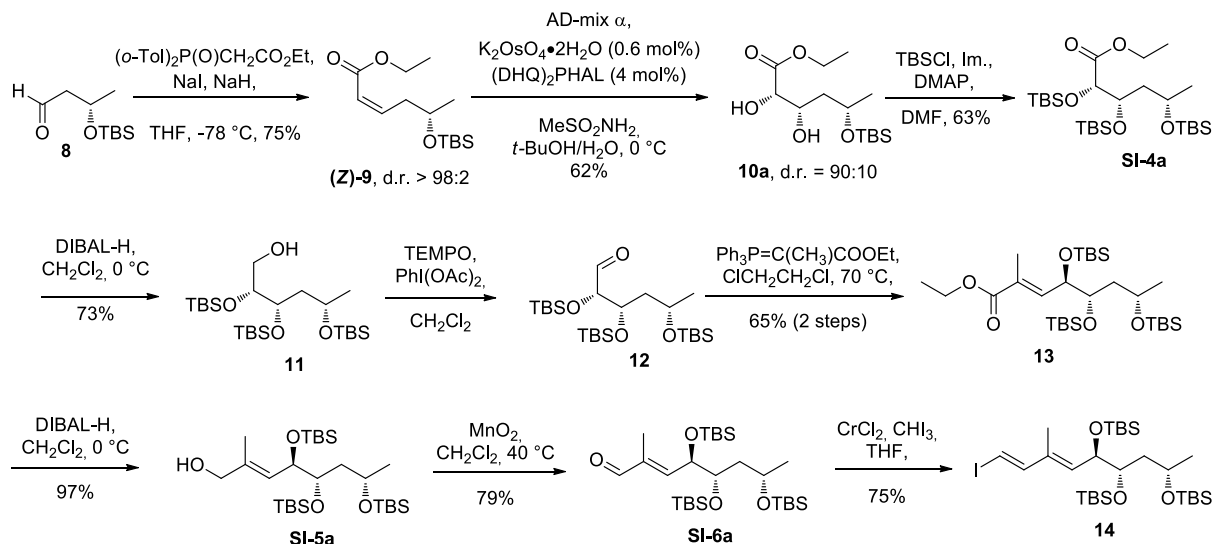
### (6*S*,7*S*,9*E*,12*R*)-6-(*tert*-Butyldimethylsilyloxy)-12-isopropyl-7-methoxacyclododec-9-en-2-one (SI-3)

Anhydrous  $\text{LiCl}$  (2.71 mmol, 115 mg) was placed in an argon-flushed flask and dried for 30 min at 150  $^\circ\text{C}$  under high vacuum.  $\text{Zn}$  powder (3.68 mmol, 241 mg) was added under argon and the heterogeneous mixture was dried again for 30 min at 150  $^\circ\text{C}$  under high vacuum. After cooling to 25  $^\circ\text{C}$ , the flask was evacuated and refilled with argon three times. THF (2.2 mL) was added and the  $\text{Zn}$  was activated with 1,2-dibromoethane (0.71 mmol, 63  $\mu\text{L}$ ) and  $\text{TMSCl}$  (0.49 mmol, 63  $\mu\text{L}$ ). After stirring for 10 minutes a solution of SI-1, prepared as previously described<sup>1</sup> (192 mg, 0.39 mmol) in THF (0.5 mL) was added. The reaction mixture was then stirred at room temperature for 12 h before being hydrolyzed with a saturated aqueous solution of  $\text{NH}_4\text{Cl}$ . The aqueous phase was extracted with ethyl acetate, and the combined organic phases were washed with brine and dried over  $\text{MgSO}_4$ . After being filtered and

concentrated under reduced pressure, the crude product was purified by preparative TLC (elution with heptane/ethyl acetate 90:10, to give **SI-3** (112 mg, 0.30 mmol, 77 %) as a colorless oil.

The spectroscopic data are in agreement with those reported in the literature.<sup>1</sup>

## 2.1 Variation of the C12',C13',C15' stereocluster



### (S,Z)-Ethyl 5-((*tert*-butyldimethylsilyl)oxy)hex-2-enoate ((Z)-9)

To a stirred solution of  $(o\text{-Tol})_2\text{P(O)CH}_2\text{CO}_2\text{Et}$  (4.70 g, 13.50 mmol, 1.3 eq.) in dry THF (105 mL), under a nitrogen atmosphere, were added NaI (1.56 g, 10.40 mmol) at  $0\text{ }^\circ\text{C}$ . After 5 min, NaH (60% dispersion, 540 mg, 13.50 mmol, 1.3 eq.) was added. The resulting solution was cooled to  $-78\text{ }^\circ\text{C}$  and **8**<sup>3</sup> (2.10 g, 10.40 mmol) was added dropwise. After stirring 3 h at  $-78\text{ }^\circ\text{C}$ , saturated aqueous  $\text{NH}_4\text{Cl}$  solution was added and the reaction mixture was extracted three times with  $\text{Et}_2\text{O}$ . The combined organic extracts were washed with brine, dried over  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (cyclohexane/ $\text{EtOAc}$  9:1) to afford **(Z)-9** (2.11 g, 7.75 mmol, 75 %) as a pale yellow oil.

**<sup>1</sup>H NMR** ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  6.35 (dt,  $J = 11.6, 6.3\text{ Hz}$ , 1H), 5.84 (dt,  $J = 11.6, 1.7\text{ Hz}$ , 1H), 4.17 (q,  $J = 7.1\text{ Hz}$ , 2H), 3.96 (dq,  $J = 6.6, 6.1, 5.0\text{ Hz}$ , 1H), 2.88-5.68 (2H), 1.29 (t,  $J = 7.1\text{ Hz}$ , 3H), 1.16 (d,  $J = 6.1\text{ Hz}$ , 3H), 0.88 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H).

**<sup>13</sup>C NMR** ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  166.4, 146.9, 120.7, 67.9, 59.8, 38.6, 25.8 (3C), 23.7, 18.0, 14.2, -4.5, -4.8.

**HRMS-ESI** calculated for  $\text{C}_{14}\text{H}_{29}\text{O}_3\text{Si}$  :  $m/z$  273.1886 ( $[\text{M}+\text{H}]^+$ ), found :  $m/z$  273.1881 ( $[\text{M}+\text{H}]^+$ ).

$[\alpha]_D^{20} = +12.9$  (c 1.4,  $\text{CHCl}_3$ ).

### (2S,3S,5S)-Ethyl 5-((*tert*-butyldimethylsilyl)oxy)-2,3-dihydroxyhexanoate (10a)

To a stirred solution of AD-mix  $\alpha$  (5.06 g, 0.4 % osmium, 1 %  $(\text{DHQ})_2\text{PHAL}$ ) in a mixture 1:1  $t\text{-BuOH}/\text{H}_2\text{O}$  (30:30 mL) were added successively methanesulfonamide (300 mg, 3.15 mmol 0.9 eq.), potassium osmate(VI) dihydrate (10 mg, 27.14  $\mu\text{mol}$ , 0.6 mol%) and  $(\text{DHQ})_2\text{PHAL}$  (114 mg, 0.15 mmol, 4 mol%). The mixture was stirred at room temperature until two clear phases were produced. The solution was

cooled to 0 °C, whereupon the inorganic salts partially precipitate, and **(Z)-9** (1.00 g, 3.68 mmol) was then added. After stirring 48 h at 0 °C, Na<sub>2</sub>SO<sub>3</sub> (9.2 g) was added and the reaction mixture was stirred for 30 min at room temperature. The mixture was extracted three times with EtOAc. The combined organic extracts were washed with an aqueous KOH solution (2M), brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude product was purified by chromatography (cyclohexane/EtOAc 8:2) to give an inseparable mixture of diastereoisomers (700 mg, 2.29 mmol, 62 %, 90:10 in favor of the desired diastereoisomer **10a**) as a colorless oil.

**<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)** δ 4.34-4.18 (5H), 3.29 (br s, 1H), 3.00 (br s, 1H), 1.80 (m, 1H), 1.40 (m, 1H), 1.32 (t, *J* = 7.1 Hz, 3H), 1.22 (d, *J* = 6.2 Hz, 3H), 0.89 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H).

**<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)** δ 172.6, 74.3, 70.1, 66.5, 61.8, 39.3, 25.8 (3C), 23.1, 17.9, 14.2, -4.5, -5.1.

**HRMS-ESI** calculated for C<sub>14</sub>H<sub>31</sub>O<sub>5</sub>Si : *m/z* 307.1941 ([M+H]<sup>+</sup>), found : *m/z* 307.1940 ([M+H]<sup>+</sup>).

#### **(2S,3S,5S)-Ethyl 2,3,5-tris((*tert*-butyldimethylsilyl)oxy)hexanoate (SI-4a)**

To a stirred solution of **10a** (700 mg, 2.29 mmol) in dry DMF (23 mL), under a nitrogen atmosphere, were added *tert*-butyldimethylsilyl chloride (2.07 g, 13.70 mmol, 6 eq.), imidazole (622 mg, 9.15 mmol, 4 eq.) and DMAP (56 mg, 0.46 mmol, 0.2 eq.). The reaction mixture was stirred at room temperature for 48 h. The resulting solution was hydrolyzed with water and the aqueous layer was extracted three times with a mixture of cyclohexane and DCM (9:1). The combined organic extracts were washed with water, brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude product was purified by chromatography (cyclohexane/EtOAc 20:1) to give an inseparable mixture of diastereoisomers (766 mg, 1.43 mmol, 63 %, 90:10 in favor of the desired diastereoisomer **SI-4a**) as a colorless oil.

**<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)** δ 4.15 (q, *J* = 7.1 Hz, 2H), 4.15 (d, *J* = 2.3 Hz, 1H), 4.07 (ddd, *J* = 7.5, 4.3, 2.3 Hz, 1H), 3.89 (m, 1H), 1.79 (ddd, *J* = 14.1, 7.8, 4.1 Hz, 1H), 1.59 (ddd, *J* = 14.1, 7.6, 4.6 Hz, 1H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.16 (d, *J* = 6.1 Hz, 3H), 0.92 (s, 9H), 0.88 (s, 9H), 0.87 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H), 0.08 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H).

**<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)** δ 171.7, 77.5, 73.3, 65.8, 60.5, 44.6, 25.93 (3C), 25.90 (3C), 25.8 (3C), 24.6, 18.4, 18.1, 18.0, 14.2, -3.5, -4.0, -4.3, -4.6, -4.9, -5.3.

**HRMS-ESI** calculated for C<sub>26</sub>H<sub>58</sub>O<sub>5</sub>NaSi<sub>3</sub> : *m/z* 557.3490 ([M+Na]<sup>+</sup>), found : *m/z* 557.3492 ([M+Na]<sup>+</sup>).

#### **(2R,3S,5S)-2,3,5-tris((*tert*-Butyldimethylsilyl)oxy)hexan-1-ol (11)**

To a stirred solution of **SI-4a** (766 mg, 1.43 mmol) in dry DCM (12 mL), under a nitrogen atmosphere, was added DIBAL-H (2.2 mL, 1.5 M in toluene, 3.15 mmol, 2.2 eq.) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h. Saturated aqueous Rochelle salt solution was then added, and the resulting mixture warmed to room temperature and vigorously stirred overnight. The aqueous layer was extracted with Et<sub>2</sub>O and the combined organic extracts were washed with water, brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude alcohol was purified by chromatography (cyclohexane/EtOAc 95:5) to afford **11** (511 mg, 1.04 mmol, 73 %) as a pure diastereoisomer and **11b** (51 mg, 0.10 mmol, 7 %).

**<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)** δ 3.97-3.90 (2H), 3.73 (dd, *J* = 12.5, 6.6 Hz, 1H), 3.63-3.57 (2H), 1.69 (ddd, *J* = 14.2, 8.3, 3.8 Hz, 1H), 1.50 (ddd, *J* = 14.2, 7.5, 3.6 Hz, 1H), 1.17 (d, *J* = 6.2 Hz, 3H), 0.92 (s, 9H), 0.89 (s, 9H), 0.88 (s, 9H), 0.13 (s, 3H), 0.11 (s, 3H), 0.10 (s, 3H), 0.10 (s, 3H), 0.08 (s, 6H).

**<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)** δ 76.4, 73.6, 66.2, 63.7, 45.5, 26.0 (3C), 25.94 (3C), 25.93 (3C), 24.9, 18.3, 18.2, 18.0, -3.4, -3.9, -4.2, -4.3, -4.5, -4.6.

**HRMS-ESI** calculated for C<sub>24</sub>H<sub>57</sub>O<sub>4</sub>Si<sub>3</sub>: *m/z* 493.3565 ([M+H]<sup>+</sup>), found: *m/z* 493.3561 ([M+H]<sup>+</sup>).

**[α]<sub>D</sub><sup>20</sup>** = + 9.7 (c 0.9, CHCl<sub>3</sub>).

#### **(2*S*,3*S*,5*S*)-2,3,5-tris((*tert*-Butyldimethylsilyl)oxy)hexanal (**12**)**

To a stirred solution of **11** (500 mg, 1.01 mmol) in dry DCM (2.0 mL), under a nitrogen atmosphere, were added iodosobenzene diacetate (360 mg, 1.12 mmol, 1.1 eq.) and TEMPO (16 mg, 0.10 mmol, 0.1 eq.) at 0 °C. The reaction mixture was stirred at room temperature for 5 h. Water was then added to the reaction mixture which was extracted three times with DCM. The combined organic extracts were washed with water, brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude aldehyde **12** was used in the next step without further purification.

**<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)** δ 9.62 (d, *J* = 1.9 Hz, 1H), 4.08 (m, 1H), 3.91 (ddd, *J* = 7.9, 6.1, 4.2 Hz, 1H), 3.87 (dd ap.t, *J* = 2.0 Hz, 1H), 1.75 (ddd, *J* = 14.1, 7.9, 4.3 Hz, 1H), 1.61 (ddd, *J* = 14.1, 7.2, 4.2 Hz, 1H), 1.17 (d, *J* = 6.1 Hz, 3H), 0.94 (s, 9H), 0.89 (s, 9H), 0.87 (s, 9H), 0.13 (s, 3H), 0.11 (s, 6H), 0.08 (s, 9H).

#### **(4*R*,5*S*,7*S*,*E*)-Ethyl 4,5,7-tris((*tert*-butyldimethylsilyl)oxy)-2-methyloct-2-enoate (**13**)**

To a stirred solution of crude aldehyde **12** in 1,2-dichloroethane (5.0 mL), under a nitrogen atmosphere, was added (1-ethoxycarbonyl ethylidene)triphenyl phosphorane (550 mg, 1.50 mmol, 1.5 eq.) at room temperature. The reaction mixture was warmed to 70 °C and stirred for 48 h. The resulting solution was then cooled to room temperature, the solvent was removed under reduced pressure and the residue purified by chromatography (cyclohexane/EtOAc 95:5) to give **13** (375 mg, 0.65 mmol, 65 %) as a colorless oil.

**<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)** δ 6.69 (dq, *J* = 9.1, 1.4 Hz, 1H), 4.32 (dd, *J* = 9.2, 2.8 Hz, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.96 (m, 1H), 3.88 (dt, *J* = 7.8, 2.9 Hz, 1H), 1.87 (d, *J* = 1.4 Hz, 3H), 1.56 (ddd, *J* = 14.1, 8.6, 3.1 Hz, 1H), 1.38 (ddd, *J* = 14.1, 8.3, 3.8 Hz, 1H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.15 (d, *J* = 6.2 Hz, 3H), 0.89 (s, 18H), 0.87 (s, 9H), 0.12 (s, 3H), 0.09 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H), 0.04 (s, 3H), 0.01 (s, 3H).

**<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)** δ 167.9, 141.8, 127.4, 74.4, 74.3, 66.0, 60.6, 44.8, 26.0 (3C), 25.92 (3C), 25.88 (3C), 24.9, 18.3, 18.2, 18.0, 14.2, 13.4, -3.3, -3.7, -4.2, -4.3, -4.5, -4.8.

**HRMS-ESI** calculated for C<sub>29</sub>H<sub>62</sub>O<sub>5</sub>NaSi<sub>3</sub>: *m/z* 597.3803 ([M+Na]<sup>+</sup>), found: *m/z* 597.3807 ([M+Na]<sup>+</sup>).

**[α]<sub>D</sub><sup>20</sup>** = + 4.4 (c 0.4, CHCl<sub>3</sub>).

#### **(4*R*,5*S*,7*S*,*E*)-4,5,7-tris((*tert*-Butyldimethylsilyl)oxy)-2-methyloct-2-en-1-ol (**SI-5a**)**

To a stirred solution of **13** (375 mg, 0.65 mmol) in dry DCM (4.0 mL), under a nitrogen atmosphere, was added DIBAL-H (0.95 mL, 1.5 M in toluene, 1.43 mmol, 2.2 eq.) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h. Saturated aqueous Rochelle salt solution was then added, and the resulting mixture warmed to room temperature and vigorously stirred overnight. The aqueous layer was extracted with Et<sub>2</sub>O and the combined organic extracts were washed with water, brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude alcohol was purified by chromatography (cyclohexane/EtOAc 9:1) to afford **SI-5a** (338 mg, 0.63 mmol, 97 %) as a colorless oil.

**<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)** δ 5.45 (dq, *J* = 8.9, 1.2 Hz, 1H), 4.27 (dd, *J* = 8.8, 2.6 Hz, 1H), 4.02 (s, 2H), 3.96 (m, 1H), 3.83 (dt, *J* = 7.7, 2.8 Hz, 1H), 1.71 (d, *J* = 1.2 Hz, 3H), 1.54 (ddd, *J* = 14.1, 8.6, 3.1 Hz, 1H), 1.37 (ddd, *J* = 14.1, 7.9, 3.4 Hz, 1H), 1.15 (d, *J* = 6.2 Hz, 3H), 0.89 (s, 9H), 0.89 (s, 9H), 0.88 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H), 0.07 (s, 6H), 0.04 (s, 3H), 0.01 (s, 3H).

**<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)** δ 135.4, 126.6, 74.7, 73.7, 68.7, 66.2, 44.7, 26.1 (3C), 26.0 (3C), 25.9 (3C), 25.0, 18.3, 18.2, 18.0, 14.5, -3.2, -3.5, -4.1, -4.3, -4.5, -4.6.

**HRMS-ESI** calculated for C<sub>27</sub>H<sub>60</sub>O<sub>4</sub>NaSi<sub>3</sub> : *m/z* 555.3697 ([M+Na]<sup>+</sup>), found : *m/z* 555.3699 ([M+Na]<sup>+</sup>).

**[α]<sub>D</sub><sup>20</sup>** = + 12.3 (c 1.0, CHCl<sub>3</sub>).

#### **(4*R*,5*S*,7*S*,*E*)-4,5,7-tris((*tert*-Butyldimethylsilyl)oxy)-2-methyloct-2-enal (SI-6a)**

To a stirred solution of **SI-5a** (338 mg, 0.63 mmol) in dry DCM (6.3 mL), under a nitrogen atmosphere, was added MnO<sub>2</sub> (830 mg, 9.52 mmol, 15 eq.) at room temperature. The reaction mixture was warmed to 40 °C and vigorously stirred for 48 h. The resulting mixture was cooled to room temperature and filtered through celite with DCM. The solvent was then removed under reduced pressure to give **SI-6a** (265 mg, 0.50 mmol, 79 %) as a colorless oil which was used in the next step without further purification.

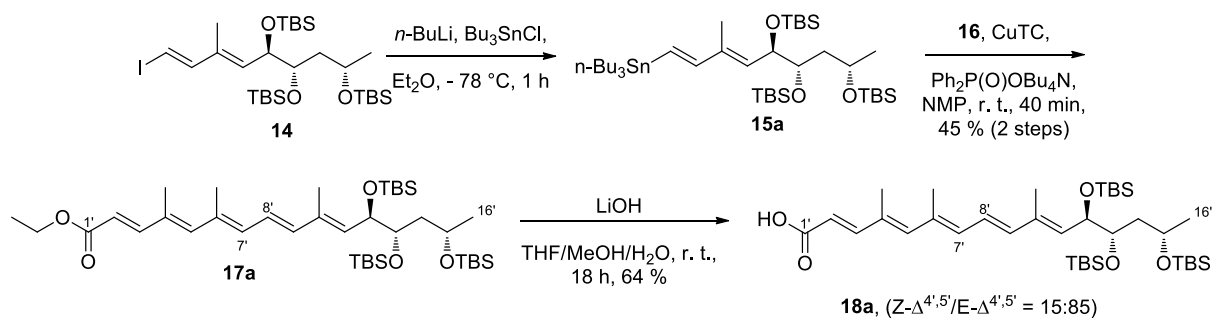
**<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)** δ 9.45 (s, 1H), 6.44 (dq, *J* = 8.9, 1.4 Hz, 1H), 4.49 (dd, *J* = 8.9, 2.6 Hz, 1H), 3.99-3.93 (2H), 1.80 (d, *J* = 1.4 Hz, 3H), 1.51 (ddd, *J* = 14.1, 8.9, 3.0 Hz, 1H), 1.36 (ddd, *J* = 14.1, 7.9, 3.0 Hz, 1H), 1.15 (d, *J* = 6.2 Hz, 3H), 0.89 (s, 18H), 0.87 (s, 9H), 0.14 (s, 3H), 0.11 (s, 3H), 0.07 (s, 6H), 0.05 (s, 3H), 0.01 (s, 3H).

#### **(1*E*,3*E*)-(5*R*,6*S*,8*S*)-tris-(*tert*-Butyldimethylsilyloxy)-1-iodo-3-methyl-nona-1,3-diene (14)**

To a stirred solution of CrCl<sub>2</sub> (368 mg, 3.00 mmol, 6 eq.) in dry THF (3.0 mL), under a nitrogen atmosphere, was added a solution of **SI-6a** (265 mg, 0.50 mmol) and CHI<sub>3</sub> (590 mg, 1.49 mmol, 3 eq.) in dry THF (2.1 mL) dropwise. The reaction mixture was stirred at room temperature for 12 h. The resulting mixture was hydrolyzed with water and diluted with Et<sub>2</sub>O. The aqueous layer was extracted three times with Et<sub>2</sub>O and the combined organic extracts were washed with water, brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude product was then purified by chromatography (cyclohexane/toluene 100:1) to afford **14** (250 mg, 0.38 mmol, 75 %) as a pale yellow oil.

**<sup>1</sup>H NMR (C<sub>6</sub>D<sub>6</sub>, 300 MHz)** δ 7.05 (d, *J* = 14.1 Hz, 1H), 6.01 (d, *J* = 14.1 Hz, 1H), 5.56 (dq, *J* = 9.1, 1.2 Hz, 1H), 4.40 (dd, *J* = 9.1, 2.8 Hz, 1H), 4.12 (m, 1H), 4.05 (dt, *J* = 7.8, 2.8 Hz, 1H), 1.69 (ddd, *J* = 14.1, 8.9, 2.8 Hz, 1H), 1.57 (ddd, *J* = 14.1, 7.9, 2.9 Hz, 1H), 1.47 (d, *J* = 1.2 Hz, 3H), 1.13 (d, *J* = 6.2 Hz, 3H), 1.03 (s, 9H), 1.00 (s, 18H), 0.25 (s, 3H), 0.23 (s, 3H), 0.14 (s, 3H), 0.11 (s, 3H), 0.10 (s, 3H), 0.06 (s, 3H).

**<sup>13</sup>C NMR (C<sub>6</sub>D<sub>6</sub>, 100 MHz)** δ 149.6, 135.0, 134.6, 76.6, 75.4, 74.7, 66.9, 45.7, 26.7 (3C), 26.6 (3C), 26.5 (3C), 25.6, 19.0, 18.9, 18.7, 13.1, -2.6, -2.8, -3.6, -3.7, -3.9, -4.1.



**(1E,3E)-(5R,6S,8S)-tris-(tert-Butyldimethylsilyloxy)-1-tributylstannyl-3-methyl-nona-1,3-diene (15a)**

To a stirred solution of **14** (250 mg, 0.38 mmol) in dry Et<sub>2</sub>O (2.0 mL), under a nitrogen atmosphere, was added *n*-BuLi (0.17 mL, 2 M in hexane, 0.57 mmol, 1.5 eq.) at -78 °C. The reaction mixture was stirred for 20 min at -78 °C and Bu<sub>3</sub>SnCl (0.17 mL, 0.57 mmol, 1.5 eq.) was added. The resulting solution was stirred at -78 °C for another 20 min and allowed to warm to room temperature for 1 h. Saturated aqueous NaHCO<sub>3</sub> solution was then added and the aqueous layer was extracted three times with Et<sub>2</sub>O. The combined organic extracts were washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude **15a** was used in the next step without further purification.

**(2E,4E,6E,8E,10E,12R,13S,15S)-Ethyl-12,13,15-tris((tert-butyldimethylsilyl)oxy)-4,6,10-trimethylhexadeca-2,4,6,8,10-pentaenoate (17a)**

To a stirred solution of crude **15a** and tetra-*n*-butylammonium diphenylphosphinate (415 mg, 0.89 mmol, 2.3 eq.) in dry NMP (2.7 mL), under a nitrogen atmosphere, was added 0.2 mL of a solution of **16** in NMP (240 mg, 0.77 mmol, 2 eq., 1.8 mL). After addition of CuTC (150 mg, 0.77 mmol, 2 eq.), the rest of the **16** solution was added dropwise and the resulting mixture was stirred at room temperature for 40 min. The reaction mixture was then diluted with Et<sub>2</sub>O and filtered through neutral alumina oxide. The filtrate was washed with water, brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude product was then purified by preparative TLC (cyclohexane/EtOAc 9:1) to afford **17a** (120 mg, 0.17 mmol, 45 % for two steps) as a yellow oil. NMR analysis showed the presence of mixture of isomers 4'E/4'Z = 93:7.

**<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz, 4'E isomer)** δ 7.95 (d, *J* = 15.3 Hz, 1H, *Z* isomer), 7.38 (d, *J* = 15.5 Hz, 1H, *E* isomer), 6.50 (dd, *J* = 14.9, 11.1 Hz, 1H), 6.37 (d, *J* = 14.9 Hz, 1H), 6.36 (s, 1H), 6.27 (d, *J* = 11.1 Hz, 1H), 5.87 (d, *J* = 15.5 Hz, 1H), 5.57 (d, *J* = 9.1 Hz, 1H), 4.35 (dd, *J* = 9.1, 2.8 Hz, 1H), 4.23 (q, *J* = 7.1 Hz, 2H), 3.96 (m, 1H), 3.87 (dt, *J* = 7.6, 2.9 Hz, 1H), 2.06 (s, 3H), 2.03 (s, 3H), 1.85 (s, 3H), 1.53 (m, 1H), 1.36 (m, 1H), 1.32 (t, *J* = 7.1 Hz, 3H), 1.14 (d, *J* = 6.1 Hz, 3H), 0.89 (s, 9H), 0.88 (s, 9H), 0.87 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H), 0.08 (s, 3H), 0.06 (s, 3H), 0.03 (s, 3H), 0.00 (s, 3H).

**<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz, 4'E isomer)** δ 167.5, 150.7, 143.7, 139.7, 135.1, 134.7, 134.0, 133.9, 132.2, 123.7, 116.1, 74.8, 74.1, 66.2, 60.2, 44.9, 26.1 (3C), 26.0 (3C), 25.9 (3C), 25.0, 18.33, 18.27, 18.0, 17.1, 14.3, 14.2, 13.4, -3.3, -3.5, -4.2, -4.3, -4.6, -4.7.

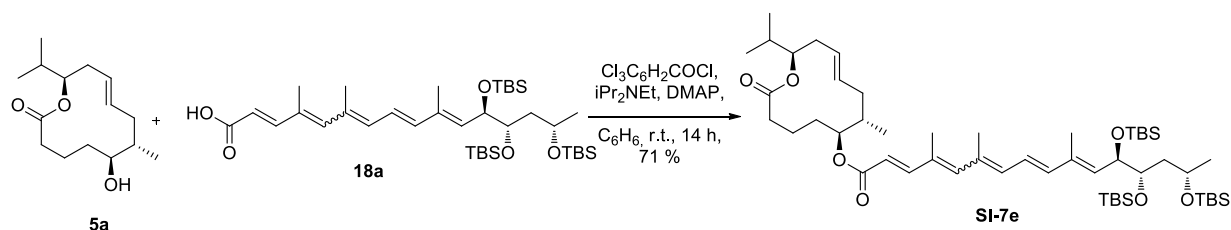
**(2E,4E,6E,8E,10E,12R,13S,15S)-12,13,15-tris((tert-Butyldimethylsilyl)oxy)-4,6,10-trimethylhexadeca-2,4,6,8,10-pentaenoic acid (18a)**

To a stirred solution of **17a** (117 mg, 0.16 mmol) in a mixture THF/MeOH/H<sub>2</sub>O (3.5/0.9/0.9 mL) was added LiOH (40 mg, 1.65 mmol, 10 eq.). The resulting mixture was stirred at room temperature for 18 h. After addition of saturated aqueous NH<sub>4</sub>Cl solution, the mixture was extracted three times with EtOAc and the combined organic extracts were washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude material was purified by preparative TLC (cyclohexane/EtOAc 7:3) to afford **18a** (72 mg, 0.11 mmol, 64 %) as a yellow oil. NMR analysis showed the presence of mixture of isomers 4'E/4'Z = 85:15.

**<sup>1</sup>H NMR (d<sub>6</sub>-Acetone, 300 MHz, 4'E isomer)** δ 7.93 (d, *J* = 15.5 Hz, 1H, *Z* isomer), 7.35 (d, *J* = 15.6 Hz, 1H, *E* isomer), 6.67 (dd, *J* = 15.1, 11.1 Hz, 1H), 6.46 (d, *J* = 15.1 Hz, 1H), 6.46 (s, 1H), 6.39 (d, *J* = 11.1 Hz, 1H), 5.87 (d, *J* = 15.6 Hz, 1H), 5.63 (d, *J* = 9.1 Hz, 1H), 4.49 (dd, *J* = 9.1, 2.8 Hz, 1H), 4.06 (m, 1H), 3.97 (dt, *J* = 7.6, 2.9 Hz, 1H), 2.09 (s, 3H), 2.06 (s, 3H), 1.93 (s, 3H), 1.64 (ddd, *J* = 14.1, 8.8, 3.1 Hz, 1H), 1.41 (ddd, *J* = 14.1, 7.7, 3.2 Hz, 1H), 1.17 (d, *J* = 6.2 Hz, 3H), 0.91 (s, 18H), 0.89 (s, 9H), 0.17 (s, 3H), 0.15 (s, 3H), 0.11 (s, 3H), 0.10 (s, 3H), 0.09 (s, 3H), 0.05 (s, 3H).

**<sup>13</sup>C NMR (d<sub>6</sub>-Acetone, 100 MHz, 4'E isomer)** δ 168.1, 151.6, 144.3, 140.3, 136.2, 135.5, 135.4, 135.0, 133.3, 125.3, 117.3, 75.9, 75.2, 67.1, 45.8, 26.6 (3C), 26.5 (3C), 26.4 (3C), 25.5, 19.0, 18.9, 18.7, 17.2, 14.4, 13.9, -2.9, -3.0, -3.7, -3.8, -4.1, -4.3.

**HRMS-ESI** calculated for C<sub>37</sub>H<sub>70</sub>O<sub>5</sub>NaSi<sub>3</sub> : *m/z* 701.4423 ([M+Na]<sup>+</sup>), found : *m/z* 701.4423 ([M+Na]<sup>+</sup>).



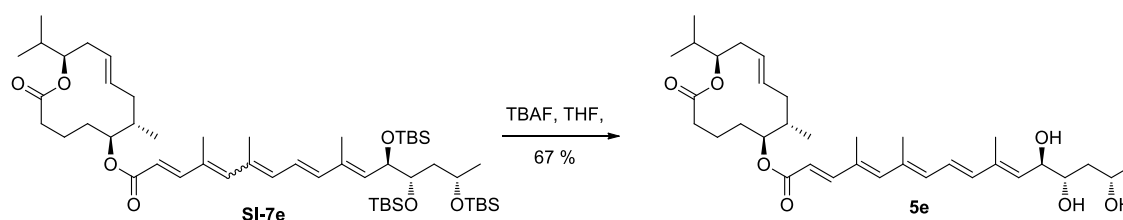
**(6S,7S,9E,12R)-7-Methyl-2-oxo-12-(propan-2-yl)-1-oxacyclododec-9-en-6-yl (2E,4E,6E,8E,10E,12R,13S,15S)-12,13,15-tris[(tert-butyldimethylsilyl)oxy]-4,6,10-trimethylhexadeca-2,4,6,8,10-pentaenoate (SI-7e)**

To a solution of **18a** (22 mg, 0.03 mmol) in benzene (0.4 mL) were added diisopropylethyl amine (23 μL, 0.12 mmol, 6 eq.), 2,4,6-trichlorobenzoyl chloride (11 μL, 0.06 mmol, 3 eq.), and DMAP (20 mg). The reaction mixture was stirred at room temperature for 15 min and **5a** (5.5 mg, 0.02 mmol) was added. After being stirred at room temperature for 14 h, an aqueous saturated solution of sodium hydrogenocarbonate was added to the reaction mixture. The aqueous layer was extracted three times with benzene. The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude product was purified on preparative TLC eluting with heptane/ethyl acetate 90:10 to give **SI-7e** (13 mg, 0.014 mmol, 71 %) as a yellow oil. A (4'E)/(4'Z) = 61:39 mixture could be detected by <sup>1</sup>H analysis.

**<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)** δ 7.93 (d, *J* = 15.5 Hz, 1H, *Z* isomer), 7.36 (d, *J* = 15.5 Hz, 1H, *E* isomer), 6.51 (dd, *J* = 14.8, 11.8 Hz, 1H), 6.37 (d, *J* = 14.8 Hz, 1H), 6.34 (s, 1H), 6.26 (d, *J* = 11.8 Hz, 1H), 5.85 (d, *J* = 15.5 Hz, 1H), 5.56 (d, *J* = 9.0 Hz, 1H), 5.51 (m, 1H), 5.25 (m, 1H), 4.82-4.73 (2H), 4.34 (dd, *J* = 2.8, 8.8 Hz, 1H), 3.94 (m, 1H), 3.86 (td, *J* = 2.8, 7.7 Hz, 1H), 2.49 (m, 1H), 2.30 (m, 1H), 2.14-2.06 (2H), 2.05 (s, 3H),



2.02 (s, 3H), 1.95 (m, 1H), 1.84 (s, 3H), 1.87-1.61 (6H), 1.13 (d,  $J = 6.1$  Hz, 3H), 0.94 (s, 3H), 0.93 (s, 3H), 0.91 (s, 3H), 0.90 (s, 3H), 0.88 (s, 9H), 0.87 (s, 9H), 0.86 (s, 9H), 0.10 (s, 3H), 0.08 (s, 3H), 0.05 (s, 6H), 0.02 (s, 3H), -0.01 (s, 3H).



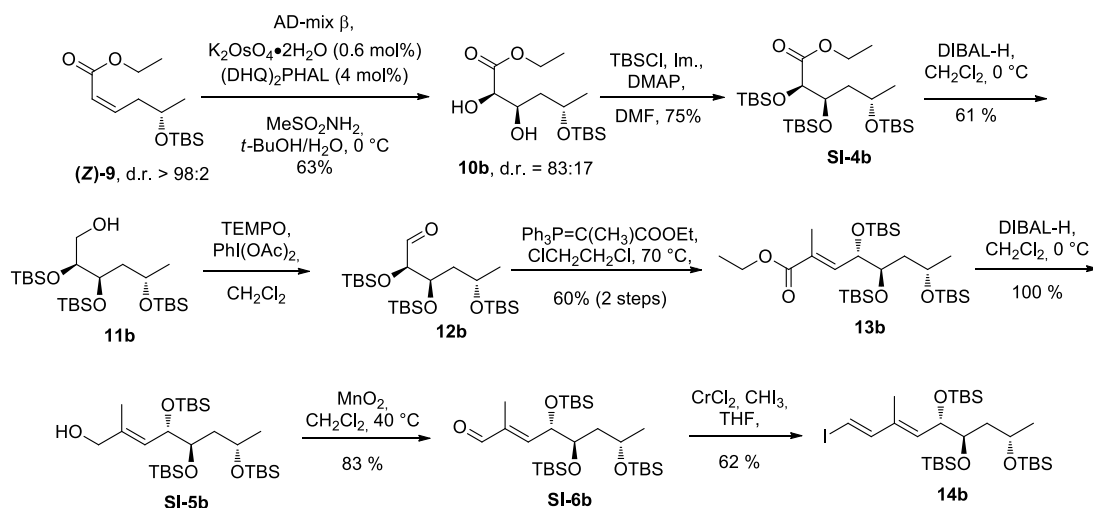
**(6*S*,7*S*,9*E*,12*R*)-7-Methyl-2-oxo-12-(propan-2-yl)-1-oxacyclododec-9-en-6-yl-(2*E*,4*E*,6*E*,8*E*,10*E*,12*R*,13*S*,15*S*)-12,13,15-trihydroxy-4,6,10-trimethylhexadeca-2,4,6,8,10-pentaenoate (5e)**

To a solution of **SI-7e** (13 mg, 0.015 mmol) in THF (0.1 mL) was added TBAF (0.130 mmol, 1M in THF, 9 eq). The solution was stirred at room temperature for 4 h.  $\text{CaCO}_3$  (40 mg), Dowex 50WX8-400 (110 mg) and MeOH (0.3 mL) were added and the reaction mixture was stirred for 1 h. After being filtered and concentrated under reduced pressure, the crude product was purified by TLC preparative ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$  90:10) to give **5e** (6 mg, 0.01 mmol, 67 %). A (4'*E*)/(4'*Z*) = 56:44 mixture could be detected by  $^1\text{H}$  analysis.

**$^1\text{H}$  NMR (Acetone- $d_6$ , 400 MHz)**  $\delta$  7.93 (d,  $J = 15.6$  Hz, 1H, *Z* isomer), 7.37 (d,  $J = 15.5$  Hz, 1H, *E* isomer), 6.63 (dd,  $J = 11.1, 15.0$  Hz, 1H), 6.47 (s, 1H), 6.36 (d,  $J = 15.0$  Hz, 1H), 6.17 (d,  $J = 11.1$  Hz, 1H), 5.89 (d,  $J = 15.5$  Hz, 1H), 5.68 (d,  $J = 8.5$  Hz, 1H), 5.50 (m, 1H), 5.30 (m, 1H), 4.78-4.67 (2H), 4.38 (m, 1H), 4.04 (m, 1H), 3.88 (m, 1H), 3.81 (m, 1H), 3.69 (m, 1H), 3.63 (m, 1H), 2.49 (m, 1H), 2.32 (m, 1H), 2.12-2.08 (2H), 2.06 (s, 3H), 1.97 (s, 3H), 1.95-1.92 (2H), 1.90 (s, 3H), 1.80-1.75 (4H), 1.70-1.62 (2H), 1.54-1.49 (2H), 1.13 (d,  $J = 6.1$  Hz, 3H), 0.92 (s, 3H), 0.90 (s, 3H), 0.87 (s, 3H).

**$^{13}\text{C}$  NMR (Acetone- $d_6$ , 100 MHz)**  $\delta$  173.9, 167.8, 152.2, 144.1, 141.6, 137.3, 136.5, 136.1, 134.1, 133.0, 128.0, 125.8, 120.6, 118.4, 80.2, 77.3, 73.5, 73.3, 65.9, 43.1, 39.8, 37.9, 37.0, 36.1, 34.1, 25.6, 22.0, 21.6, 20.9, 19.9, 19.4, 18.1, 15.3, 14.3.

**HRMS-ESI** calculated for  $\text{C}_{34}\text{H}_{52}\text{O}_7\text{Na}$ :  $m/z$  595.3605 ( $[\text{M}+\text{Na}]^+$ ), found:  $m/z$  595.3600 ( $[\text{M}+\text{Na}]^+$ ).



### **(2R,3R,5S)-Ethyl 5-((tert-butyldimethylsilyl)oxy)-2,3-dihydroxyhexanoate (10b)**

To a stirred solution of AD-mix  $\beta$  (5.06 g, 0.4 % osmium, 1 %  $(DHQD)_2PHAL$ ) in a mixture 1:1  $t-BuOH/H_2O$  (30:30 mL) were added successively methanesulfonamide (300 mg, 3.15 mmol, 0.9 eq.), potassium osmate(VI) dihydrate (10 mg, 27.14  $\mu$ mol, 0.6 mol%) and  $(DHQD)_2PHAL$  (114 mg, 0.14 mmol, 4 mol%). The mixture was stirred at room temperature until two clear phases were produced. The solution was cooled to 0 °C, whereupon the inorganic salts partially precipitate, and **(Z)-9** (950 mg, 3.49 mmol) was then added. After stirring 15 h at 0 °C,  $Na_2SO_3$  (9.2 g) was added and the reaction mixture was stirred for 30 min at room temperature. The mixture was extracted three times with EtOAc. The combined organic extracts were washed with an aqueous KOH solution (2M), brine, dried over  $MgSO_4$ , filtered and concentrated under reduced pressure. The crude product was purified by chromatography (cyclohexane/EtOAc 8:2) to give an inseparable mixture of diastereoisomers (675 mg, 2.20 mmol, 63 %, 83:17 in favor of the desired diastereoisomer **10b**) as a colorless oil.

**$^1H$  NMR (CDCl<sub>3</sub>, 300 MHz)**  $\delta$  4.29 (q,  $J$  = 7.1 Hz, 2H), 4.24-3.98 (3H), 1.76 (ddd,  $J$  = 14.4, 9.9, 8.8 Hz, 1H), 1.56 (ddd,  $J$  = 14.4, 4.3, 2.3 Hz, 1H), 1.32 (t,  $J$  = 7.1 Hz, 3H), 1.21 (d,  $J$  = 6.0 Hz, 3H), 0.90 (s, 9H), 0.12 (s, 3H), 0.11 (s, 3H).

**$^{13}C$  NMR (CDCl<sub>3</sub>, 100 MHz)**  $\delta$  172.4, 74.2, 72.8, 69.2, 61.7, 40.5, 25.8 (3C), 24.3, 17.9, 14.2, -4.0, -4.8.

**HRMS-ESI** calculated for  $C_{14}H_{31}O_5Si$  :  $m/z$  307.1941 ( $[M+H]^+$ ), found : 307.1942 ( $[M+H]^+$ ).

### **(2R,3R,5S)-Ethyl 2,3,5-tris((tert-butyldimethylsilyl)oxy)hexanoate (SI-4b)**

To a stirred solution of **10b** (650 mg, 2.12 mmol) in dry DMF (20 mL), under a nitrogen atmosphere, were added *tert*-butyldimethylsilyl chloride (1.9 g, 12.70 mmol, 6 eq.), imidazole (580 mg, 8.50 mmol, 4 eq.) and DMAP (52 mg, 0.42 mmol, 0.2 eq.). The reaction mixture was stirred at room temperature for 48 h. The resulting solution was hydrolyzed with water and the aqueous layer was extracted three times with a mixture of cyclohexane and DCM (9:1). The combined organic extracts were washed with water, brine, dried over  $MgSO_4$ , filtered and concentrated under reduced pressure. The crude product was purified by chromatography (cyclohexane/EtOAc 20:1) to give an inseparable mixture of diastereoisomers (853 mg, 1.59 mmol, 75 %, 83:17 in favor of the desired diastereoisomer **SI-4b**) as a colorless oil.

**<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)** δ 4.22-4.10 (3H), 4.01-3.95 (2H), 1.85 (ddd, *J* = 14.1, 6.9, 6.0 Hz, 1H), 1.63 (ddd, *J* = 14.1, 6.9, 5.5 Hz, 1H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.12 (d, *J* = 6.1 Hz, 3H), 0.92 (s, 9H), 0.89 (s, 9H), 0.88 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H), 0.07 (s, 6H), 0.06 (s, 6H).

**<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)** δ 171.8, 77.3, 72.8, 65.9, 60.5, 43.8, 25.9 (3C), 25.8 (3C), 25.7 (3C), 23.6, 18.3, 18.1, 18.0, 14.2, -4.3, -4.5, -4.6, -4.7, -4.9, -5.2.

**HRMS-ESI** calculated for C<sub>26</sub>H<sub>58</sub>O<sub>5</sub>NaSi<sub>3</sub> : *m/z* 557.3490 ([M+Na]<sup>+</sup>), found : *m/z* 557.3494 ([M+Na]<sup>+</sup>).

#### **(2*S*,3*R*,5*S*)-2,3,5-tris((*tert*-Butyldimethylsilyl)oxy)hexan-1-ol (11b)**

To a stirred solution of **SI-4b** (853 mg, 1.59 mmol) in dry DCM (13 mL), under a nitrogen atmosphere, was added DIBAL-H (2.3 mL, 1.5 M in toluene, 3.51 mmol, 2.2 eq.) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h. Saturated aqueous Rochelle salt solution was then added, and the resulting mixture warmed to room temperature and vigorously stirred overnight. The aqueous layer was extracted with Et<sub>2</sub>O and the combined organic extracts were washed with water, brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude alcohol was purified by chromatography (cyclohexane/EtOAc 95:5) to afford **11b** (475 mg, 0.96 mmol, 61 %) as a pure diastereoisomer and **11** (100 mg, 0.20 mmol, 12 %).

**<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)** δ 3.97 (ddq ap.sextet, *J* = 6.2 Hz, 1H), 3.84 (td, *J* = 6.3, 3.1 Hz, 1H), 3.76-3.67 (2H), 3.60 (dd, *J* = 10.3, 3.3 Hz, 1H), 1.76 (dt, *J* = 14.1, 6.4 Hz, 1H), 1.62 (dt, *J* = 14.1, 6.4 Hz, 1H), 1.14 (d, *J* = 6.0 Hz, 3H), 0.92 (s, 9H), 0.90 (s, 9H), 0.89 (s, 18H), 0.12 (s, 3H), 0.12 (s, 3H), 0.11 (s, 3H), 0.09 (s, 3H), 0.06 (s, 6H).

**<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)** δ 76.1, 72.7, 65.9, 63.8, 44.7, 25.95 (3C), 25.90 (6C), 23.5, 18.2, 18.1, 18.0, -4.2, -4.3, -4.4, -4.6 (3C).

**HRMS-ESI** calculated for C<sub>24</sub>H<sub>57</sub>O<sub>4</sub>Si<sub>3</sub> : *m/z* 493.3565 ([M+H]<sup>+</sup>), found : *m/z* 493.3566 ([M+H]<sup>+</sup>).

[α]<sub>D</sub><sup>20</sup> = + 0.5 (c 0.8, CHCl<sub>3</sub>).

#### **(2*R*,3*R*,5*S*)-2,3,5-tris((*tert*-Butyldimethylsilyl)oxy)hexanal (12b)**

To a stirred solution of **11b** (475 mg, 0.96 mmol) in dry DCM (2.0 mL), under a nitrogen atmosphere, were added iodosobenzene diacetate (342 mg, 1.06 mmol, 1.1 eq.) and TEMPO (15 mg, 0.10 mmol, 0.1 eq.) at 0 °C. The reaction mixture was stirred at room temperature for 5 h. Water was then added to the reaction mixture which was extracted three times with DCM. The combined organic extracts were washed with water, brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude aldehyde **12b** was used in the next step without further purification.

**<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)** δ 9.62 (d, *J* = 2.1 Hz, 1H), 4.04 (td, *J* = 6.7, 2.1 Hz, 1H), 3.97 (dd ap.t, *J* = 2.1 Hz, 1H), 3.94 (m, 1H), 1.79 (ddd ap. dt, *J* = 14.0, 6.4 Hz, 1H), 1.68 (ddd, *J* = 14.0, 7.0, 5.9 Hz, 1H), 1.16 (d, *J* = 6.1 Hz, 3H), 0.95 (s, 9H), 0.90 (s, 9H), 0.89 (s, 9H), 0.12 (s, 3H), 0.10 (s, 6H), 0.09 (s, 3H), 0.07 (s, 6H).

#### **(4*S*,5*R*,7*S*,*E*)-Ethyl 4,5,7-tris((*tert*-butyldimethylsilyl)oxy)-2-methyloct-2-enoate (13b)**

To a stirred solution of crude aldehyde **12b** in 1,2-dichloroethane (4.8 mL), under a nitrogen atmosphere, was added (1-ethoxycarbonyl ethylidene)triphenyl phosphorane (525 mg, 1.45 mmol, 1.5 eq.) at room temperature. The reaction mixture was warmed to 70 °C and stirred for 48 h. The resulting

solution was then cooled to room temperature, the solvent was removed under reduced pressure and the residue purified by chromatography (cyclohexane/EtOAc 95:5) to give **13b** (330 mg, 0.57 mmol, 60 %) as a colorless oil.

**<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)** δ 6.66 (dq, *J* = 9.1, 1.4 Hz, 1H), 4.34 (dd, *J* = 9.2, 3.4 Hz, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.98 (ddq ap. sextet, *J* = 6.2 Hz, 1H), 3.74 (ddd, *J* = 6.8, 5.6, 3.4 Hz, 1H), 1.86 (d, *J* = 1.4 Hz, 3H), 1.71 (ddd, *J* = 13.7, 6.8, 6.7 Hz, 1H), 1.50 (ddd, *J* = 13.7, 6.9, 5.7 Hz, 1H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.12 (d, *J* = 6.0 Hz, 3H), 0.89 (s, 9H), 0.88 (s, 18H), 0.08 (s, 3H), 0.06 (s, 9H), 0.04 (s, 3H), 0.00 (s, 3H).

**<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)** δ 167.8, 141.9, 127.7, 73.8, 73.7, 65.9, 60.6, 44.3, 25.9 (6C), 25.8 (3C), 23.7, 18.2, 18.1, 18.0, 14.2, 13.3, -4.0, -4.3, -4.4, -4.6 (2C), -4.8.

**HRMS-ESI** calculated for C<sub>29</sub>H<sub>62</sub>O<sub>5</sub>NaSi<sub>3</sub> : *m/z* 597.3803 ([M+Na]<sup>+</sup>), found : *m/z* 597.3804 ([M+Na]<sup>+</sup>).

**[α]<sub>D</sub><sup>20</sup>** = -6.5 (c 1.0, CHCl<sub>3</sub>).

#### **(4*S*,5*R*,7*S*,*E*)-4,5,7-tris((*tert*-Butyldimethylsilyl)oxy)-2-methyloct-2-en-1-ol (SI-5b)**

To a stirred solution of **13b** (330 mg, 0.57 mmol) in dry DCM (3.5 mL), under a nitrogen atmosphere, was added DIBAL-H (0.84 mL, 1.5 M in toluene, 1.25 mmol, 2.2 eq.) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h. Saturated aqueous Rochelle salt solution was then added, and the resulting mixture warmed to room temperature and vigorously stirred overnight. The aqueous layer was extracted with Et<sub>2</sub>O and the combined organic extracts were washed with water, brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude alcohol was purified by chromatography (cyclohexane/EtOAc 9:1) to afford **SI-5b** (315 mg, 0.59 mmol, 100 %) as a colorless oil.

**<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)** δ 5.43 (dq, *J* = 9.1, 1.4 Hz, 1H), 4.28 (dd, *J* = 9.1, 3.1 Hz, 1H), 4.02 (s, 2H), 3.99 (m, 1H), 3.69 (ddd, *J* = 7.2, 5.4, 3.1 Hz, 1H), 1.75-1.66 (m, 1H), 1.69 (d, *J* = 1.4 Hz, 3H), 1.46 (ddd, *J* = 13.7, 7.2, 5.3 Hz, 1H), 1.12 (d, *J* = 6.0 Hz, 3H), 0.89 (s, 9H), 0.89 (s, 9H), 0.88 (s, 9H), 0.09 (s, 3H), 0.06 (s, 9H), 0.04 (s, 3H), 0.00 (s, 3H).

**<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)** δ 135.6, 126.8, 74.1, 73.4, 68.6, 66.1, 44.1, 25.97 (3C), 25.95 (3C), 25.93 (3C), 23.7, 18.2, 18.1 (2C), 14.5, -3.9, -4.0, -4.4, -4.6, -4.68, -4.70.

**HRMS-ESI** calculated for C<sub>27</sub>H<sub>60</sub>O<sub>4</sub>NaSi<sub>3</sub> : *m/z* 555.3697 ([M+Na]<sup>+</sup>), found : *m/z* 555.3699 ([M+Na]<sup>+</sup>).

**[α]<sub>D</sub><sup>20</sup>** = -14.9 (c 1.1, CHCl<sub>3</sub>).

#### **(4*S*,5*R*,7*S*,*E*)-4,5,7-tris((*tert*-Butyldimethylsilyl)oxy)-2-methyloct-2-enal (SI-6b)**

To a stirred solution of **SI-5b** (315 mg, 0.59 mmol) in dry DCM (6.0 mL), under a nitrogen atmosphere, was added MnO<sub>2</sub> (771 mg, 8.87 mmol, 15 eq.) at room temperature. The reaction mixture was warmed to 40 °C and vigorously stirred for 48 h. The resulting mixture was cooled to room temperature and filtered through celite with DCM. The solvent was then removed under reduced pressure to give **SI-6b** (260 mg, 0.49 mmol, 83 %) as a colorless oil which was used in the next step without further purification.

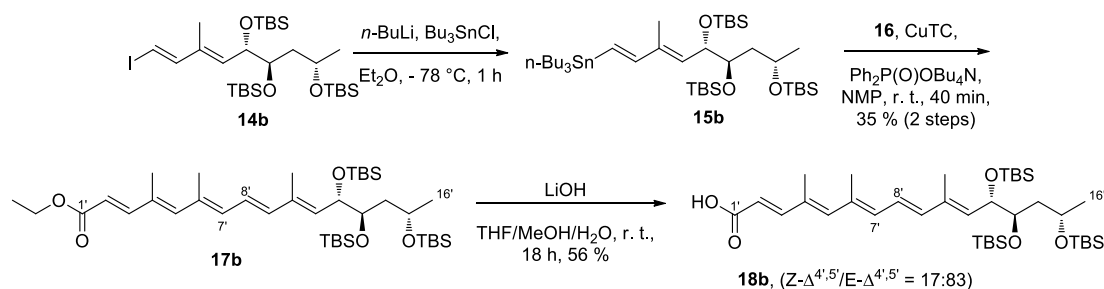
**<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)** δ 9.46 (s, 1H), 6.42 (dq, *J* = 8.9, 1.4 Hz, 1H), 4.51 (dd, *J* = 8.9, 3.1 Hz, 1H), 3.96 (ddq ap. sextet, *J* = 6.4 Hz, 1H), 3.85 (ddd, *J* = 6.6, 6.1, 3.1 Hz, 1H), 1.78 (d, *J* = 1.4 Hz, 3H), 1.69 (dt, *J* = 13.6, 6.6 Hz, 1H), 1.44 (dt, *J* = 13.8, 5.9 Hz, 1H), 1.12 (d, *J* = 6.0 Hz, 3H), 0.89 (s, 9H), 0.89 (s, 18H), 0.10 (s, 3H), 0.08 (s, 3H), 0.06 (s, 9H), 0.00 (s, 3H).

**(1*E*,3*E*)-(5*S*,6*R*,8*S*)-tris-(*tert*-Butyldimethylsilyloxy)-1-iodo-3-methyl-nona-1,3-diene (14b)**

To a stirred solution of CrCl<sub>2</sub> (361 mg, 2.94 mmol, 6 eq.) in dry THF (3.0 mL), under a nitrogen atmosphere, was added a solution of **SI-6b** (260 mg, 0.49 mmol) and CHI<sub>3</sub> (580 mg, 1.47 mmol, 3 eq.) in dry THF (2.0 mL) dropwise. The reaction mixture was stirred at room temperature for 12 h. The resulting mixture was hydrolyzed with water and diluted with Et<sub>2</sub>O. The aqueous layer was extracted three times with Et<sub>2</sub>O and the combined organic extracts were washed with water, brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude product was then purified by chromatography (cyclohexane/toluene 100:1) to afford **14b** (200 mg, 0.31 mmol, 62 %) as a pale yellow oil.

<sup>1</sup>H NMR (C<sub>6</sub>D<sub>6</sub>, 300 MHz) δ 7.03 (d, *J* = 14.7 Hz, 1H), 6.01 (d, *J* = 14.7 Hz, 1H), 5.49 (dq, *J* = 8.6, 1.2 Hz, 1H), 4.38 (dd, *J* = 9.2, 3.6 Hz, 1H), 4.09 (ddq ap. sextet, *J* = 6.3 Hz, 1H), 3.85 (td, *J* = 6.2, 3.6 Hz, 1H), 1.91 (dt, *J* = 13.7, 6.6 Hz, 1H), 1.65 (dt, *J* = 13.8, 6.1 Hz, 1H), 1.46 (d, *J* = 1.2 Hz, 3H), 1.16 (d, *J* = 6.0 Hz, 3H), 1.02 (s, 9H), 1.01 (s, 9H), 0.98 (s, 9H), 0.17 (s, 6H), 0.16 (s, 3H), 0.14 (s, 3H), 0.07 (s, 3H), 0.02 (s, 3H).

<sup>13</sup>C NMR (C<sub>6</sub>D<sub>6</sub>, 100 MHz) δ 149.5, 135.3, 134.9, 76.8, 74.6, 74.2, 66.8, 45.4, 26.6 (3C), 26.5 (6C), 24.5, 18.8, 18.73, 18.67, 13.1, -3.3, -3.5, -3.7, -3.9, -4.0, -4.2.



**(1*E*,3*E*)-(5*S*,6*R*,8*S*)-tris-(*tert*-Butyldimethylsilyloxy)-1-tributylstannyl-3-methyl-nona-1,3-diene (15b)**

To a stirred solution of **14b** (200 mg, 0.31 mmol) in dry Et<sub>2</sub>O (1.6 mL), under a nitrogen atmosphere, was added *n*-BuLi (0.23 mL, 2 M in hexane, 0.46 mmol, 1.5 eq.) at -78 °C. The reaction mixture was stirred for 20 min at -78 °C and Bu<sub>3</sub>SnCl (0.14 mL, 0.46 mmol, 1.5 eq.) was added. The resulting solution was stirred at -78 °C for another 20 min and allowed to warm to room temperature for 1 h. Saturated aqueous NaHCO<sub>3</sub> solution was then added and the aqueous layer was extracted three times with Et<sub>2</sub>O. The combined organic extracts were washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude **15b** was used in the next step without further purification.

**(2*E*,4*E*,6*E*,8*E*,10*E*,12*S*,13*R*,15*S*)-ethyl-12,13,15-tris((*tert*-Butyldimethylsilyl)oxy)-4,6,10-trimethylhexadeca-2,4,6,8,10-pentaenoate (17b)**

To a stirred solution of crude **15b** and tetra-*n*-butylammonium diphenylphosphinate (325 mg, 0.70 mmol, 2.3 eq.) in dry NMP (2.1 mL), under a nitrogen atmosphere, was added 0.2 mL of a solution of **16** in NMP (187 mg, 0.61 mmol, 2 eq., 1.4 mL). After addition of CuTC (117 mg, 0.61 mmol, 2 eq.), the rest of the **16** solution was added dropwise and the resulting mixture was stirred at room temperature for 40 min. The reaction mixture was then diluted with Et<sub>2</sub>O and filtered through neutral alumina oxide. The filtrate was washed with water, brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced

pressure. The crude product was then purified by preparative TLC (cyclohexane/EtOAc 9:1) to afford **17b** (76 mg, 0.11 mmol, 35 % for two steps) as a yellow oil. NMR analysis showed the presence of mixture of isomers  $4'E/4'Z = 92:8$ .

**$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz,  $4'E$  isomer)**  $\delta$  7.95 (d,  $J = 15.3$  Hz, 1H,  $Z$  isomer), 7.38 (d,  $J = 15.5$  Hz, 1H,  $E$  isomer), 6.51 (dd,  $J = 14.9, 11.1$  Hz, 1H), 6.36 (d,  $J = 15.0$  Hz, 1H), 6.36 (s, 1H), 6.28 (d,  $J = 11.1$  Hz, 1H), 5.88 (d,  $J = 15.5$  Hz, 1H), 5.54 (d,  $J = 9.1$  Hz, 1H), 4.37 (dd,  $J = 9.2, 3.4$  Hz, 1H), 4.23 (q,  $J = 7.1$  Hz, 2H), 3.98 (ddq ap. sextet,  $J = 6.3$  Hz, 1H), 3.72 (ddd,  $J = 6.7, 5.5, 3.5$  Hz, 1H), 2.06 (s, 3H), 2.03 (s, 3H), 1.84 (s, 3H), 1.70 (dt,  $J = 13.7, 6.8$  Hz, 1H), 1.49 (dt,  $J = 13.7, 6.8$  Hz, 1H), 1.32 (t,  $J = 7.1$  Hz, 3H), 1.11 (d,  $J = 6.0$  Hz, 3H), 0.89 (s, 9H), 0.88 (s, 9H), 0.88 (s, 9H), 0.08 (s, 3H), 0.06 (s, 9H), 0.03 (s, 3H), -0.01 (s, 3H).

**$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz,  $4'E$  isomer)**  $\delta$  167.5, 150.7, 143.6, 139.5, 135.1, 135.0, 134.2, 134.1, 132.2, 123.8, 116.2, 74.1, 73.8, 66.1, 60.2, 44.3, 26.0 (3C), 25.9 (6C), 23.7, 18.2, 18.1 (2C), 17.1, 14.3, 14.2, 13.4, -3.3, -3.5, -4.2, -4.3, -4.6, -4.7.

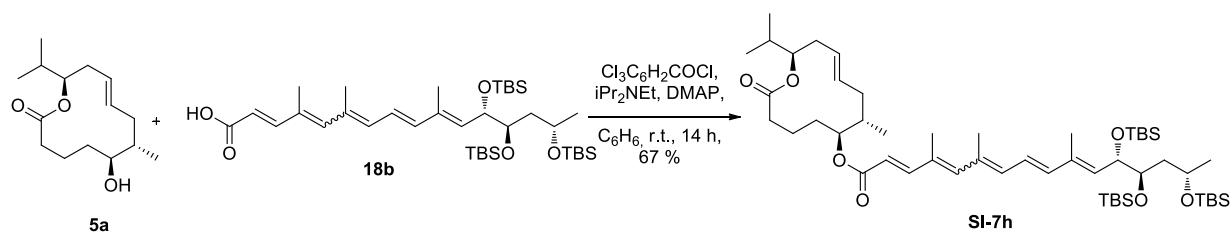
**(2*E*,4*E*,6*E*,8*E*,10*E*,12*S*,13*R*,15*S*)-12,13,15-tris(*tert*-butyldimethylsilyloxy)-4,6,10-trimethylhexadeca-2,4,6,8,10-pentaenoic acid (**18b**)**

To a stirred solution of **17b** (76 mg, 0.11 mmol) in a mixture THF/MeOH/H<sub>2</sub>O (2.3/0.6/0.6 mL) was added LiOH (27 mg, 1.12 mmol, 10 eq.). The resulting mixture was stirred at room temperature for 18 h. After addition of saturated aqueous NH<sub>4</sub>Cl solution, the mixture was extracted three times with EtOAc and the combined organic extracts were washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude material was purified by preparative TLC (cyclohexane/EtOAc 7:3) to afford **18b** (42 mg, 61.90  $\mu\text{mol}$ , 56 %) as a yellow oil. NMR analysis showed the presence of mixture of isomers  $4'E/4'Z = 83:17$ .

**$^1\text{H}$  NMR ( $\text{d}_6$ -Acetone, 300 MHz,  $4'E$  isomer)**  $\delta$  7.94 (d,  $J = 15.8$  Hz, 1H,  $Z$  isomer), 7.35 (d,  $J = 15.5$  Hz, 1H,  $E$  isomer), 6.67 (dd,  $J = 15.0, 11.1$  Hz, 1H), 6.48 (d,  $J = 15.0$  Hz, 1H), 6.46 (s, 1H), 6.40 (d,  $J = 11.1$  Hz, 1H), 5.87 (d,  $J = 15.5$  Hz, 1H), 5.62 (d,  $J = 9.3$  Hz, 1H), 4.53 (dd,  $J = 9.3, 3.2$  Hz, 1H), 4.06 (ddq ap. sextet,  $J = 6.2$  Hz, 1H), 3.85 (dt,  $J = 6.1, 3.4$  Hz, 1H), 2.09 (s, 3H), 2.05 (s, 3H), 1.91 (s, 3H), 1.70 (dt,  $J = 13.8, 6.7$  Hz, 1H), 1.55 (dt,  $J = 13.7, 6.2$  Hz, 1H), 1.13 (d,  $J = 6.0$  Hz, 3H), 0.91 (s, 18H), 0.90 (s, 9H), 0.14 (s, 3H), 0.12 (s, 3H), 0.09 (s, 6H), 0.08 (s, 3H), 0.04 (s, 3H).

**$^{13}\text{C}$  NMR ( $\text{d}_6$ -Acetone, 100 MHz,  $4'E$  isomer)**  $\delta$  168.1, 151.6, 144.3, 140.2, 136.2, 135.7, 135.5, 135.3, 133.3, 125.4, 117.3, 75.2, 74.6, 66.9, 45.4, 26.52 (3C), 26.48 (3C), 26.4 (3C), 24.4, 18.9, 18.8, 18.7, 17.2, 14.4, 13.9, -3.4, -3.7, -4.0, -4.1, -4.2, -4.3.

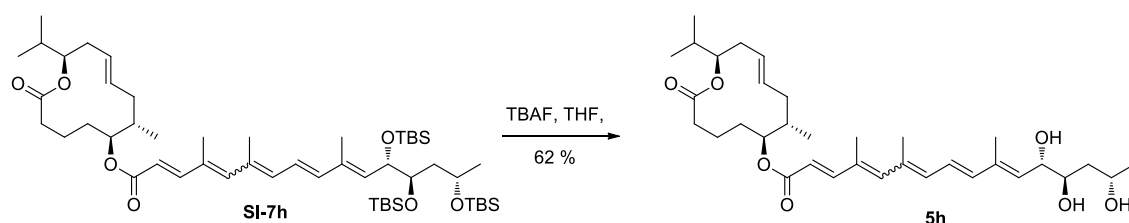
**HRMS-ESI** calculated for  $\text{C}_{37}\text{H}_{70}\text{O}_5\text{NaSi}_3$  :  $m/z$  701.4423 ( $[\text{M}+\text{Na}]^+$ ), found :  $m/z$  701.4431 ( $[\text{M}+\text{Na}]^+$ ).



**(6*S*,7*S*,9*E*,12*R*)-7-Methyl-2-oxo-12-(propan-2-yl)-1-oxacyclododec-9-en-6-yl  
(2*E*,4*E*,6*E*,8*E*,10*E*,12*S*,13*R*,15*S*)-12,13,15-tris[(tert-butyldimethylsilyl)oxy]-4,6,10-trimethylhexadeca-2,4,6,8,10-pentaenoate (SI-7h)**

To a solution of **18b** (22 mg, 0.03 mmol) in benzene (0.4 mL) were added diisopropylethyl amine (23  $\mu$ L, 0.13 mmol, 5.6 eq.), 2,4,6-trichlorobenzoyl chloride (11  $\mu$ L ; 0.07 mmol, 3 eq.), and DMAP (20 mg). The reaction mixture was stirred at room temperature for 15 min and **5a** (6.5 mg, 0.03 mmol) was added. After being stirred at room temperature for 14 h, an aqueous saturated solution of sodium hydrogenocarbonate was added to the reaction mixture. The aqueous layer was extracted three times with benzene. The combined organic layers were washed with brine, dried over  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. The crude product was purified on preparative TLC eluting with heptane/ ethyl acetate 90:10 to give **SI-7h** (18 mg, 0.02 mmol, 67 %) as a yellow oil. A (4'*E*)/(4'*Z*) = 71:29 mixture could be detected by  $^1\text{H}$  analysis.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  7.93 (d,  $J$  = 15.5 Hz, 1H, *Z* isomer), 7.36 (d,  $J$  = 15.5 Hz, 1H, *E* isomer), 6.49 (dd,  $J$  = 14.8, 11.2 Hz, 1H), 6.37 (d,  $J$  = 14.8 Hz, 1H), 6.36 (s, 1H), 6.28 (d,  $J$  = 11.2 Hz, 1H), 5.85 (d,  $J$  = 15.5 Hz, 1H), 5.52 (d,  $J$  = 9.0 Hz, 1H), 5.45 (m, 1H), 5.27 (m, 1H), 4.82-4.70 (2H), 4.36 (dd,  $J$  = 9.1, 3.6 Hz, 1H), 3.97 (m, 1H), 3.71 (m, 1H), 2.49 (m, 1H), 2.30 (m, 1H), 2.15-2.06 (2H), 2.04 (s, 3H), 2.03 (s, 3H), 1.98-1.96 (m, 1H), 1.85 (s, 3H), 1.87-1.61 (6H), 1.13 (d,  $J$  = 6.0 Hz, 3H), 0.95 (s, 3H), 0.93 (s, 3H), 0.92 (s, 3H), 0.90 (s, 3H), 0.89 (s, 9H), 0.87 (s, 9H), 0.85 (s, 9H), 0.06 (s, 3H), 0.04 (s, 9H), 0.02 (s, 3H), -0.02 (s, 3H).



**(6*S*,7*S*,9*E*,12*R*)-7-Methyl-2-oxo-12-(propan-2-yl)-1-oxacyclododec-9-en-6-yl  
(2*E*,4*E*,6*E*,8*E*,10*E*,12*S*,13*R*,15*S*)-12,13,15-trihydroxy-4,6,10-trimethylhexadeca-2,4,6,8,10-pentaenoate (5h)**

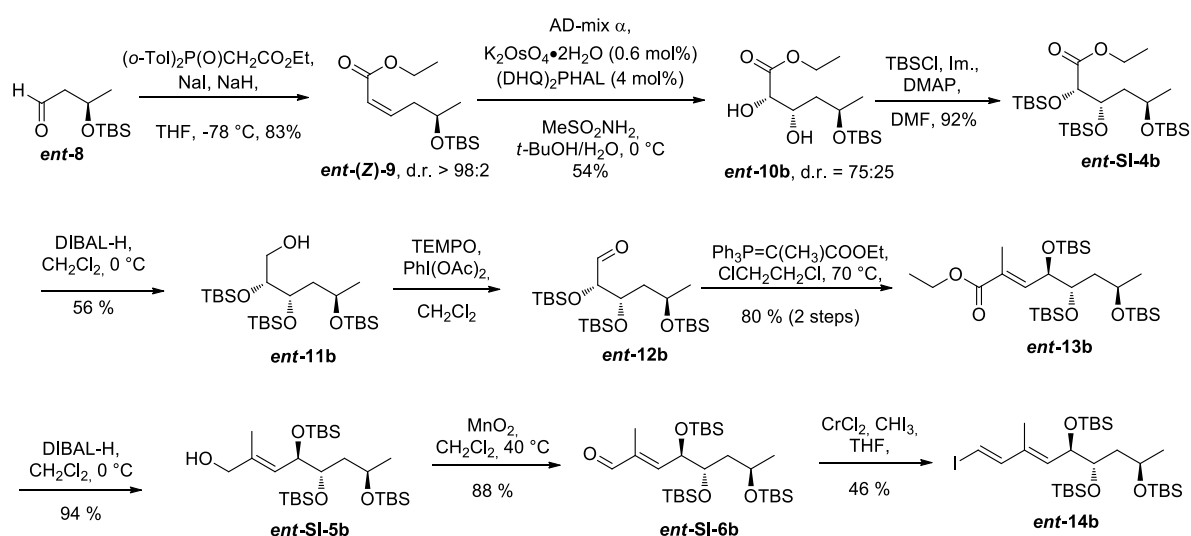
To a solution of **SI-7h** (18 mg, 0.019 mmol) in THF (0.2 mL) was added TBAF (0.18 mmol, 1M in THF, 9.5 eq). The solution was stirred at room temperature for 4 h.  $\text{CaCO}_3$  (50 mg), Dowex 50WX8-400 (150 mg) and MeOH (0.4 mL) were added and the reaction mixture was stirred for 1 h. After being filtered and concentrated under reduced pressure, the crude product was purified by TLC preparative

(CH<sub>2</sub>Cl<sub>2</sub>/MeOH 90:10) to give **5h** (7 mg, 0.011 mmol, 62 %). A (4'E)/(4'Z) = 65:35 mixture could be detected by <sup>1</sup>H analysis.

**<sup>1</sup>H NMR (Acetone-d<sub>6</sub>, 400 MHz)** δ 7.92 (d, *J* = 15.6 Hz, 1H, *Z* isomer), 7.37 (d, *J* = 15.5 Hz, 1H, *E* isomer), 6.63 (dd, *J* = 11.1, 15.0 Hz, 1H), 6.47 (s, 1H), 6.36 (d, *J* = 15.0 Hz, 1H), 6.17 (d, *J* = 11.1 Hz, 1H), 5.89 (d, *J* = 15.5 Hz, 1H), 5.66 (m, 1H), 5.50 (m, 1H), 5.30 (m, 1H), 4.78-4.66 (2H), 4.37 (m, 1H), 4.18 (s, 1H), 4.09 (s, 1H), 3.99 (m, 1H), 3.85 (s, 1H), 3.80 (m, 1H), 2.50 (m, 1H), 2.32 (m, 1H), 2.12-2.08 (2H), 2.06 (s, 3H), 1.97 (s, 3H), 1.95-1.92 (2H), 1.90 (s, 3H), 1.80-1.75 (4H), 1.70-1.62 (2H), 1.54-1.49 (2H), 1.13 (d, *J* = 6.1 Hz, 3H), 0.92 (s, 3H), 0.90 (s, 3H), 0.87 (s, 3H).

**NMR <sup>13</sup>C (Acetone-d<sub>6</sub>, 100 MHz)** δ 173.9, 167.8, 152.2, 144.1, 141.6, 137.3, 136.5, 136.1, 134.1, 133.1, 128.0, 125.8, 120.6, 118.4, 80.2, 77.3, 76.6, 73.1, 68.8, 42.3, 39.8, 37.9, 37.0, 36.1, 34.1, 25.4, 22.0, 21.6, 20.9, 19.9, 19.4, 18.1, 15.3, 14.3.

**HRMS-ESI** calculated for C<sub>34</sub>H<sub>52</sub>O<sub>7</sub>Na : *m/z* 595.3605 ([M+Na]<sup>+</sup>), found: *m/z* 595.3618 ([M+Na]<sup>+</sup>).



### (*R,Z*)-Ethyl 5-((*tert*-butyldimethylsilyl)oxy)hex-2-enoate (**ent-(Z)-9**)

To a stirred solution of (o-Tol)<sub>2</sub>P(O)CH<sub>2</sub>CO<sub>2</sub>Et<sup>2</sup> (2.86 g, 8.23 mmol, 1.3 eq.) in dry THF (64 mL), under a nitrogen atmosphere, were added NaI (950 mg, 6.33 mmol, 1 eq.) at 0 °C. After 5 min, NaH (60 % dispersion, 330 mg, 8.23 mmol, 1.3 eq.) was added. The resulting solution was cooled to -78 °C and **ent-8** (1.28 g, 6.33 mmol) was added dropwise. After stirring 3 h at -78 °C, saturated aqueous NH<sub>4</sub>Cl solution was added and the reaction mixture was extracted three times with Et<sub>2</sub>O. The combined organic extracts were washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (cyclohexane/EtOAc 9:1) to afford **ent-(Z)-9** (1.40 g, 5.14 mmol, 83 %) as a pale yellow oil.

**<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)** δ 6.35 (dt, *J* = 11.6, 6.3 Hz, 1H), 5.84 (dt, *J* = 11.6, 1.7 Hz, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 3.97 (dq, *J* = 6.6, 6.1, 5.0 Hz, 1H), 2.87-2.67 (2H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.16 (d, *J* = 6.1 Hz, 3H), 0.88 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H).

**<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)** δ 166.5, 146.9, 120.7, 67.9, 59.8, 38.6, 25.8 (3C), 23.7, 18.0, 14.3, -4.5, -4.8.

**HRMS-ESI** calculated for C<sub>14</sub>H<sub>29</sub>O<sub>3</sub>Si : *m/z* 273.1886 ([M+H]<sup>+</sup>), found : *m/z* 273.1883 ([M+H]<sup>+</sup>).

[α]<sub>D</sub><sup>20</sup> = -12.7 (c 0.9, CHCl<sub>3</sub>).



**(2S,3S,5R)-Ethyl 5-((*tert*-butyldimethylsilyl)oxy)-2,3-dihydroxyhexanoate (*ent*-10b)**

To a stirred solution of AD-mix  $\alpha$  (7.15 g, 0.4 % osmium, 1 % (DHQ)<sub>2</sub>PHAL) in a mixture 1:1 *t*-BuOH/H<sub>2</sub>O (42:42 mL) were added successively methanesulfonamide (420 mg, 4.41 mmol 0.9 eq.), potassium osmate(VI) dihydrate (14 mg, 37.97  $\mu$ mol, 0.6 mol%) and (DHQ)<sub>2</sub>PHAL (160 mg, 0.20 mmol, 4 mol%). The mixture was stirred at room temperature until two clear phases were produced. The solution was cooled to 0 °C, whereupon the inorganic salts partially precipitate, and *ent*-(*Z*)-9 (1.40 g, 5.14 mmol) was then added. After stirring 15 h at 0 °C, Na<sub>2</sub>SO<sub>3</sub> (12.9 g) was added and the reaction mixture was stirred for 30 min at room temperature. The mixture was extracted three times with EtOAc. The combined organic extracts were washed with an aqueous KOH solution (2M), brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude product was purified by chromatography (cyclohexane/EtOAc 8:2) to give an inseparable mixture of diastereoisomers (840 mg, 2.74 mmol, 54 %, 75:25 in favor of the desired diastereoisomer *ent*-10b) as a colorless oil.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  4.29 (q, *J* = 7.1 Hz, 2H), 4.24-3.98 (3H), 1.76 (ddd, *J* = 14.4, 9.9, 8.8 Hz, 1H), 1.55 (ddd, *J* = 14.4, 4.3, 2.3 Hz, 1H), 1.33 (t, *J* = 7.1 Hz, 3H), 1.21 (d, *J* = 6.0 Hz, 3H), 0.90 (s, 9H), 0.12 (s, 3H), 0.11 (s, 3H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  172.4, 74.2, 72.8, 69.2, 61.7, 40.5, 25.8 (3C), 24.3, 17.9, 14.2, -4.0, -4.8.

HRMS-ESI calculated for C<sub>14</sub>H<sub>30</sub>O<sub>5</sub>NaSi : *m/z* 329.1760 ([M+Na]<sup>+</sup>), found : *m/z* 329.1762 ([M+Na]<sup>+</sup>).

**(2S,3S,5R)-Ethyl 2,3,5-tris(*tert*-butyldimethylsilyloxy)hexanoate (*ent*-SI-4b)**

To a stirred solution of *ent*-10b (840 mg, 2.74 mmol) in dry DMF (26 mL), under a nitrogen atmosphere, were added *tert*-butyldimethylsilyl chloride (2.5 g, 16.58 mmol, 6 eq.), imidazole (750 mg, 10.92 mmol, 4 eq.) and DMAP (67 mg, 0.55 mmol, 0.2 eq.). The reaction mixture was stirred at room temperature for 48 h. The resulting solution was hydrolyzed with water and the aqueous layer was extracted three times with a mixture of cyclohexane and DCM (9:1). The combined organic extracts were washed with water, brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude product was purified by chromatography (cyclohexane/EtOAc 20:1) to give an inseparable mixture of diastereoisomers (1.35 g, 2.53 mmol, 92 %, 75:25 in favor of the desired diastereoisomer *ent*-SI-4b) as a colorless oil.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  4.22-4.10 (3H), 4.01-3.95 (2H), 1.85 (ddd, *J* = 14.1, 6.9, 6.0 Hz, 1H), 1.63 (ddd, *J* = 14.1, 6.9, 5.5 Hz, 1H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.13 (d, *J* = 6.1 Hz, 3H), 0.92 (s, 9H), 0.89 (s, 9H), 0.88 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H), 0.07 (s, 6H), 0.06 (s, 6H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  171.8, 77.3, 72.8, 65.9, 60.5, 43.8, 25.9 (3C), 25.8 (3C), 25.7 (3C), 23.6, 18.3, 18.1, 18.0, 14.2, -4.3, -4.5, -4.6, -4.7, -4.9, -5.2.

HRMS-ESI calculated for C<sub>26</sub>H<sub>58</sub>O<sub>5</sub>NaSi<sub>3</sub> : *m/z* 557.3490 ([M+Na]<sup>+</sup>), found : *m/z* 557.3490 ([M+Na]<sup>+</sup>).

**(2R,3S,5R)-2,3,5-tris(*tert*-Butyldimethylsilyl)oxy)hexan-1-ol (*ent*-11b)**

To a stirred solution of *ent*-SI-4b (1.34 g, 2.51 mmol) in dry DCM (20 mL), under a nitrogen atmosphere, was added DIBAL-H (3.7 mL, 1.5 M in toluene, 5.52 mmol, 2.2 eq.) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h. Saturated aqueous Rochelle salt solution was then added, and the resulting mixture warmed to room temperature and vigorously stirred overnight. The aqueous layer was extracted with Et<sub>2</sub>O and the combined organic extracts were washed with water, brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude alcohol was purified by

chromatography (cyclohexane/EtOAc 95:5) to afford **ent-11b** (693 mg, 1.41 mmol, 56 %) as a pure diastereoisomer and **ent-11a** (223 mg, 0.45 mmol, 18 %).

**<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)** δ 3.97 (ddq ap.sextet, *J* = 6.2 Hz, 1H), 3.84 (td, *J* = 6.3, 3.1 Hz, 1H), 3.76-3.67 (2H), 3.60 (dd, *J* = 10.3, 3.3 Hz, 1H), 1.76 (dt, *J* = 14.1, 6.4 Hz, 1H), 1.62 (dt, *J* = 14.1, 6.4 Hz, 1H), 1.14 (d, *J* = 6.0 Hz, 3H), 0.93 (s, 9H), 0.90 (s, 9H), 0.89 (s, 18H), 0.12 (s, 3H), 0.12 (s, 3H), 0.11 (s, 3H), 0.09 (s, 3H), 0.06 (s, 6H).

**<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)** δ 76.1, 72.7, 65.9, 63.8, 44.7, 25.94 (3C), 25.90 (6C), 23.5, 18.2, 18.1, 18.0, -4.2, -4.3, -4.4, -4.6 (3C).

**HRMS-ESI** calculated for C<sub>24</sub>H<sub>57</sub>O<sub>4</sub>Si<sub>3</sub> : *m/z* 493.3565 ([M+H]<sup>+</sup>), found : *m/z* 493.3557 ([M+H]<sup>+</sup>).

[α]<sub>D</sub><sup>20</sup> = + 0.1 (c 1.6, CHCl<sub>3</sub>).

#### **(2*S*,3*S*,5*R*)-2,3,5-tris(*tert*-Butyldimethylsilyloxy)hexanal (*ent*-12b)**

To a stirred solution of **ent-11b** (616 mg, 1.25 mmol) in dry DCM (2.7 mL), under a nitrogen atmosphere, were added iodosobenzene diacetate (445 mg, 1.38 mmol, 1.1 eq.) and TEMPO (20 mg, 0.12 mmol, 0.1 eq.) at 0 °C. The reaction mixture was stirred at room temperature for 5 h. Water was then added to the reaction mixture which was extracted three times with DCM. The combined organic extracts were washed with water, brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude aldehyde **ent-12b** was used in the next step without further purification.

**<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)** δ 9.62 (d, *J* = 2.1 Hz, 1H), 4.04 (td, *J* = 6.7, 2.1 Hz, 1H), 3.97 (dd ap. t, *J* = 2.1 Hz, 1H), 3.94 (m, 1H), 1.79 (ddd ap. dt, *J* = 14.0, 6.4 Hz, 1H), 1.68 (ddd, *J* = 14.0, 7.0, 5.9 Hz, 1H), 1.15 (d, *J* = 6.1 Hz, 3H), 0.94 (s, 9H), 0.90 (s, 9H), 0.89 (s, 9H), 0.11 (s, 3H), 0.09 (s, 6H), 0.08 (s, 3H), 0.07 (s, 6H).

#### **(4*R*,5*S*,7*R*,*E*)-Ethyl 4,5,7-tris(*tert*-butyldimethylsilyloxy)-2-methyloct-2-enoate (*ent*-13b)**

To a stirred solution of crude aldehyde **ent-12b** in 1,2-dichloroethane (6.5 mL), under a nitrogen atmosphere, was added (1-ethoxycarbonyl ethylidene)triphenyl phosphorane (680 mg, 1.87 mmol, 1.5 eq.) at room temperature. The reaction mixture was warmed to 70 °C and stirred for 48 h. The resulting solution was then cooled to room temperature, the solvent was removed under reduced pressure and the residue purified by chromatography (cyclohexane/EtOAc 95:5) to give **ent-13b** (575 mg, 1.00 mmol, 80 %) as a colorless oil.

**<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)** δ 6.66 (dq, *J* = 9.1, 1.4 Hz, 1H), 4.34 (dd, *J* = 9.2, 3.4 Hz, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.98 (ddq ap. sextet, *J* = 6.2 Hz, 1H), 3.74 (ddd, *J* = 6.8, 5.6, 3.4 Hz, 1H), 1.86 (d, *J* = 1.4 Hz, 3H), 1.71 (ddd, *J* = 13.7, 6.8, 6.7 Hz, 1H), 1.50 (ddd, *J* = 13.7, 6.9, 5.7 Hz, 1H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.12 (d, *J* = 6.0 Hz, 3H), 0.89 (s, 9H), 0.89 (s, 18H), 0.08 (s, 3H), 0.06 (s, 9H), 0.04 (s, 3H), 0.00 (s, 3H).

**<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)** δ 167.8, 141.9, 127.8, 73.8, 73.7, 65.9, 60.6, 44.3, 25.9 (6C), 25.8 (3C), 23.7, 18.2, 18.1, 18.0, 14.2, 13.3, -4.0, -4.3, -4.4, -4.6 (2C), -4.8.

**HRMS-ESI** calculated for C<sub>29</sub>H<sub>62</sub>O<sub>5</sub>NaSi<sub>3</sub> : *m/z* 597.3803 ([M+Na]<sup>+</sup>), found : *m/z* 597.3805 ([M+Na]<sup>+</sup>).

[α]<sub>D</sub><sup>20</sup> = + 5.4 (c 0.1, CHCl<sub>3</sub>).

**(4*R*,5*S*,7*R*,*E*)-4,5,7-tris((*tert*-Butyldimethylsilyl)oxy)-2-methyloct-2-en-1-ol (*ent*-SI-5b)**

To a stirred solution of ***ent*-13b** (575 mg, 1.00 mmol) in dry DCM (20 mL), under a nitrogen atmosphere, was added DIBAL-H (1.5 mL, 1.5 M in toluene, 2.20 mmol, 2.2 eq.) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h. Saturated aqueous Rochelle salt solution was then added, and the resulting mixture warmed to room temperature and vigorously stirred overnight. The aqueous layer was extracted with Et<sub>2</sub>O and the combined organic extracts were washed with water, brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude alcohol was purified by chromatography (cyclohexane/EtOAc 9:1) to afford ***ent*-SI-5b** (500 mg, 0.94 mmol, 94 %) as a colorless oil.

**<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)** δ 5.43 (dq, *J* = 9.1, 1.4 Hz, 1H), 4.28 (dd, *J* = 9.1, 3.1 Hz, 1H), 4.02 (s, 2H), 4.00 (m, 1H), 3.69 (ddd, *J* = 7.2, 5.4, 3.1 Hz, 1H), 1.69 (d, *J* = 1.4 Hz, 3H), 1.46 (ddd, *J* = 13.7, 7.2, 5.3 Hz, 1H), 1.75-1.66 (m, 1H), 1.12 (d, *J* = 6.0 Hz, 3H), 0.89 (s, 9H), 0.89 (s, 9H), 0.88 (s, 9H), 0.09 (s, 3H), 0.06 (s, 9H), 0.04 (s, 3H), 0.00 (s, 3H).

**<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)** δ 135.6, 126.8, 74.1, 73.4, 68.6, 66.1, 44.1, 25.98 (3C), 25.96 (3C), 25.94 (3C), 23.7, 18.2, 18.1 (2C), 14.5, -3.9, -4.0, -4.4, -4.6, -4.69, -4.71.

**HRMS-ESI** calculated for C<sub>27</sub>H<sub>60</sub>O<sub>4</sub>NaSi<sub>3</sub> : *m/z* 555.3697 ([M+Na]<sup>+</sup>), found : *m/z* 555.3698 ([M+Na]<sup>+</sup>).

**[α]<sup>20</sup><sub>D</sub>** = + 3.5 (c 0.1, CHCl<sub>3</sub>).

**(4*R*,5*S*,7*R*,*E*)-4,5,7-tris((*tert*-Butyldimethylsilyl)oxy)-2-methyloct-2-enal (*ent*-SI-6b)**

To a stirred solution of ***ent*-SI-5b** (500 mg, 0.94 mmol) in dry DCM (6.3 mL), under a nitrogen atmosphere, was added MnO<sub>2</sub> (1.23 g, 14.1 mmol, 15 eq.) at room temperature. The reaction mixture was warmed to 40 °C and vigorously stirred for 48 h. The resulting mixture was cooled to room temperature and filtered through celite with DCM. The solvent was then removed under reduced pressure to give ***ent*-SI-6b** (440 mg, 0.83 mmol, 88 %) as a colorless oil which was used in the next step without further purification.

**<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)** δ 9.46 (s, 1H), 6.42 (dq, *J* = 8.9, 1.4 Hz, 1H), 4.51 (dd, *J* = 8.9, 3.1 Hz, 1H), 3.96 (ddq ap. sextet, *J* = 6.4 Hz 1H), 3.84 (ddd, *J* = 6.6, 6.1, 3.1 Hz, 1H), 1.78 (d, *J* = 1.4 Hz, 3H), 1.69 (dt, *J* = 13.6, 6.6 Hz, 1H), 1.44 (dt, *J* = 13.8, 5.9 Hz, 1H), 1.12 (d, *J* = 6.0 Hz, 3H), 0.89 (s, 9H), 0.89 (s, 18H), 0.10 (s, 3H), 0.08 (s, 3H), 0.06 (s, 9H), 0.00 (s, 3H).

**(1*E*,3*E*)-(5*R*,6*S*,8*R*)-tris-(*tert*-Butyldimethylsilyloxy)-1-iodo-3-methyl-nona-1,3-diene (*ent*-14b)**

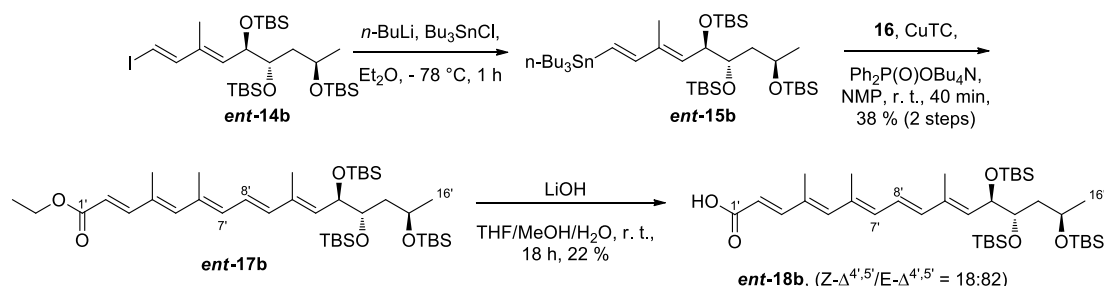
To a stirred solution of CrCl<sub>2</sub> (612 mg, 4.98 mmol, 6 eq.) in dry THF (3.0 mL), under a nitrogen atmosphere, was added a solution of ***ent*-SI-6b** (440 mg, 0.83 mmol) and CHI<sub>3</sub> (980 mg, 2.49 mmol, 3 eq.) in dry THF (2.1 mL) dropwise. The reaction mixture was stirred at room temperature for 12 h. The resulting mixture was hydrolyzed with water and diluted with Et<sub>2</sub>O. The aqueous layer was extracted three times with Et<sub>2</sub>O and the combined organic extracts were washed with water, brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude product was then purified by chromatography (cyclohexane/toluene 100:1) to afford ***ent*-14b** (252 mg, 0.38 mmol, 46 %) as a pale yellow oil.

**<sup>1</sup>H NMR (C<sub>6</sub>D<sub>6</sub>, 300 MHz)** δ 7.03 (d, *J* = 14.7 Hz, 1H), 6.01 (d, *J* = 14.7 Hz, 1H), 5.49 (dq, *J* = 8.6, 1.2 Hz, 1H), 4.38 (dd, *J* = 9.2, 3.6 Hz, 1H), 4.09 (ddq ap. sextet, *J* = 6.3 Hz, 1H), 3.85 (td, *J* = 6.2, 3.6 Hz, 1H), 1.91

(dt,  $J = 13.7, 6.6$  Hz, 1H), 1.65 (dt,  $J = 13.8, 6.1$  Hz, 1H), 1.46 (d,  $J = 1.2$  Hz, 3H), 1.16 (d,  $J = 6.0$  Hz, 3H), 1.02 (s, 9H), 1.01 (s, 9H), 0.98 (s, 9H), 0.17 (s, 6H), 0.16 (s, 3H), 0.14 (s, 3H), 0.07 (s, 3H), 0.02 (s, 3H).

$^{13}\text{C}$  NMR ( $\text{C}_6\text{D}_6$ , 100 MHz)  $\delta$  149.5, 135.3, 134.9, 76.8, 74.6, 74.2, 66.8, 45.4, 26.6 (3C), 26.5 (6C), 24.5, 18.8, 18.74, 18.68, 13.1, -3.3, -3.5, -3.7, -3.9, -4.0, -4.2.

HRMS-ESI calculated for  $\text{C}_{28}\text{H}_{59}\text{O}_3\text{NaSi}_3$  :  $m/z$  677.2709 ( $[\text{M}+\text{Na}]^+$ ), found :  $m/z$  677.2710 ( $[\text{M}+\text{Na}]^+$ ).



#### (1E,3E)-(5R,6S,8R)-tris-(*tert*-Butyldimethylsilyloxy)-1-tributylstannyl-3-methyl-nona-1,3-diene (**ent-15b**)

To a stirred solution of **ent-14b** (250 mg, 0.38 mmol) in dry  $\text{Et}_2\text{O}$  (2 mL), under a nitrogen atmosphere, was added  $n\text{-BuLi}$  (0.3 mL, 1.9 M in hexane, 0.57 mmol, 1.5 eq.) at  $-78^\circ\text{C}$ . The reaction mixture was stirred for 20 min at  $-78^\circ\text{C}$  and  $\text{Bu}_3\text{SnCl}$  (0.17 mL, 0.57 mmol, 1.5 eq.) was added. The resulting solution was stirred at  $-78^\circ\text{C}$  for another 20 min and allowed to warm to room temperature for 1 h. Saturated aqueous  $\text{NaHCO}_3$  solution was then added and the aqueous layer was extracted three times with  $\text{Et}_2\text{O}$ . The combined organic extracts were washed with brine, dried over  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. The crude **ent-15b** was used in the next step without further purification.

#### (2E,4E,6E,8E,10E,12R,13S,15R)-Ethyl-12,13,15-tris((*tert*-butyldimethylsilyl)oxy)-4,6,10-trimethylhexadeca-2,4,6,8,10-pentaenoate (**ent-17b**)

To a stirred solution of crude **ent-15b** and tetra- $n$ -butylammonium diphenylphosphinate (406 mg, 0.88 mmol, 2.3 eq.) in dry NMP (2.5 mL), under a nitrogen atmosphere, was added 0.2 mL of a solution of **16** in NMP (234 mg, 0.76 mmol, 2 eq., 1.7 mL). After addition of CuTC (145 mg, 0.76 mmol, 2 eq.), the rest of the **16** solution was added dropwise and the resulting mixture was stirred at room temperature for 40 min. The reaction mixture was then diluted with  $\text{Et}_2\text{O}$  and filtered through neutral alumina oxide. The filtrate was washed with water, brine, dried over  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. The crude product was then purified by preparative TLC (cyclohexane/ $\text{EtOAc}$  9:1) to afford **ent-11b** (103 mg, 0.15 mmol, 38 % for two steps) as a yellow oil. NMR analysis showed the presence of mixture of isomers  $4'E/4'Z = 93:7$ .

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz,  $4'E$  isomer)  $\delta$  7.95 (d,  $J = 15.3$  Hz, 1H,  $Z$  isomer), 7.38 (d,  $J = 15.5$  Hz, 1H,  $E$  isomer), 6.51 (dd,  $J = 14.9, 11.1$  Hz, 1H), 6.36 (d,  $J = 15.0$  Hz, 1H), 6.36 (s, 1H), 6.28 (d,  $J = 11.1$  Hz, 1H), 5.88 (d,  $J = 15.5$  Hz, 1H), 5.54 (d,  $J = 9.1$  Hz, 1H), 4.37 (dd,  $J = 9.2, 3.4$  Hz, 1H), 4.23 (q,  $J = 7.1$  Hz, 2H), 3.98 (ddq ap. sextet,  $J = 6.3$  Hz, 1H), 3.72 (ddd,  $J = 6.7, 5.5, 3.5$  Hz, 1H), 2.06 (s, 3H), 2.03 (s, 3H), 1.84

(s, 3H), 1.69 (dt,  $J = 13.7, 6.8$  Hz, 1H), 1.48 (dt,  $J = 13.7, 6.8$  Hz, 1H), 1.32 (t,  $J = 7.1$  Hz, 3H), 1.11 (d,  $J = 6.0$  Hz, 3H), 0.89 (s, 9H), 0.88 (s, 9H), 0.88 (s, 9H), 0.08 (s, 3H), 0.06 (s, 9H), 0.03 (s, 3H), -0.01 (s, 3H).

**$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz, 4'E isomer)**  $\delta$  167.5, 150.7, 143.6, 139.5, 135.1, 135.0, 134.2, 134.1, 132.2, 123.8, 116.2, 74.1, 73.8, 66.1, 60.2, 44.3, 26.0 (3C), 25.9 (6C), 23.8, 18.2, 18.1 (2C), 17.2, 14.3, 14.2, 13.4, -3.3, -3.5, -4.2, -4.3, -4.6, -4.7.

**HRMS-ESI** calculated for  $\text{C}_{39}\text{H}_{74}\text{O}_5\text{NaSi}_3$  :  $m/z$  729.4736 ( $[\text{M}+\text{Na}]^+$ ), found :  $m/z$  729.4754 ( $[\text{M}+\text{Na}]^+$ ).

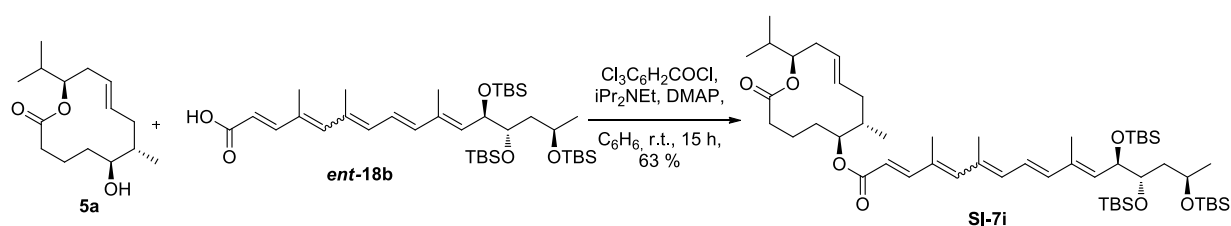
**(2E,4E,6E,8E,10E,12R,13S,15R)-12,13,15-tris((tert-Butyldimethylsilyl)oxy)-4,6,10-trimethylhexadeca-2,4,6,8,10-pentaenoic acid (ent-18b)**

To a stirred solution of **ent-17b** (97 mg, 0.14 mmol) in a mixture THF/MeOH/H<sub>2</sub>O (2.9/0.8/0.8 mL) was added LiOH (57 mg, 1.37 mmol, 10 eq.). The resulting mixture was stirred at room temperature for 18 h. After addition of saturated aqueous NH<sub>4</sub>Cl solution, the mixture was extracted three times with EtOAc and the combined organic extracts were washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude material was purified by preparative TLC (cyclohexane/EtOAc 7:3) to afford **ent-18b** (20 mg, 29.47  $\mu\text{mol}$ , 22 %) as a yellow oil. NMR analysis showed the presence of mixture of isomers 4'E/4'Z = 82:18.

**$^1\text{H}$  NMR ( $d_6$ -Acetone, 300 MHz, 4'E isomer)**  $\delta$  7.94 (d,  $J = 15.8$  Hz, 1H, Z isomer), 7.35 (d,  $J = 15.5$  Hz, 1H, E isomer), 6.67 (dd,  $J = 15.0, 11.1$  Hz, 1H), 6.48 (d,  $J = 15.0$  Hz, 1H), 6.45 (s, 1H), 6.39 (d,  $J = 11.1$  Hz, 1H), 5.87 (d,  $J = 15.5$  Hz, 1H), 5.61 (d,  $J = 9.3$  Hz, 1H), 4.52 (dd,  $J = 9.3, 3.2$  Hz, 1H), 4.05 (ddq ap. sextet,  $J = 6.2$  Hz, 1H), 3.85 (dt,  $J = 6.1, 3.4$  Hz, 1H), 2.08 (s, 3H), 2.05 (s, 3H), 1.91 (s, 3H), 1.69 (dt,  $J = 13.8, 6.7$  Hz, 1H), 1.54 (dt,  $J = 13.7, 6.2$  Hz, 1H), 1.12 (d,  $J = 6.0$  Hz, 3H), 0.90 (s, 18H), 0.89 (s, 9H), 0.13 (s, 3H), 0.11 (s, 3H), 0.08 (s, 6H), 0.07 (s, 3H), 0.03 (s, 3H).

**$^{13}\text{C}$  NMR ( $d_6$ -Acetone, 100 MHz, 4'E isomer)**  $\delta$  168.1, 151.6, 144.3, 140.2, 136.2, 135.7, 135.5, 135.3, 133.3, 125.4, 117.3, 75.2, 74.6, 66.9, 45.4, 26.52 (3C), 26.48 (3C), 26.4 (3C), 24.4, 18.9, 18.8, 18.7, 17.2, 14.4, 13.9, -3.4, -3.7, -4.0, -4.1, -4.2, -4.3.

**HRMS-ESI** calculated for  $\text{C}_{39}\text{H}_{74}\text{O}_5\text{NaSi}_3$  :  $m/z$  701.4423 ( $[\text{M}+\text{Na}]^+$ ), found :  $m/z$  701.4434 ( $[\text{M}+\text{Na}]^+$ ).



**(2E,4E,6E,8E,10E,12R,13S,15R)-(6S,7S,12R,E)-12-Isopropyl-7-methyl-2-oxooxacyclododec-9-en-6-yl 12,13,15-tris((tert-butyldimethylsilyl)oxy)-4,6,10-trimethylhexadeca-2,4,6,8,10-pentaenoate (SI-7i)**

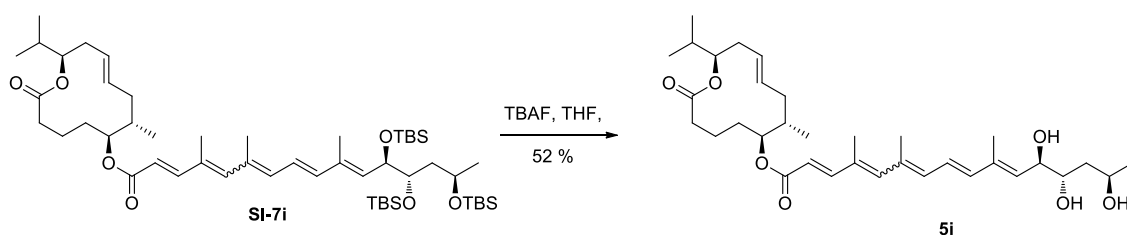
To a stirred solution of **ent-18b** (20 mg, 0.029 mmol, 1.5 eq.) in benzene (0.3 mL) were added diisopropylethylamine (18.7  $\mu\text{L}$ , 0.11 mmol, 5.6 eq.), 2,4,6-trichlorobenzoyl chloride (9.2  $\mu\text{L}$ , 0.059 mmol, 3 eq.) and DMAP (16.8 mg, 0.137 mmol, 7 eq.). The reaction mixture was stirred at room temperature for 20 min and **5a** (5 mg, 0.019 mmol) was added. The resulting mixture was stirred at room temperature for 15 h and an aqueous saturated solution of sodium hydrogenocarbonate was added. The aqueous layer was extracted three times with benzene and the combined organic extracts

were washed with brine, dried over  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. The crude product was purified over preparative TLC (cyclohexane/EtOAc 9:1) to afford **SI-7i** (11.3 mg, 0.012 mmol, 63%) as a yellow oil. NMR analysis showed the presence of mixture of isomers  $4'E/4'Z = 77:23$ .

**$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz,  $4'E$  isomer)**  $\delta$  7.95 (d,  $J = 15.4$  Hz, 1H, Z isomer), 7.38 (d,  $J = 15.5$  Hz, 1H, E isomer), 6.50 (dd,  $J = 14.8, 11.1$  Hz, 1H), 6.36 (d,  $J = 14.8$  Hz, 1H), 6.35 (s, 1H), 6.28 (d,  $J = 11.2$  Hz, 1H), 5.87 (d,  $J = 15.5$  Hz, 1H), 5.53 (d,  $J = 8.8$  Hz, 1H), 5.46 (m, 1H), 5.28 (m, 1H), 4.83-4.72 (2H), 4.37 (dd,  $J = 9.2, 3.3$  Hz, 1H), 3.98 (m, 1H), 3.72 (m, 1H), 2.49 (m, 1H), 2.30 (m, 1H), 2.15-2.06 (2H), 2.06 (s, 3H), 2.04 (s, 3H), 1.96-1.94 (1H), 1.91-1.65 (8H), 1.83 (s, 3H), 1.53-1.44 (1H), 1.11 (d,  $J = 6.0$  Hz, 3H), 0.93 (d,  $J = 6.8$  Hz, 3H), 0.92 (d,  $J = 6.8$  Hz, 3H), 0.91 (d,  $J = 7.3$  Hz, 3H), 0.89 (s, 9H), 0.88 (s, 9H), 0.87 (s, 9H), 0.08 (s, 3H), 0.06 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H).

**$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz,  $4'E$  isomer)**  $\delta$  173.0, 166.8, 150.7, 143.6, 139.5, 135.1, 135.0, 134.8, 134.2, 134.1, 132.3, 126.0, 123.8, 116.4, 78.6, 75.9, 74.1, 73.8, 66.1, 44.3, 38.0, 36.1, 35.5, 34.4, 32.3, 29.6, 26.0 (3C), 25.9 (6C), 23.7, 20.4, 19.2, 18.5, 18.3, 18.2, 18.1 (2C), 17.1, 14.2, 13.4, -3.9, -4.1, -4.4, -4.6, -4.7, -4.8.

**HRMS-ESI** calculated for  $\text{C}_{52}\text{H}_{94}\text{O}_7\text{NaSi}_3$  :  $m/z$  937.6200 ( $[\text{M}+\text{Na}]^+$ ), found :  $m/z$  937.6189 ( $[\text{M}+\text{Na}]^+$ ).



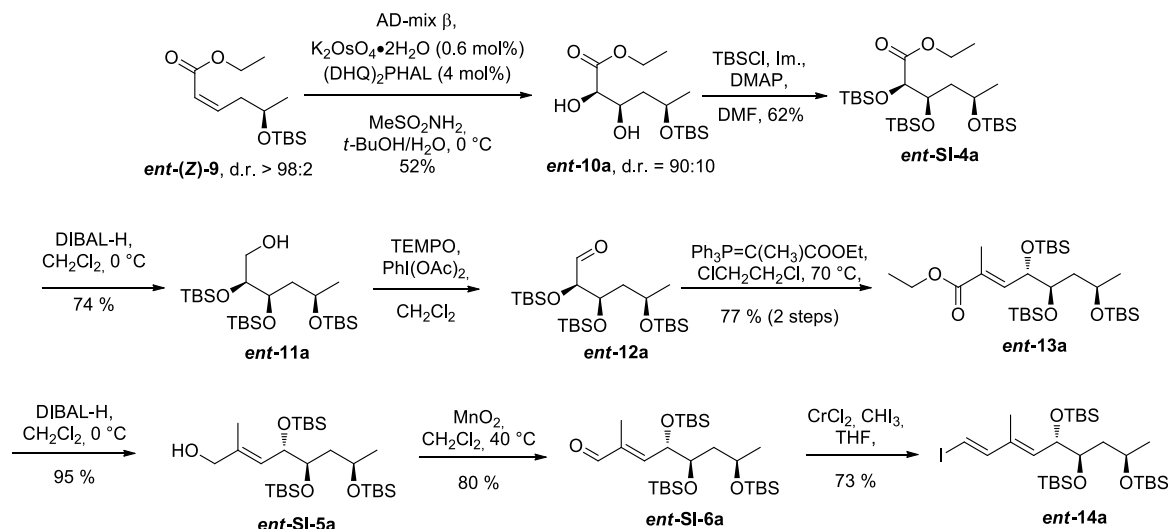
**(2E,4E,6E,8E,10E,12R,13S,15R)-(6S,7S,12R,E)-12-Isopropyl-7-methyl-2-oxooxacyclododec-9-en-6-yl 12,13,15-trihydroxy-4,6,10-trimethylhexadeca-2,4,6,8,10-pentaenoate (5i).**

To a stirred solution of **SI-7i** (11.3 mg, 0.012 mmol) in THF (0.1 mL) was added TBAF (0.11 mmol, 1M in THF, 9 eq.). The reaction mixture was stirred at room temperature for 5 h.  $\text{CaCO}_3$  (22 mg), Dowex 50WX8-400 (69 mg) and MeOH (0.15 mL) were added and the reaction mixture was stirred for 1 h. The resulting mixture was filtered and concentrated under reduce pressure. The crude product was then purified by preparative TLC ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$  9:1) to give **5i** (3.6 mg, 6.3  $\mu\text{mol}$ , 52%) as a yellow foam. NMR analysis showed the presence of mixture of isomers  $4'E/4'Z = 64:36$ . It should be noticed that due to instability, this product decomposed over time.

**$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz,  $4'E$  isomer)**  $\delta$  7.92 (d,  $J = 15.4$  Hz, 1H, Z isomer), 7.37 (d,  $J = 15.5$  Hz, 1H, E isomer), 6.57 (dd,  $J = 15.1, 11.1$  Hz, 1H), 6.39 (d,  $J = 15.0$  Hz, 1H), 6.35 (s, 1H), 6.25 (d,  $J = 11.0$  Hz, 1H), 5.87 (d,  $J = 15.5$  Hz, 1H), 5.61 (m, 1H), 5.46 (m, 1H), 5.28 (m, 1H), 4.82-4.71 (2H), 4.50 (m, 1H), 4.10 (m, 1H), 3.95 (m, 1H), 2.49 (m, 1H), 2.30 (m, 1H), 2.15-1.58 (21 H including 2.05 (s, 3H), 2.03 (s, 3H), 1.91 (s, 3H)), 1.24 (d,  $J = 6.2$  Hz, 3H), 0.93 (d,  $J = 6.7$  Hz, 3H), 0.92 (d,  $J = 6.9$  Hz, 3H), 0.91 (d,  $J = 6.7$  Hz, 3H).

**$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz,  $4'E$  isomer)**  $\delta$  173.0, 166.7, 150.5, 143.3, 142.6, 140.4, 138.6, 134.8, 133.5, 133.2, 129.7, 126.0, 124.7, 123.4, 84.0, 78.6, 78.4, 75.9, 74.2, 41.9, 38.0, 36.1, 35.5, 34.4, 32.3, 29.7, 26.9, 20.3, 19.2, 18.5, 18.2, 17.4, 14.2, 13.2.

**HRMS-ESI** calculated for  $\text{C}_{34}\text{H}_{50}\text{O}_6\text{Na}$  :  $m/z$  577.3500 ( $[\text{M}+\text{Na}]^+[-\text{H}_2\text{O}]$ ), found :  $m/z$  577.3490 ( $[\text{M}+\text{Na}]^+[-\text{H}_2\text{O}]$ ).



### (2R,3R,5R)-Ethyl 5-((*tert*-butyldimethylsilyl)oxy)-2,3-dihydroxyhexanoate (*ent*-10a)

To a stirred solution of AD-mix  $\beta$  (4.60 g, 0.4 % osmium, 1 % (DHQD)<sub>2</sub>PHAL) in a mixture 1:1 *t*-BuOH/H<sub>2</sub>O (27:27 mL) were added successively methanesulfonamide (270 mg, 2.84 mmol, 0.9 eq.), potassium osmate(VI) dihydrate (9 mg, 24.43  $\mu$ mol, 0.6 mol%) and (DHQD)<sub>2</sub>PHAL (103 mg, 0.13 mmol, 4 mol%). The mixture was stirred at room temperature until two clear phases were produced. The solution was cooled to 0 °C, whereupon the inorganic salts partially precipitate, and *ent*-(*Z*)-9 (800 mg, 2.94 mmol) was then added. After stirring 48 h at 0 °C, Na<sub>2</sub>SO<sub>3</sub> (8.3 g) was added and the reaction mixture was stirred for 30 min at room temperature. The mixture was extracted three times with EtOAc. The combined organic extracts were washed with an aqueous KOH solution (2M), brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The reaction crude was purified by chromatography (cyclohexane/EtOAc 8:2) to give an inseparable mixture of diastereoisomers (470 mg, 1.53 mmol, 52 %, 90:10 in favor of the desired diastereoisomer *ent*-10a) as a colorless oil.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  4.35-4.19 (5H), 3.30 (br s, 1H), 3.01 (br s, 1H), 1.80 (m, 1H), 1.40 (m, 1H), 1.32 (t, *J* = 7.1 Hz, 3H), 1.22 (d, *J* = 6.2 Hz, 3H), 0.90 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  172.6, 74.3, 70.1, 66.5, 61.8, 39.3, 25.8 (3C), 23.1, 17.9, 14.2, -4.5, -5.1.

HRMS-ESI calculated for C<sub>14</sub>H<sub>31</sub>O<sub>5</sub>Si : *m/z* 307.1941 ([M+H]<sup>+</sup>), found : *m/z* 307.1943 ([M+H]<sup>+</sup>).

### (2R,3R,5R)-Ethyl 2,3,5-tris(*tert*-butyldimethylsilyloxy)hexanoate (*ent*-SI-4a)

To a stirred solution of *ent*-10a (470 mg, 1.53 mmol) in dry DMF (15 mL), under a nitrogen atmosphere, were added *tert*-butyldimethylsilyl chloride (1.39 g, 9.20 mmol, 6 eq.), imidazole (420 mg, 6.14 mmol, 4 eq.) and DMAP (38 mg, 0.31 mmol, 0.2 eq.). The reaction mixture was stirred at room temperature for 48 h. The resulting solution was hydrolyzed with water and the aqueous layer was extracted three times with a mixture of cyclohexane and DCM (9:1). The combined organic extracts were washed with water, brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude product was purified by chromatography (cyclohexane/EtOAc 20:1) to give an inseparable mixture of diastereoisomers (503 mg, 0.94 mmol, 62 %, 90:10 in favor of the desired diastereoisomer *ent*-SI-4a) as a colorless oil.

**<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)** δ 4.15 (q, *J* = 7.1 Hz, 2H), 4.15 (d, *J* = 2.3 Hz, 1H), 4.07 (ddd, *J* = 7.5, 4.3, 2.3 Hz, 1H), 3.89 (m, 1H), 1.79 (ddd, *J* = 14.1, 7.8, 4.1 Hz, 1H), 1.59 (ddd, *J* = 14.1, 7.6, 4.6 Hz, 1H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.16 (d, *J* = 6.1 Hz, 3H), 0.92 (s, 9H), 0.88 (s, 9H), 0.87 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H), 0.08 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H).

**<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)** δ 171.7, 77.5, 73.3, 65.8, 60.5, 44.6, 25.9 (3C), 25.9 (3C), 25.8 (3C), 24.6, 18.4, 18.1, 18.0, 14.2, -3.5, -4.0, -4.3, -4.6, -4.9, -5.3.

**HRMS-ESI** calculated for C<sub>26</sub>H<sub>58</sub>O<sub>5</sub>NaSi<sub>3</sub> : *m/z* 557.3490 ([M+Na]<sup>+</sup>), found : *m/z* 557.3488 ([M+Na]<sup>+</sup>).

#### **(2*S*,3*R*,5*R*)-2,3,5-tris(*tert*-Butyldimethylsilyloxy)hexan-1-ol (*ent*-11a)**

To a stirred solution of ***ent*-SI-4a** (503 mg, 0.94 mmol) in dry DCM (8 mL), under a nitrogen atmosphere, was added DIBAL-H (1.4 mL, 1.5 M in toluene, 2.07 mmol, 2.2 eq.) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h. Saturated aqueous Rochelle salt solution was then added, and the resulting mixture warmed to room temperature and vigorously stirred overnight. The aqueous layer was extracted with Et<sub>2</sub>O and the combined organic extracts were washed with water, brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude alcohol was purified by chromatography (cyclohexane/EtOAc 95:5) to afford ***ent*-11a** (341 mg, 0.69 mmol, 74 %) as a pure diastereoisomer and ***ent*-11b** (30 mg, 60.9 μmol, 6 %).

**<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)** δ 3.97-3.90 (2H), 3.73 (dd, *J* = 12.5, 6.6 Hz, 1H), 3.63-3.57 (2H), 1.69 (ddd, *J* = 14.2, 8.3, 3.8 Hz, 1H), 1.50 (ddd, *J* = 14.2, 7.5, 3.6 Hz, 1H), 1.17 (d, *J* = 6.2 Hz, 3H), 0.92 (s, 9H), 0.89 (s, 9H), 0.88 (s, 9H), 0.13 (s, 3H), 0.11 (s, 3H), 0.10 (s, 3H), 0.10 (s, 3H), 0.08 (s, 6H).

**<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)** δ 76.4, 73.6, 66.2, 63.7, 45.5, 26.0 (3C), 25.9 (3C), 25.9 (3C), 24.9, 18.3, 18.2, 18.0, -3.4, -3.9, -4.2, -4.3, -4.5, -4.6.

**HRMS-ESI** calculated for C<sub>24</sub>H<sub>57</sub>O<sub>4</sub>Si<sub>3</sub> : *m/z* 493.3565 ([M+H]<sup>+</sup>), found : 493.3562 ([M+H]<sup>+</sup>).

[α]<sub>D</sub><sup>20</sup> = -7.5 (c 0.6, CHCl<sub>3</sub>).

#### **(2*R*,3*R*,5*R*)-2,3,5-tris((*tert*-Butyldimethylsilyl)oxy)hexanal (*ent*-12a)**

To a stirred solution of ***ent*-11a** (340 mg, 0.69 mmol) in dry DCM (1.5 mL), under a nitrogen atmosphere, were added iodosobenzene diacetate (245 mg, 0.76 mmol, 1.1 eq.) and TEMPO (11 mg, 760 μmol, 0.1 eq.) at 0 °C. The reaction mixture was stirred at room temperature for 5 h. Water was then added to the reaction mixture which was extracted three times with DCM. The combined organic extracts were washed with water, brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude aldehyde ***ent*-12a** was used in the next step without further purification.

**<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)** δ 9.62 (d, *J* = 1.9 Hz, 1H), 4.08 (m, 1H), 3.91 (ddd, *J* = 7.9, 6.1, 4.2 Hz, 1H), 3.87 (dd ap. t, *J* = 2.0 Hz, 1H), 1.75 (ddd, *J* = 14.1, 7.9, 4.3 Hz, 1H), 1.61 (ddd, *J* = 14.1, 7.2, 4.2 Hz, 1H), 1.17 (d, *J* = 6.1 Hz, 3H), 0.94 (s, 9H), 0.89 (s, 9H), 0.87 (s, 9H), 0.13 (s, 3H), 0.11 (s, 6H), 0.08 (s, 9H).

#### **(4*S*,5*R*,7*R*,*E*)-Ethyl 4,5,7-tris((*tert*-butyldimethylsilyl)oxy)-2-methyloct-2-enoate (*ent*-13a)**

To a stirred solution of crude aldehyde ***ent*-12a** in 1,2-dichloroethane (3.5 mL), under a nitrogen atmosphere, was added (1-ethoxycarbonyl ethylidene)triphenyl phosphorane (375 mg, 1.03 mmol, 1.5 eq.) at room temperature. The reaction mixture was warmed to 70 °C and stirred for 48 h. The resulting solution was then cooled to room temperature, the solvent was removed under reduced pressure and



the residue purified by chromatography (cyclohexane/EtOAc 95:5) to give **ent-13a** (305 mg, 0.53 mmol, 77 %) as a colorless oil.

**<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)**  $\delta$  6.69 (dq,  $J$  = 9.1, 1.4 Hz, 1H), 4.32 (dd,  $J$  = 9.2, 2.8 Hz, 1H), 4.20 (q,  $J$  = 7.1 Hz, 2H), 3.96 (m, 1H), 3.88 (dt,  $J$  = 7.8, 2.9 Hz, 1H), 1.87 (d,  $J$  = 1.4 Hz, 3H), 1.56 (ddd,  $J$  = 14.1, 8.6, 3.1 Hz, 1H), 1.38 (ddd,  $J$  = 14.1, 8.3, 3.8 Hz, 1H), 1.30 (t,  $J$  = 7.1 Hz, 3H), 1.15 (d,  $J$  = 6.2 Hz, 3H), 0.89 (s, 18H), 0.87 (s, 9H), 0.12 (s, 3H), 0.09 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H), 0.04 (s, 3H), 0.01 (s, 3H).

**<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)**  $\delta$  167.9, 141.8, 127.4, 74.4, 74.3, 66.0, 60.6, 44.8, 26.0 (3C), 25.93 (3C), 25.89 (3C), 24.9, 18.3, 18.2, 18.0, 14.2, 13.4, -3.3, -3.7, -4.2, -4.3, -4.5, -4.8.

**HRMS-ESI** calculated for C<sub>29</sub>H<sub>62</sub>O<sub>5</sub>NaSi<sub>3</sub> :  $m/z$  597.3803 ([M+Na]<sup>+</sup>), found :  $m/z$  597.3809 ([M+Na]<sup>+</sup>).

**[ $\alpha$ ]<sup>20</sup><sub>D</sub>** = -10.4 (c 0.5, CHCl<sub>3</sub>).

#### **(4*S*,5*R*,7*R*,*E*)-4,5,7-tris((*tert*-Butyldimethylsilyl)oxy)-2-methyloct-2-en-1-ol (*ent*-SI-5a)**

To a stirred solution of **ent-13a** (305 mg, 0.53 mmol) in dry DCM (3.2 mL), under a nitrogen atmosphere, was added DIBAL-H (0.78 mL, 1.5 M in toluene, 1.17 mmol, 2.2 eq.) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h. Saturated aqueous Rochelle salt solution was then added, and the resulting mixture warmed to room temperature and vigorously stirred overnight. The aqueous layer was extracted with Et<sub>2</sub>O and the combined organic extracts were washed with water, brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude alcohol was purified by chromatography (cyclohexane/EtOAc 9:1) to afford **ent-SI-5a** (270 mg, 0.51 mmol, 95 %) as a colorless oil.

**<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)**  $\delta$  5.45 (dq,  $J$  = 8.9, 1.2 Hz, 1H), 4.27 (dd,  $J$  = 8.8, 2.6 Hz, 1H), 4.02 (s, 2H), 3.96 (m, 1H), 3.83 (dt,  $J$  = 7.7, 2.8 Hz, 1H), 1.71 (d,  $J$  = 1.2 Hz, 3H), 1.54 (ddd,  $J$  = 14.1, 8.6, 3.1 Hz, 1H), 1.37 (ddd,  $J$  = 14.1, 7.9, 3.4 Hz, 1H), 1.15 (d,  $J$  = 6.2 Hz, 3H), 0.89 (s, 9H), 0.89 (s, 9H), 0.88 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H), 0.07 (s, 6H), 0.04 (s, 3H), 0.01 (s, 3H).

**<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)**  $\delta$  135.4, 126.6, 74.7, 73.7, 68.7, 66.2, 44.7, 26.1 (3C), 26.0 (3C), 25.9 (3C), 25.0, 18.3, 18.2, 18.0, 14.5, -3.2, -3.5, -4.1, -4.3, -4.5, -4.6.

**HRMS-ESI** calculated for C<sub>27</sub>H<sub>60</sub>O<sub>4</sub>NaSi<sub>3</sub> :  $m/z$  555.3697 ([M+Na]<sup>+</sup>), found :  $m/z$  555.3705 ([M+Na]<sup>+</sup>).

**[ $\alpha$ ]<sup>20</sup><sub>D</sub>** = -19.5 (c 0.4, CHCl<sub>3</sub>).

#### **(4*S*,5*R*,7*R*,*E*)-4,5,7-tris((*tert*-Butyldimethylsilyl)oxy)-2-methyloct-2-enal (*ent*-SI-6a)**

To a stirred solution of **ent-SI-5a** (270 mg, 0.51 mmol) in dry DCM (5.2 mL), under a nitrogen atmosphere, was added MnO<sub>2</sub> (661 mg, 7.60 mmol, 15 eq.) at room temperature. The reaction mixture was warmed to 40 °C and vigorously stirred for 48 h. The resulting mixture was cooled to room temperature and filtered through celite with DCM. The solvent was then removed under reduced pressure to give **ent-SI-6a** (215 mg, 0.40 mmol, 80 %) as a colorless oil which was used in the next step without further purification.

**<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)**  $\delta$  9.45 (s, 1H), 6.44 (dq,  $J$  = 8.9, 1.4 Hz, 1H), 4.49 (dd,  $J$  = 8.9, 2.6 Hz, 1H), 3.99-3.93 (2H), 1.80 (d,  $J$  = 1.4 Hz, 3H), 1.51 (ddd,  $J$  = 14.1, 8.9, 3.0 Hz, 1H), 1.36 (ddd,  $J$  = 14.1, 7.9, 3.0 Hz, 1H), 1.15 (d,  $J$  = 6.2 Hz, 3H), 0.89 (s, 18H), 0.87 (s, 9H), 0.14 (s, 3H), 0.11 (s, 3H), 0.07 (s, 6H), 0.05 (s, 3H), 0.01 (s, 3H).

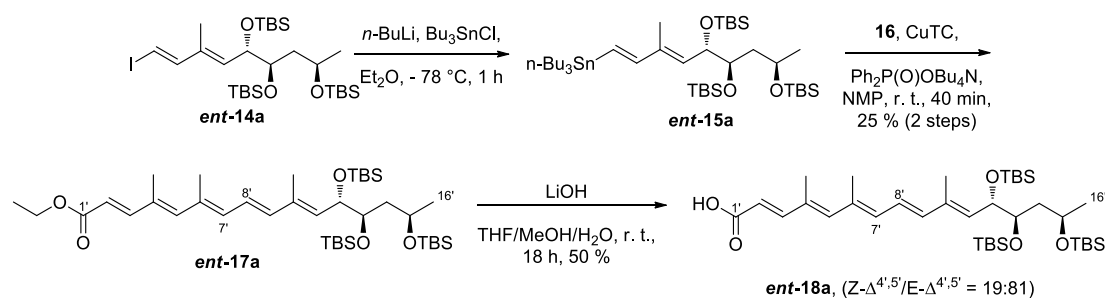
**(1*E*,3*E*)-(5*S*,6*R*,8*R*)-tris-(*tert*-Butyldimethylsilyloxy)-1-iodo-3-methyl-nona-1,3-diene (*ent*-14a)**

To a stirred solution of CrCl<sub>2</sub> (300 mg, 2.43 mmol, 6 eq.) in dry THF (2.5 mL), under a nitrogen atmosphere, was added a solution of *ent*-SI-6a (215 mg, 0.40 mmol) and CHI<sub>3</sub> (480 mg, 1.21 mmol, 3 eq.) in dry THF (1.6 mL) dropwise. The reaction mixture was stirred at room temperature for 12 h. The resulting mixture was hydrolyzed with water and diluted with Et<sub>2</sub>O. The aqueous layer was extracted three times with Et<sub>2</sub>O and the combined organic extracts were washed with water, brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude product was then purified by chromatography (cyclohexane/toluene 100:1) to afford *ent*-14a (194 mg, 0.30 mmol, 73 %) as a pale yellow oil.

<sup>1</sup>H NMR (C<sub>6</sub>D<sub>6</sub>, 300 MHz) δ 7.05 (d, *J* = 14.1 Hz, 1H), 6.01 (d, *J* = 14.1 Hz, 1H), 5.56 (dq, *J* = 9.1, 1.2 Hz, 1H), 4.40 (dd, *J* = 9.1, 2.8 Hz, 1H), 4.12 (m, 1H), 4.05 (dt, *J* = 7.8, 2.8 Hz, 1H), 1.69 (ddd, *J* = 14.1, 8.9, 2.8 Hz, 1H), 1.57 (ddd, *J* = 14.1, 7.9, 2.9 Hz, 1H), 1.47 (d, *J* = 1.2 Hz, 3H), 1.15 (d, *J* = 6.2 Hz, 3H), 1.03 (s, 9H), 1.00 (s, 18H), 0.25 (s, 3H), 0.23 (s, 3H), 0.14 (s, 3H), 0.11 (s, 3H), 0.10 (s, 3H), 0.06 (s, 3H).

<sup>13</sup>C NMR (C<sub>6</sub>D<sub>6</sub>, 100 MHz) δ 149.6, 135.0, 134.6, 76.6, 75.4, 74.7, 66.9, 45.7, 26.7 (3C), 26.6 (3C), 26.5 (3C), 25.6, 19.0, 18.9, 18.7, 13.1, -2.6, -2.8, -3.6, -3.7, -3.9, -4.1.

[α]<sub>D</sub><sup>20</sup> = -6.7 (c 0.9, CHCl<sub>3</sub>).



**(1*E*,3*E*)-(5*S*,6*R*,8*R*)-tris-(*tert*-Butyldimethylsilyloxy)-1-tributylstannyl-3-methyl-nona-1,3-diene (*ent*-15a)**

To a stirred solution of *ent*-14a (200 mg, 0.31 mmol) in dry Et<sub>2</sub>O (1.6 mL), under a nitrogen atmosphere, was added *n*-BuLi (0.23 mL, 2 M in hexane, 0.46 mmol, 1.5 eq.) at -78 °C. The reaction mixture was stirred for 20 min at -78 °C and Bu<sub>3</sub>SnCl (0.11 mL, 0.37 mmol, 1.2 eq.) was added. The resulting solution was stirred at -78 °C for another 20 min and allowed to warm to room temperature for 1 h. Saturated aqueous NaHCO<sub>3</sub> solution was then added and the aqueous layer was extracted three times with Et<sub>2</sub>O. The combined organic extracts were washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude *ent*-15a was used in the next step without further purification.

**(2*E*,4*E*,6*E*,8*E*,10*E*,12*S*,13*R*,15*R*)-Ethyl-12,13,15-tris((*tert*-butyldimethylsilyl)oxy)-4,6,10-trimethylhexadeca-2,4,6,8,10-pentaenoate (*ent*-17a)**

To a stirred solution of crude *ent*-15a and tetra-*n*-butylammonium diphenylphosphinate (325 mg, 0.70 mmol, 2.3 eq.) in dry NMP (2.1 mL), under a nitrogen atmosphere, was added 0.2 mL of a solution of **16** in NMP (187 mg, 0.61 mmol, 2 eq., 1.4 mL). After addition of CuTC (117 mg, 0.61 mmol, 2 eq.), the rest of the **16** solution was added dropwise and the resulting mixture was stirred at room temperature for 40 min. The reaction mixture was then diluted with Et<sub>2</sub>O and filtered through neutral alumina oxide.

The filtrate was washed with water, brine, dried over  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. The crude product was then purified by preparative TLC (cyclohexane/EtOAc 9:1) to afford **ent-17a** (58 mg, 0.08 mmol, 25 % for two steps) as a yellow oil. NMR analysis showed the presence of mixture of isomers  $4'E/4'Z = 93:7$ .

**$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz,  $4'E$  isomer)**  $\delta$  7.95 (d,  $J = 15.3$  Hz, 1H, Z isomer), 7.38 (d,  $J = 15.5$  Hz, 1H, E isomer), 6.50 (dd,  $J = 14.9, 11.1$  Hz, 1H), 6.37 (d,  $J = 14.9$  Hz, 1H), 6.35 (s, 1H), 6.27 (d,  $J = 11.1$  Hz, 1H), 5.87 (d,  $J = 15.5$  Hz, 1H), 5.57 (d,  $J = 9.1$  Hz, 1H), 4.35 (dd,  $J = 9.1, 2.8$  Hz, 1H), 4.23 (q,  $J = 7.1$  Hz, 2H), 3.96 (m, 1H), 3.87 (dt,  $J = 7.6, 2.9$  Hz, 1H), 2.06 (s, 3H), 2.03 (s, 3H), 1.85 (s, 3H), 1.53 (m, 1H), 1.36 (m, 1H), 1.32 (t,  $J = 7.1$  Hz, 3H), 1.14 (d,  $J = 6.1$  Hz, 3H), 0.89 (s, 9H), 0.88 (s, 9H), 0.87 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H), 0.08 (s, 3H), 0.06 (s, 3H), 0.03 (s, 3H), 0.00 (s, 3H).

**$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz,  $4'E$  isomer)**  $\delta$  167.5, 150.7, 143.7, 139.7, 135.1, 134.7, 134.0, 133.9, 132.1, 123.7, 116.1, 74.8, 74.1, 66.2, 60.1, 44.9, 26.1 (3C), 26.0 (3C), 25.9 (3C), 25.0, 18.32, 18.27, 18.0, 17.1, 14.3, 14.2, 13.4, -3.3, -3.5, -4.2, -4.3, -4.6, -4.7.

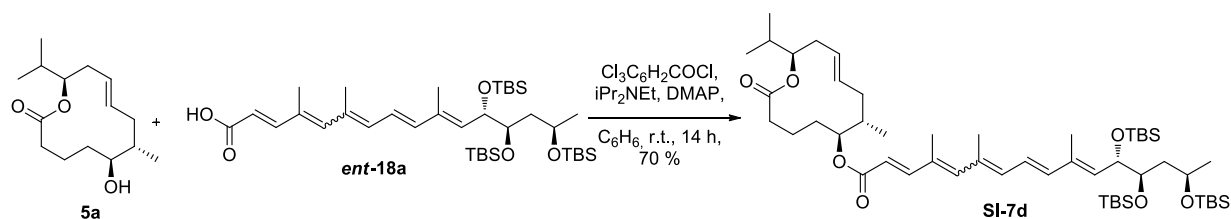
**(2E,4E,6E,8E,10E,12S,13R,15R)-12,13,15-tris((tert-Butyldimethylsilyl)oxy)-4,6,10-trimethylhexadeca-2,4,6,8,10-pentaenoic acid (**ent-18a**)**

To a stirred solution of **ent-17a** (58 mg, 0.08 mmol) in a mixture THF/MeOH/ $\text{H}_2\text{O}$  (2.3/0.6/0.6 mL) was added LiOH (20 mg, 0.82 mmol, 10 eq.). The resulting mixture was stirred at room temperature for 18 h. After addition of saturated aqueous  $\text{NH}_4\text{Cl}$  solution, the mixture was extracted three times with EtOAc and the combined organic extracts were washed with brine, dried over  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. The crude material was purified by preparative TLC (cyclohexane/EtOAc 7:3) to afford **ent-18a** (27 mg, 40.24  $\mu\text{mol}$ , 50 %) as a yellow oil. NMR analysis showed the presence of mixture of isomers  $4'E/4'Z = 81:19$ .

**$^1\text{H}$  NMR ( $\text{d}_6$ -Acetone, 300 MHz,  $4'E$  isomer)**  $\delta$  7.93 (d,  $J = 15.5$  Hz, 1H, Z isomer), 7.35 (d,  $J = 15.6$  Hz, 1H, E isomer), 6.67 (dd,  $J = 15.1, 11.1$  Hz, 1H), 6.46 (d,  $J = 15.1$  Hz, 1H), 6.46 (s, 1H), 6.39 (d,  $J = 11.1$  Hz, 1H), 5.87 (d,  $J = 15.6$  Hz, 1H), 5.63 (d,  $J = 9.1$  Hz, 1H), 4.49 (dd,  $J = 9.1, 2.8$  Hz, 1H), 4.06 (m, 1H), 3.97 (dt,  $J = 7.6, 2.9$  Hz, 1H), 2.09 (s, 3H), 2.06 (s, 3H), 1.93 (s, 3H), 1.64 (ddd,  $J = 14.1, 8.8, 3.1$  Hz, 1H), 1.41 (ddd,  $J = 14.1, 7.7, 3.2$  Hz, 1H), 1.17 (d,  $J = 6.2$  Hz, 3H), 0.91 (s, 18H), 0.89 (s, 9H), 0.17 (s, 3H), 0.15 (s, 3H), 0.11 (s, 3H), 0.10 (s, 3H), 0.09 (s, 3H), 0.05 (s, 3H).

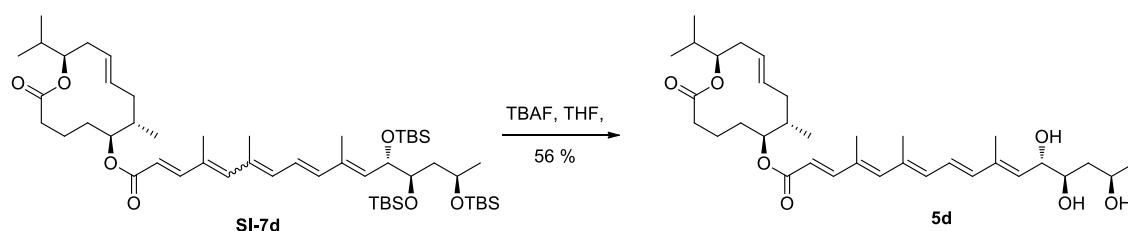
**$^{13}\text{C}$  NMR ( $\text{d}_6$ -Acetone, 100 MHz,  $4'E$  isomer)**  $\delta$  168.1, 151.6, 144.3, 140.3, 136.2, 135.5, 135.4, 135.0, 133.3, 125.3, 117.3, 75.9, 75.2, 67.1, 45.8, 26.6 (3C), 26.5 (3C), 26.4 (3C), 25.5, 19.0, 18.9, 18.7, 17.2, 14.4, 13.9, -2.9, -3.0, -3.7, -3.8, -4.1, -4.3.

**HRMS-ESI** calculated for  $\text{C}_{37}\text{H}_{70}\text{O}_5\text{NaSi}_3$  :  $m/z$  701.4423 ( $[\text{M}+\text{Na}]^+$ ), found :  $m/z$  701.4424 ( $[\text{M}+\text{Na}]^+$ ).



**(6*S*,7*S*,9*E*,12*R*)-7-Methyl-2-oxo-12-(propan-2-yl)-1-oxacyclododec-9-en-6-yl  
(2*E*,4*E*,6*E*,8*E*,10*E*,12*S*,13*R*,15*R*)-12,13,15-tris[(*tert*-butyldimethylsilyl)oxy]-4,6,10-trimethylhexadeca-2,4,6,8,10-pentaenoate (**SI-7d**)**

To a solution of **ent-18a** (26 mg, 0.03 mmol) in benzene (0.4 mL) were added diisopropylethyl amine (23  $\mu\text{L}$ , 0.13 mmol, 5.6 eq.), 2,4,6-trichlorobenzoyl chloride (11  $\mu\text{L}$ , 0.07 mmol, 3 eq.), and DMAP (20 mg). The reaction mixture was stirred at room temperature for 15 min and **5a** (7 mg, 0.027 mmol) was added. After being stirred at room temperature for 14 h, an aqueous saturated solution of sodium hydrogenocarbonate was added to the reaction mixture. The aqueous layer was extracted three times with benzene. The combined organic layers were washed with brine, dried over  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. The crude product was purified on preparative TLC eluting with heptane/ethyl acetate 90:10 to give **SI-7d** (17 mg, 0.019 mmol, 70 %) as a yellow oil.



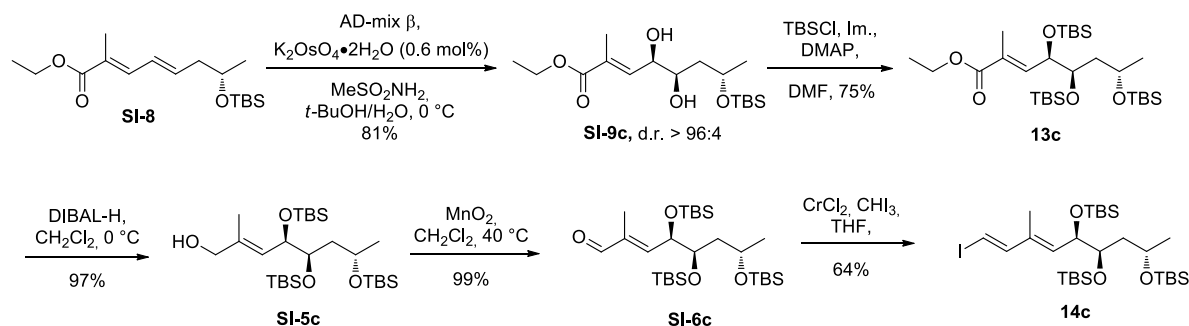
**(2*E*,4*E*,6*E*,8*E*,10*E*,12*S*,13*R*,15*R*)-(6*S*,7*S*,12*R*,*E*)-12-Isopropyl-7-methyl-2-oxooxacyclododec-9-en-6-yl  
12,13,15-trihydroxy-4,6,10-trimethylhexadeca-2,4,6,8,10-pentaenoate (**5d**)**

To a solution of **SI-7d** (17 mg, 0.018 mmol) in THF (0.3 mL) was added TBAF (0.16 mmol, 1M in THF, 9 eq). The solution was stirred at room temperature for 4 h.  $\text{CaCO}_3$  (40 mg), Dowex 50WX8-400 (120 mg) and MeOH (0.3 mL) were added and the reaction mixture was stirred for 1 h. After being filtered and concentrated under reduced pressure, the crude product was purified by TLC preparative ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$  90:10) to give **5d** (6 mg, 0.010 mmol, 56 %). A (4'*E*)/(4'*Z*) = 59:41 mixture could be detected by  $^1\text{H}$  analysis.

**NMR  $^1\text{H}$  (Acetone- $\text{d}_6$ , 300 MHz)**  $\delta$  7.91 (d,  $J$  = 15.6 Hz, 1H, *Z* isomer), 7.37 (d,  $J$  = 15.5 Hz, 1H, *E* isomer), 6.63 (dd,  $J$  = 11.1, 15.0 Hz, 1H), 6.47 (s, 1H), 6.36 (d,  $J$  = 15.0 Hz, 1H), 6.17 (d,  $J$  = 11.1 Hz, 1H), 5.89 (d,  $J$  = 15.5 Hz, 1H), 5.66 (m, 1H), 5.50 (m, 1H), 5.30 (m, 1H), 4.78-4.66 (2H), 4.37 (m, 1H), 4.04 (m, 1H), 3.86 (m, 1H), 3.80 (m, 1H), 3.69 (s, 1H), 3.63 (s, 1H), 2.50 (m, 1H), 2.32 (m, 1H), 2.12-2.08 (2H), 2.06 (s, 3H), 1.97 (s, 3H), 1.95-1.92 (2H), 1.90 (s, 3H), 1.80-1.75 (4H), 1.70-1.62 (2H), 1.54-1.49 (2H), 1.13 (d,  $J$  = 6.1 Hz, 3H), 0.92 (s, 3H), 0.90 (s, 3H), 0.87 (s, 3H).

**NMR  $^{13}\text{C}$  (Acetone- $d_6$ , 75 MHz)**  $\delta$  173.9, 167.8, 152.2, 144.1, 141.6, 137.3, 136.5, 136.1, 134.1, 133.0, 128.0, 125.7, 120.6, 118.3, 80.3, 77.3, 73.5, 73.3, 65.9, 43.1, 39.7, 37.9, 37.0, 36.1, 34.1, 25.7, 22.0, 21.6, 20.9, 19.9, 19.4, 18.1, 15.3, 14.3.

**HRMS-ESI** calculated for  $\text{C}_{34}\text{H}_{52}\text{O}_7\text{Na}$ :  $m/z$  595.3605 ( $[\text{M}+\text{Na}]^+$ ), found:  $m/z$  595.3618 ( $[\text{M}+\text{Na}]^+$ ).



**(4*R*,5*R*,7*S*,*E*)-Ethyl 7-((*tert*-butyldimethylsilyl)oxy)-4,5-dihydroxy-2-methyloct-2-enoate (SI-9c)**

To a stirred solution of AD-mix  $\beta$  (6.8 g, 0.4 % osmium, 1 % (DHQD) $_2$ PHAL) in a mixture 1:1 *t*-BuOH/ $\text{H}_2\text{O}$  (40:40 mL) were added successively methanesulfonamide (392 mg, 4.12 mmol, 0.9 eq.) and potassium osmate(VI) dihydrate (36 mg, 97.71  $\mu\text{mol}$ , 0.6 mol%). The mixture was stirred at room temperature until two clear phases were produced. The solution was cooled to 0  $^\circ\text{C}$ , whereupon the inorganic salts partially precipitate, and **SI-8**<sup>1</sup> (1.54 g, 4.9 mmol) was added. After stirring 48 h at 0  $^\circ\text{C}$ ,  $\text{Na}_2\text{SO}_3$  (12.3 g) was added and the reaction mixture was stirred for 30 min at room temperature. The mixture was extracted three times with EtOAc. The combined organic extracts were washed with an aqueous KOH solution (2M), brine, dried over  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. The crude product was purified by chromatography (cyclohexane/EtOAc 8:2) to give **SI-9c** (1.37 g, 3.96 mmol, 81 %, d.r. > 94:6) as a colorless oil.

**$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)**  $\delta$  6.67 (dq,  $J$  = 8.9, 1.4 Hz, 1H), 4.27-4.17 (4H), 3.93 (ddd,  $J$  = 10.5, 6.1, 2.1 Hz, 1H), 1.92 (d,  $J$  = 1.4 Hz, 3H), 1.75 (ddd,  $J$  = 14.2, 10.5, 3.6 Hz, 1H), 1.45 (ddd,  $J$  = 14.2, 5.2, 2.1 Hz, 1H), 1.30 (t,  $J$  = 7.1 Hz, 3H), 1.25 (d,  $J$  = 6.3 Hz, 3H), 0.90 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H).

**$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz)**  $\delta$  167.7, 139.0, 131.1, 72.1, 71.2, 67.4, 60.8, 39.8, 25.7 (3C), 22.6, 17.9, 14.2, 13.3, -4.5, -5.1

**HRMS-ESI** calculated for  $\text{C}_{17}\text{H}_{35}\text{O}_5\text{NaSi}$ :  $m/z$  369.2073 ( $[\text{M}+\text{Na}]^+$ ), found:  $m/z$  369.2068 ( $[\text{M}+\text{Na}]^+$ ).

$[\alpha]^{20}_{\text{D}} = +14.7$  (c 1.0,  $\text{CHCl}_3$ ).

**(4*R*,5*R*,7*S*,*E*)-Ethyl 4,5,7-tris((*tert*-butyldimethylsilyl)oxy)-2-methyloct-2-enoate (13c)**

To a stirred solution of **SI-9c** (1.31 g, 3.78 mmol) in dry DMF (38 mL), under a nitrogen atmosphere, were added *tert*-butyldimethylsilyl chloride (3.42 g, 22.7 mmol, 6 eq.), imidazole (1.03 g, 15.1 mmol, 4 eq.) and DMAP (92 mg, 0.75 mmol, 0.2 eq.). The reaction mixture was stirred at room temperature for 48 h. The resulting solution was hydrolyzed with water and the aqueous layer was extracted three times with a mixture of cyclohexane and DCM (9:1). The combined organic extracts were washed with water, brine, dried over  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. The crude product was purified by chromatography (cyclohexane/EtOAc 20:1) to give **13c** (1.62 g, 2.82 mmol, 75 %) as a colorless oil.

**<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)** δ 6.71 (dq, *J* = 8.9, 1.4 Hz, 1H), 4.43 (dd, *J* = 8.9, 3.5 Hz, 1H), 4.22 (m, 2H), 4.07 (ddq ap. sextet, *J* = 6.2 Hz, 1H), 3.85 (ddd, *J* = 6.8, 5.9, 3.5 Hz, 1H), 1.93-1.84 (m, 1H), 1.88 (d, *J* = 1.4 Hz, 3H), 1.44 (m, 1H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.20 (d, *J* = 6.1 Hz, 3H), 0.89 (s, 9H), 0.88 (s, 9H), 0.87 (s, 9H), 0.09 (s, 6H), 0.08 (s, 6H), 0.05 (s, 3H), 0.01 (s, 3H).

**<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)** δ 167.9, 140.9, 128.6, 73.7, 73.0, 65.7, 60.6, 43.9, 26.0 (3C), 25.9 (3C), 25.8 (3C), 24.5, 18.1 (2C), 18.0, 14.2, 13.5, -3.8, -4.1, -4.2, -4.4, -4.5, -4.8.

**HRMS-ESI** calculated for C<sub>29</sub>H<sub>62</sub>O<sub>5</sub>NaSi<sub>3</sub> : *m/z* 597.3803 ([M+Na]<sup>+</sup>), found : *m/z* 597.3809 ([M+Na]<sup>+</sup>).

**[α]<sub>D</sub><sup>20</sup>** = +18.8 (c 0.9, CHCl<sub>3</sub>).

#### **(4*R*,5*R*,7*S*,*E*)-4,5,7-tris((*tert*-Butyldimethylsilyl)oxy)-2-methyloct-2-en-1-ol (SI-5c)**

To a stirred solution of **13c** (1.55 g, 2.70 mmol) in dry DCM (17 mL), under a nitrogen atmosphere, was added DIBAL-H (4 mL, 1.5 M in toluene, 5.94 mmol, 2.2 eq.) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h. Saturated aqueous Rochelle salt solution was then added, and the resulting mixture warmed to room temperature and vigorously stirred overnight. The aqueous layer was extracted with Et<sub>2</sub>O and the combined organic extracts were washed with water, brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude alcohol was purified by chromatography (cyclohexane/EtOAc 9:1) to afford **SI-5c** (1.4 g, 2.63 mmol, 97 %) as a colorless oil.

**<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)** δ 5.45 (dq, *J* = 9.1, 1.3 Hz, 1H), 4.37 (dd, *J* = 9.1, 3.7 Hz, 1H), 4.07 (m, 1H), 4.03 (s, 2H), 3.80 (ddd, *J* = 7.0, 5.7, 3.7 Hz, 1H), 1.91 (ddd, *J* = 13.7, 12.4, 5.7 Hz, 1H), 1.72 (d, *J* = 1.3 Hz, 3H), 1.43 (ddd ap. dt, *J* = 13.7, 6.8 Hz, 1H), 1.19 (d, *J* = 6.1 Hz, 3H), 0.89 (s, 9H), 0.88 (s, 18H), 0.09 (s, 3H), 0.08 (s, 6H), 0.04 (s, 3H), 0.02 (s, 3H), 0.00 (s, 3H).

**<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)** δ 136.9, 125.3, 73.6, 72.2, 68.8, 65.9, 43.4, 26.0 (3C), 25.9 (3C), 25.8 (3C), 24.6, 18.2, 18.1, 18.0, 14.6, -3.8, -4.1, -4.2, -4.3, -4.5, -4.7.

**HRMS-ESI** calculated for C<sub>27</sub>H<sub>60</sub>O<sub>4</sub>NaSi<sub>3</sub> : *m/z* 555.3692 ([M+Na]<sup>+</sup>), found : *m/z* 555.3689 ([M+Na]<sup>+</sup>).

**[α]<sub>D</sub><sup>20</sup>** = +11.4 (c 1.0, CHCl<sub>3</sub>).

#### **(4*R*,5*R*,7*S*,*E*)-4,5,7-tris((*tert*-Butyldimethylsilyl)oxy)-2-methyloct-2-enal (SI-6c)**

To a stirred solution of **SI-5c** (1.33 g, 2.5 mmol) in dry DCM (27 mL), under a nitrogen atmosphere, was added MnO<sub>2</sub> (4.34 g, 50 mmol, 20 eq.) at room temperature. The reaction mixture was warmed to 40 °C and vigorously stirred for 48 h. The resulting mixture was cooled to room temperature and filtered through celite with DCM. The solvent was then removed under reduced pressure to give **SI-6c** (1.32 g, 2.49 mmol, 99 %) as a yellow oil which was used in the next step without further purification.

**<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)** δ 9.46 (s, 1H), 6.43 (dq, *J* = 8.4, 1.4 Hz, 1H), 4.59 (dd, *J* = 8.4, 3.7 Hz, 1H), 4.06 (m, 1H), 3.93 (ddd, *J* = 8.6, 4.8, 3.7 Hz, 1H), 1.91 (ddd, *J* = 13.8, 7.3, 4.8 Hz, 1H), 1.82 (d, *J* = 1.4 Hz, 3H), 1.43 (ddd, *J* = 13.8, 7.6, 5.3 Hz, 1H), 1.20 (d, *J* = 6.1 Hz, 3H), 0.90 (s, 9H), 0.89 (s, 9H), 0.87 (s, 9H), 0.11 (s, 3H), 0.09 (s, 6H), 0.08 (s, 3H), 0.07 (s, 3H), 0.01 (s, 3H).

#### **(1*E*,3*E*)-(5*R*,6*R*,8*S*)-tris-(*tert*-Butyldimethylsilyloxy)-1-iodo-3-methyl-nona-1,3-diene (14c)**

To a stirred solution of CrCl<sub>2</sub> (1.71 g, 13.9 mmol, 6 eq.) in dry THF (14 mL), under a nitrogen atmosphere, was added a solution of **SI-6c** (1.23 g, 2.32 mmol) and CHI<sub>3</sub> (2.74 g, 6.96 mmol, 3 eq.) in dry THF (9.5 mL) dropwise. The reaction mixture was stirred at room temperature for 12 h. The resulting mixture

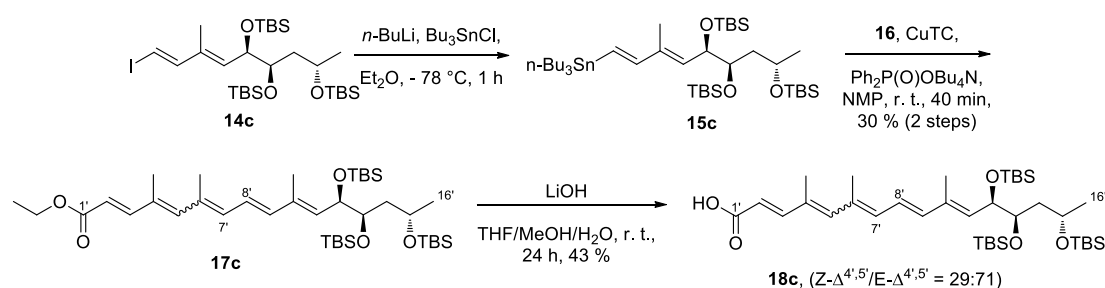
was hydrolyzed with water and diluted with Et<sub>2</sub>O. The aqueous layer was extracted three times with Et<sub>2</sub>O and the combined organic extracts were washed with water, brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude product was then purified by chromatography (cyclohexane/toluene 100:1) to afford **14c** (965 mg, 1.47 mmol, 64 %) as a pale yellow oil.

**<sup>1</sup>H NMR (C<sub>6</sub>D<sub>6</sub>, 300 MHz)**  $\delta$  7.08 (d, *J* = 14.7 Hz, 1H), 6.03 (d, *J* = 14.7 Hz, 1H), 5.52 (dq, *J* = 9.0, 1.2 Hz, 1H), 4.51 (dd, *J* = 9.0, 3.7 Hz, 1H), 4.19 (m, 1H), 4.01 (dt, *J* = 7.9, 4.3 Hz, 1H), 2.11 (ddd, *J* = 13.8, 7.5, 4.5 Hz, 1H), 1.64-1.55 (m, 1H), 1.60 (d, *J* = 1.2 Hz, 3H), 1.24 (d, *J* = 6.1 Hz, 3H), 1.03 (s, 9H), 0.98 (s, 9H), 0.94 (s, 9H), 0.17 (s, 3H), 0.16 (s, 3H), 0.15 (s, 3H), 0.12 (s, 3H), 0.09 (s, 3H), 0.03 (s, 3H).

**<sup>13</sup>C NMR (C<sub>6</sub>D<sub>6</sub>, 100 MHz)**  $\delta$  149.8, 136.1, 134.0, 76.8, 74.6, 73.0, 66.6, 44.3, 26.6 (3C), 26.5 (3C), 26.4 (3C), 25.5, 18.8, 18.7, 18.6, 13.5, -2.9, -3.4, -3.5, -3.8 (2C), -4.2.

**HRMS-ESI** calculated for C<sub>28</sub>H<sub>59</sub>O<sub>3</sub>NaSi<sub>3</sub> : *m/z* 677.2709 ([M+Na]<sup>+</sup>), found : *m/z* 677.2703 ([M+Na]<sup>+</sup>).

**[ $\alpha$ ]<sup>20</sup><sub>D</sub>** = +18.3 (c 1.1, CHCl<sub>3</sub>).



#### **(1*E*,3*E*)-(5*R*,6*R*,8*S*)-tris-(*tert*-Butyldimethylsilyloxy)-1-tributylstannyl-3-methyl-nona-1,3-diene (15c)**

To a stirred solution of **14c** (300 mg, 0.46 mmol) in dry Et<sub>2</sub>O (2.4 mL), under a nitrogen atmosphere, was added *n*-BuLi (0.34 mL, 2 M in hexane, 0.69 mmol, 1.5 eq.) at -78 °C. The reaction mixture was stirred for 20 min at -78 °C and Bu<sub>3</sub>SnCl (0.2 mL, 0.69 mmol, 1.5 eq.) was added. The resulting solution was stirred at -78 °C for another 20 min and allowed to warm to room temperature for 1 h. Saturated aqueous NaHCO<sub>3</sub> solution was then added and the aqueous layer was extracted three times with Et<sub>2</sub>O. The combined organic extracts were washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude **15c** was used in the next step without further purification.

#### **(2*E*,4*E*,6*E*,8*E*,10*E*,12*R*,13*R*,15*S*)-Ethyl 12,13,15-tris((*tert*-butyldimethylsilyl)oxy)-4,6,10-trimethylhexadeca-2,4,6,8,10-pentaenoate (17c)**

To a stirred solution of crude **15c** and tetra-*n*-butylammonium diphenylphosphinate (487 mg, 1.05 mmol, 2.3 eq.) in dry NMP (3.2 mL), under a nitrogen atmosphere, was added 0.2 mL of a solution of **16** in NMP (280 mg, 0.92 mmol, 2 eq., 2.1 mL). After addition of CuTC (242 mg, 0.92 mmol, 2 eq.), the rest of the **16** solution was added dropwise and the resulting mixture was stirred at room temperature for 40 min. The reaction mixture was then diluted with Et<sub>2</sub>O and filtered through neutral alumina oxide. The filtrate was washed with water, brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude product was then purified by preparative TLC (cyclohexane/EtOAc 9:1) to afford

**17c** (96.1 mg, 0.13 mmol, 30 % for two steps) as a yellow oil. NMR analysis showed the presence of mixture of isomers  $4'E/4'Z = 87:13$ .

**$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz,  $4'E$  isomer)**  $\delta$  7.95 (d,  $J = 15.9$  Hz, 1H,  $Z$  isomer), 7.38 (d,  $J = 15.6$  Hz, 1H,  $E$  isomer), 6.51 (dd,  $J = 15.1, 11.0$  Hz, 1H), 6.37 (d,  $J = 15.1$  Hz, 1H), 6.36 (s, 1H), 6.27 (d,  $J = 11.0$  Hz, 1H), 5.87 (d,  $J = 15.6$  Hz, 1H), 5.56 (d,  $J = 9.3$  Hz, 1H), 4.47 (dd,  $J = 9.1, 3.5$  Hz, 1H), 4.21 (q,  $J = 7.1$  Hz, 2H), 4.06 (m, 1H), 3.83 (m, 1H), 2.06 (s, 3H), 2.03 (s, 3H), 1.97-1.87 (m, 1H), 1.86 (s, 3H), 1.46-1.40 (m, 1H), 1.32 (t,  $J = 7.1$  Hz, 3H), 1.19 (d,  $J = 6.0$  Hz, 3H), 0.90 (s, 9H), 0.88 (s, 18H), 0.09 (s, 12H), 0.04 (s, 3H), -0.01 (s, 3H).

**$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz,  $4'E$  isomer)**  $\delta$  167.5, 150.8, 143.7, 139.7, 135.2, 135.1, 134.1, 134.0, 132.2, 123.7, 116.1, 73.9, 72.8, 65.9, 60.1, 43.7, 26.0 (3C), 25.9 (3C), 25.8 (3C), 24.5, 18.2, 18.1, 18.0, 17.1, 14.3, 14.2, 13.6, -3.7, -4.1, -4.2, -4.4, -4.5, -4.8.

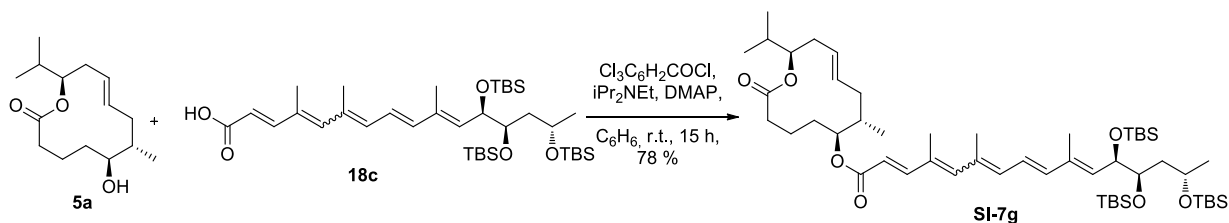
**HRMS-ESI** calculated for  $\text{C}_{39}\text{H}_{74}\text{O}_5\text{NaSi}_3$  :  $m/z$  730.4760 ( $[\text{M}+\text{Na}]^+$ ), found :  $m/z$  730.4764 ( $[\text{M}+\text{Na}]^+$ ).

**(2*E*,4*E*,6*E*,8*E*,10*E*,12*R*,13*R*,15*S*)-12,13,15-tris((*tert*-Butyldimethylsilyl)oxy)-4,6,10-trimethylhexadeca-2,4,6,8,10-pentaenoic acid (**18c**)**

To a stirred solution of **17c** (80 mg, 0.11 mmol) in a mixture THF/MeOH/ $\text{H}_2\text{O}$  (2.4/0.6/0.6 mL) was added LiOH (48 mg, 1.13 mmol, 10 eq.). The resulting mixture was stirred at room temperature for 24 h. After addition of saturated aqueous  $\text{NH}_4\text{Cl}$  solution, the mixture was extracted three times with EtOAc and the combined organic extracts were washed with brine, dried over  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. The crude material was purified by preparative TLC (cyclohexane/EtOAc 7:3) to afford **18c** (33 mg, 48.64  $\mu\text{mol}$ , 43 %) as a yellow oil. NMR analysis showed the presence of mixture of isomers  $4'E/4'Z = 72:28$ .

**$^1\text{H}$  NMR ( $\text{d}_6$ -Acetone, 300 MHz,  $4'E$  isomer)**  $\delta$  7.93 (d,  $J = 15.6$  Hz, 1H,  $Z$  isomer), 7.36 (d,  $J = 15.5$  Hz, 1H,  $E$  isomer), 6.67 (dd,  $J = 15.0, 11.0$  Hz, 1H), 6.48 (d,  $J = 15.0$  Hz, 1H), 6.46 (s, 1H), 6.39 (d,  $J = 11.0$  Hz, 1H), 5.88 (d,  $J = 15.5$  Hz, 1H), 5.64 (d,  $J = 8.6$  Hz, 1H), 4.58 (dd,  $J = 9.3, 3.5$  Hz, 1H), 4.12 (m, 1H), 3.93 (m, 1H), 2.09 (s, 3H), 2.06 (s, 3H), 1.99-1.95 (1H), 1.93 (s, 3H), 1.50-1.44 (1H), 1.21 (d,  $J = 6.3$  Hz, 3H), 0.92 (s, 9H), 0.91 (s, 9H), 0.90 (s, 9H), 0.14 (s, 6H), 0.12 (s, 3H), 0.11 (s, 3H), 0.10 (s, 3H), 0.04 (s, 3H).

**$^{13}\text{C}$  NMR ( $\text{d}_6$ -Acetone, 100 MHz,  $4'E$  isomer)**  $\delta$  168.1, 151.7, 144.3, 140.4, 136.2, 135.5, 135.0, 134.6, 134.3, 125.3, 117.2, 74.9, 73.6, 66.8, 44.7, 26.5 (3C), 26.43 (3C), 26.38 (3C), 25.3, 18.8, 18.7 (2C), 17.2, 14.4, 14.0, -3.3, -3.6, -3.7, -4.0 (2C), -4.3.



**(2*E*,4*E*,6*E*,8*E*,10*E*,12*R*,13*R*,15*S*)-(6*S*,7*S*,12*R*,*E*)-12-Isopropyl-7-methyl-2-oxooxacyclododec-9-en-6-yl 12,13,15-tris((*tert*-butyldimethylsilyl)oxy)-4,6,10-trimethylhexadeca-2,4,6,8,10-pentaenoate (**SI-7g**)**

To a stirred solution of **18c** (40 mg, 0.059 mmol, 1.5 eq.) in benzene (0.5 mL) were added diisopropylethylamine (37  $\mu\text{L}$ , 0.22 mmol, 5.6 eq.), 2,4,6-trichlorobenzoyl chloride (18.4  $\mu\text{L}$ , 0.12 mmol,

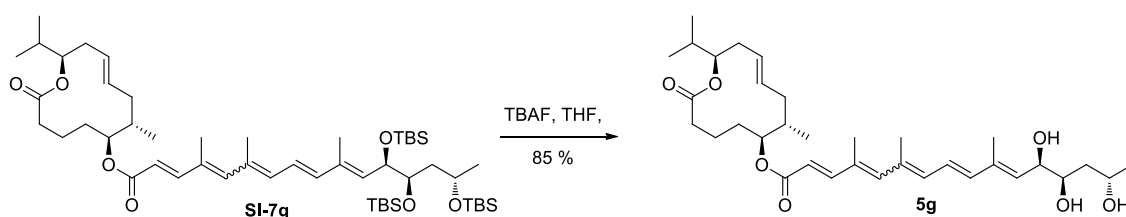


3 eq.) and DMAP (33.6 mg, 0.28 mmol, 7 eq.). The reaction mixture was stirred at room temperature for 20 min and **5a** (10 mg, 0.039 mmol) was added. The resulting mixture was stirred at room temperature for 15 h and an aqueous saturated solution of sodium hydrogenocarbonate was added. The aqueous layer was extracted three times with benzene and the combined organic extracts were washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude product was purified over preparative TLC (cyclohexane/EtOAc 9:1) to afford **SI-7g** (28 mg, 0.031 mmol, 78%) as a yellow oil. NMR analysis showed the presence of mixture of isomers 4'E/4'Z = 64:36.

**<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz, 4'E isomer)**  $\delta$  7.95 (d, *J* = 15.4 Hz, 1H, *Z* isomer), 7.38 (d, *J* = 15.5 Hz, 1H, *E* isomer), 6.50 (dd, *J* = 14.8, 11.1 Hz, 1H), 6.37 (d, *J* = 14.8 Hz, 1H), 6.36 (s, 1H), 6.29 (d, *J* = 11.1 Hz, 1H), 5.87 (d, *J* = 15.5 Hz, 1H), 5.54 (m, 1H), 5.45 (m, 1H), 5.28 (m, 1H), 4.83-4.71 (2H), 4.46 (dd, *J* = 9.1, 3.5 Hz, 1H), 4.06 (m, 1H), 3.83 (m, 1H), 2.50 (m, 1H), 2.30 (m, 1H), 2.18-2.09 (2H), 2.05 (s, 3H), 2.04 (s, 3H), 1.97-1.66 (12H including 1.86 (s, 3H)), 1.47-1.41 (1H), 1.19 (d, *J* = 5.9 Hz, 3H), 0.93 (d, *J* = 6.8 Hz, 3H), 0.92 (d, *J* = 6.8 Hz, 3H), 0.91 (d, *J* = 7.3 Hz, 3H), 0.90 (s, 9H), 0.88 (s, 18H), 0.09 (s, 9H), 0.08 (s, 3H), 0.04 (s, 3H), -0.01 (s, 3H).

**<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz, 4'E isomer)**  $\delta$  173.0, 166.8, 150.7, 143.7, 139.7, 135.1, 134.8, 134.1, 134.04, 133.98, 132.2, 126.0, 123.7, 116.4, 78.6, 75.9, 73.9, 72.8, 65.9, 43.7, 38.0, 36.1, 35.5, 34.4, 32.3, 29.6, 26.0 (3C), 25.9 (3C), 25.8 (3C), 24.6, 20.4, 19.2, 18.5, 18.3, 18.2, 18.1, 18.0, 17.1, 14.2, 13.5, -3.7, -4.1, -4.2, -4.4, -4.5, -4.8.

**HRMS-ESI** calculated for C<sub>52</sub>H<sub>94</sub>O<sub>7</sub>NaSi<sub>3</sub> : *m/z* 938.6226 ([M+Na]<sup>+</sup>), found : *m/z* 938.6232 ([M+Na]<sup>+</sup>).



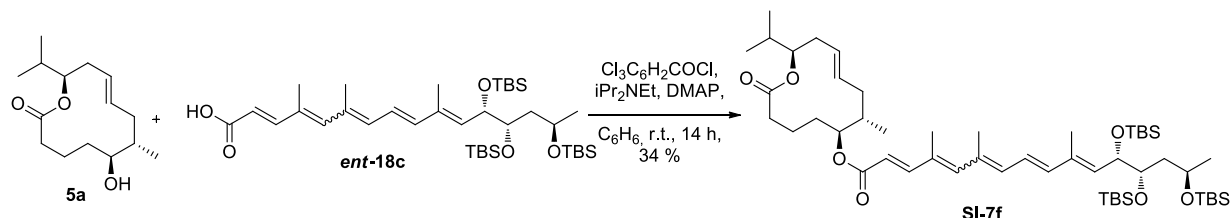
**(2E,4E,6E,8E,10E,12R,13R,15S)-(6S,7S,12R,E)-12-Isopropyl-7-methyl-2-oxooxacyclododec-9-en-6-yl 12,13,15-trihydroxy-4,6,10-trimethylhexadeca-2,4,6,8,10-pentaenoate (**5g**)**

To a stirred solution of **SI-7g** (26.1 mg, 0.028 mmol) in THF (0.3 mL) was added TBAF (0.26 mmol, 1M in THF, 9 eq.). The reaction mixture was stirred at room temperature for 6 h. CaCO<sub>3</sub> (50 mg), Dowex 50WX8-400 (160 mg) and MeOH (0.35 mL) were added and the reaction mixture was stirred for 1 h. The resulting mixture was filtered and concentrated under reduce pressure. The crude product was then purified by preparative TLC (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 9:1) to give **5g** (14.1 mg, 0.024 mmol, 85%) as a yellow foam. NMR analysis showed the presence of mixture of isomers 4'E/4'Z = 64:36. It should be noticed that due to instability, this product decomposed over time.

**<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz, 4'E isomer)**  $\delta$  7.87 (d, *J* = 15.4 Hz, 1H, *Z* isomer), 7.37 (d, *J* = 15.5 Hz, 1H, *E* isomer), 6.64-6.50 (1H), 6.37-6.07 (3H), 6.29-6.06 (2H), 5.94-5.84 (1H), 5.54-5.40 (2H), 5.34-5.23 (1H), 4.84-4.73 (2H), 4.40-4.30 (1H), 4.20-4.10 (1H), 3.90-3.73 (1H), 2.52-2.26 (2H), 2.16-1.60 (21H including 2.05 (s, 3H), 2.02 (s, 3H), 1.92 (s, 3H)), 1.35 (ddd, *J* = 10.0, 6.2, 2.7 Hz, 1H), 1.23 (d, *J* = 6.2 Hz, 3H), 0.93 (d, *J* = 6.7 Hz, 3H), 0.92 (d, *J* = 6.7 Hz, 3H), 0.91 (d, *J* = 6.7 Hz, 3H).

**$^{13}\text{C}$  NMR (CDCl<sub>3</sub>, 100 MHz, 4'E isomer)**  $\delta$  173.0, 166.8, 150.6, 143.5, 141.4, 138.6, 138.5, 134.8, 133.4, 132.5, 131.2, 126.0, 124.7, 116.6, 81.4, 78.6, 78.0, 75.9, 73.5, 42.2, 38.0, 36.1, 35.5, 34.4, 32.3, 29.7, 22.3, 20.4, 19.2, 18.5, 18.2, 14.2, 14.1, 13.1.

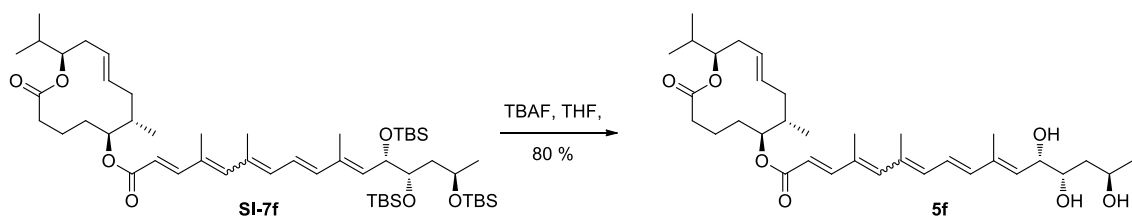
**HRMS-ESI** calculated for C<sub>34</sub>H<sub>52</sub>O<sub>7</sub>Na :  $m/z$  595.3605 ([M+Na]<sup>+</sup>), found :  $m/z$  595.3601 ([M+Na]<sup>+</sup>).



**(6S,7S,9E,12R)-7-Methyl-2-oxo-12-(propan-2-yl)-1-oxacyclododec-9-en-6-yl  
(2E,4E,6E,8E,10E,12S,13S,15R)-12,13,15-tris[(*tert*-butyldimethylsilyl)oxy]-4,6,10-trimethylhexadeca-2,4,6,8,10-pentaenoate (SI-7f)**

To a solution of **ent-18c**<sup>1</sup> (16 mg, 0.024 mmol) in benzene (0.3 mL) were added diisopropylethyl amine (20  $\mu$ L, 0.11 mmol), 2,4,6-trichlorobenzoyl chloride (10  $\mu$ L, 0.06 mmol), and DMAP (20 mg). The reaction mixture was stirred at room temperature for 15 min and **5a** (4 mg, 0.016 mmol) was added. After being stirred at room temperature for 14 h, an aqueous saturated solution of sodium hydrogenocarbonate was added to the reaction mixture. The aqueous layer was extracted three times with benzene. The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude product was purified on preparative TLC eluting with heptanes/ethyl acetate 70:30 to give **SI-7f** (5 mg, 5.5  $\mu$ mol, 34 %) as a yellow oil. A (4'E)/(4'Z) = 62:38 mixture could be detected by <sup>1</sup>H analysis.

**$^1\text{H}$  NMR (CDCl<sub>3</sub>, 300 MHz)**  $\delta$  7.94 (d,  $J$  = 15.5 Hz, 1H, Z isomer), 7.36 (d,  $J$  = 15.5 Hz, 1H, E isomer), 6.51 (dd,  $J$  = 14.8, 11.2 Hz, 1H), 6.37 (d,  $J$  = 14.8 Hz, 1H), 6.36 (s, 1H), 6.28 (d,  $J$  = 11.2 Hz, 1H), 5.85 (d,  $J$  = 15.5 Hz, 1H), 5.56 (d,  $J$  = 8.6 Hz, 1H), 5.45 (m, 1H), 5.27 (m, 1H), 4.81-4.72 (2H), 4.46 (dd,  $J$  = 9.1, 3.6 Hz, 1H), 4.05 (m, 1H), 3.82 (m, 1H), 2.49 (m, 1H), 2.30 (m, 1H), 2.15-2.06 (2H), 2.04 (s, 3H), 2.03 (s, 3H), 1.98 (m, 1H), 1.85 (s, 3H), 1.87-1.61 (6H), 1.13 (d,  $J$  = 6.0 Hz, 3H), 0.95 (s, 3H), 0.93 (s, 3H), 0.92 (s, 3H), 0.90 (s, 3H), 0.89 (s, 9H), 0.87 (s, 9H), 0.85 (s, 9H), 0.05 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H), -0.03 (s, 3H).



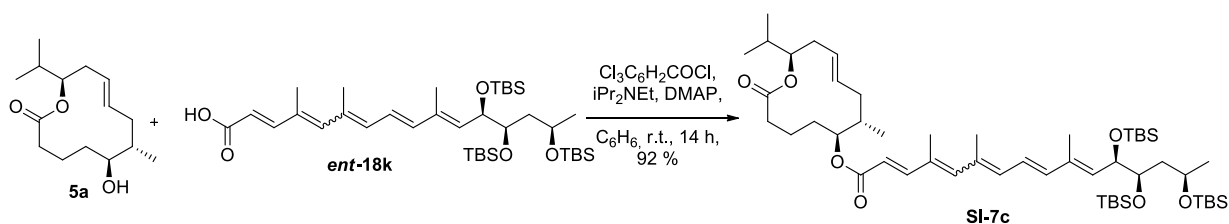
**(6*S*,7*S*,9*E*,12*R*)-7-Methyl-2-oxo-12-(propan-2-yl)-1-oxacyclododec-9-en-6-yl  
(2*E*,4*E*,6*E*,8*E*,10*E*,12*S*,13*S*,15*R*)-12,13,15-trihydroxy-4,6,10-trimethylhexadeca-2,4,6,8,10-pentaenoate (5f)**

To a solution of **SI-7f** (5 mg, 5.47  $\mu$ mol) in THF (0.1 mL) was added TBAF (0.05 mmol, 1M in THF, 9 eq.). The solution was stirred at room temperature for 4 h.  $\text{CaCO}_3$  (25 mg), Dowex 50WX8-400 (75 mg) and MeOH (0.2 mL) were added and the reaction mixture was stirred for 1 h. After being filtered and concentrated under reduced pressure, the crude product was purified by TLC preparative ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$  90:10) to give **5f** (2.5 mg, 4.37  $\mu$ mol, 80 %). A (4'*E*)/(4'*Z*) = 43:57 mixture could be detected by  $^1\text{H}$  analysis.

**$^1\text{H}$  NMR (Acetone- $d_6$ , 400 MHz)**  $\delta$  7.93 (d,  $J$  = 15.8 Hz, 1H, *Z* isomer), 7.37 (d,  $J$  = 15.5 Hz, 1H, *E* isomer), 6.63 (dd,  $J$  = 11.0, 14.4 Hz, 1H), 6.47 (s, 1H), 6.36 (d,  $J$  = 14.4 Hz, 1H), 6.17 (d,  $J$  = 11.0 Hz, 1H), 5.90 (d,  $J$  = 15.5 Hz, 1H), 5.57 (m, 1H), 5.49 (m, 1H), 5.30 (m, 1H), 4.78-4.67 (2H), 4.28 (dd,  $J$  = 7.0, 8.7 Hz, 1H), 4.01 (m, 1H), 3.79-3.70 (2H), 3.56 (m, 1H), 3.30 (m, 1H), 2.47 (m, 1H), 2.29 (m, 1H), 2.12-2.08 (2H), 2.06 (s, 3H), 1.97 (s, 3H), 1.95-1.92 (2H), 1.90 (s, 3H), 1.80-1.75 (4H), 1.70-1.62 (2H), 1.54-1.49 (2H), 1.13 (d,  $J$  = 6.1 Hz, 3H), 0.92 (s, 3H), 0.90 (s, 3H), 0.87 (s, 3H).

**$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz)**  $\delta$  173.9, 167.8, 152.2, 144.1, 141.4, 137.2, 136.5, 136.1, 134.2, 133.1, 128.1, 126.1, 120.6, 118.4, 80.2, 77.3, 73.8, 73.5, 65.7, 43.6, 39.8, 37.9, 37.0, 36.1, 34.1, 25.6, 22.0, 21.6, 20.9, 19.9, 19.4, 18.1, 15.3, 14.4.

**HRMS-ESI** calculated for  $\text{C}_{34}\text{H}_{52}\text{O}_7\text{Na}$ :  $m/z$  595.3605 ( $[\text{M}+\text{Na}]^+$ ), found:  $m/z$  595.3619 ( $[\text{M}+\text{Na}]^+$ ).



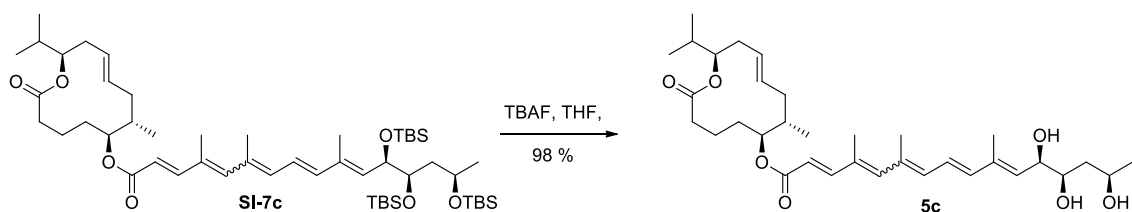
**(6*S*,7*S*,9*E*,12*R*)-7-Methyl-2-oxo-12-(propan-2-yl)-1-oxacyclododec-9-en-6-yl  
(2*E*,4*E*,6*E*,8*E*,10*E*,12*R*,13*R*,15*R*)-12,13,15-tris[(*tert*-butyldimethylsilyl)oxy]-4,6,10-trimethylhexadeca-2,4,6,8,10-pentaenoate (SI-7c)**

To a solution of **ent-18k**<sup>1</sup> (30 mg, 0.044 mmol) in benzene (0.5 mL) were added diisopropylethyl amine (33  $\mu$ L, 0.18 mmol, 5.6 eq.), 2,4,6-trichlorobenzoyl chloride (17  $\mu$ L ; 0.09 mmol, 3 eq.), and DMAP (33 mg). The reaction mixture was stirred at room temperature for 15 min and **5a** (7 mg, 0.027 mmol) was added. After being stirred at room temperature for 14 h, an aqueous saturated solution of sodium hydrogenocarbonate was added to the reaction mixture. The aqueous layer was extracted three times with benzene. The combined organic layers were washed with brine, dried over  $\text{MgSO}_4$ , filtered and

concentrated under reduced pressure. The crude product was purified on preparative TLC eluting with heptane/ethyl acetate 90:10 to give **SI-7c** (23 mg, 0.025 mmol, 92 %) as a yellow oil. A (4'E)/(4'Z) = 66:34 mixture could be detected by <sup>1</sup>H analysis.

**<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)** δ 7.95 (d, *J* = 15.5 Hz, 1H, *Z* isomer), 7.36 (d, *J* = 15.5 Hz, 1H, *E* isomer), 6.51 (dd, *J* = 14.8, 11.2 Hz, 1H), 6.37 (d, *J* = 14.8 Hz, 1H), 6.36 (s, 1H), 6.28 (d, *J* = 11.2 Hz, 1H), 5.85 (d, *J* = 15.5 Hz, 1H), 5.58 (d, *J* = 8.6 Hz, 1H), 5.45 (m, 1H), 5.27 (m, 1H), 4.81-4.70 (2H), 4.43 (dd, *J* = 9.1, 3.6 Hz, 1H), 3.91 (m, 1H), 3.65 (td, *J* = 7.8, 3.9 Hz, 1H), 2.49 (m, 1H), 2.30 (m, 1H), 2.15-2.06 (2H), 2.04 (s, 3H), 2.03 (s, 3H), 1.98-1.96 (m, 1H), 1.85 (s, 3H), 1.87-1.61 (6H), 1.13 (d, *J* = 6.0 Hz, 3H), 0.95 (s, 3H), 0.93 (s, 3H), 0.92 (s, 3H), 0.90 (s, 3H), 0.89 (s, 9H), 0.87 (s, 9H), 0.85 (s, 9H), 0.05 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H), -0.03 (s, 3H).

**HRMS-ESI** calculated for C<sub>52</sub>H<sub>94</sub>O<sub>7</sub>Si<sub>3</sub>Na : *m/z* 937.6199 ([M+Na]<sup>+</sup>), found: *m/z* 937.6199 ([M+Na]<sup>+</sup>).



**(6*S*,7*S*,9*E*,12*R*)-7-Methyl-2-oxo-12-(propan-2-yl)-1-oxacyclododec-9-en-6-yl  
(2*E*,4*E*,6*E*,8*E*,10*E*,12*R*,13*R*,15*R*)-12,13,15-trihydroxy-4,6,10-trimethylhexadeca-2,4,6,8,10-pentaenoate (**5c**)**

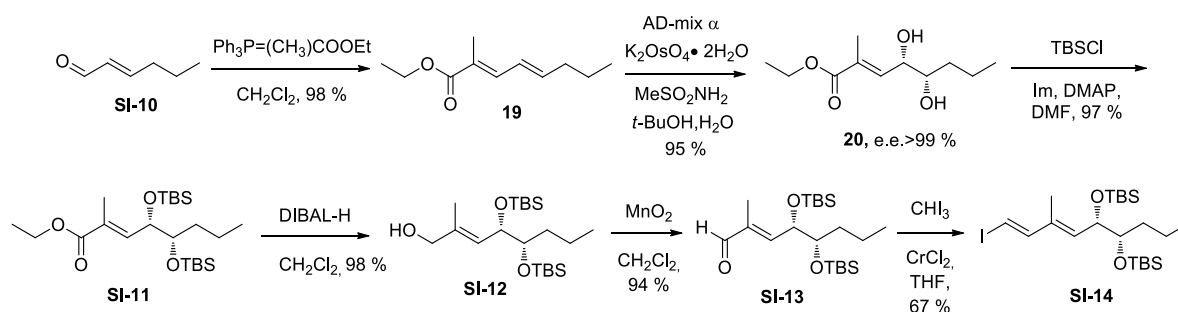
To a solution of **SI-7c** (23 mg, 0.025 mmol) in THF (0.2 mL) was added TBAF (0.2 mmol, 1M in THF, 8 eq.). The solution was stirred at room temperature for 4 h. CaCO<sub>3</sub> (90 mg), Dowex 50WX8-400 (285 mg) and MeOH (0.6 mL) were added and the reaction mixture was stirred for 1 h. After being filtered and concentrated under reduced pressure, the crude product was purified by TLC preparative (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 90:10) to give **5c** (14 mg, 0.024 mmol, 98 %). A (4'E)/(4'Z) = 60:40 mixture could be detected by <sup>1</sup>H analysis.

**<sup>1</sup>H NMR (Acetone-d<sub>6</sub>, 300 MHz)** δ 7.93 (d, *J* = 15.7 Hz, 1H, *Z* isomer), 7.38 (d, *J* = 15.6 Hz, 1H, *E* isomer), 6.63 (dd, *J* = 11.1, 14.5 Hz, 1H), 6.48 (s, 1H), 6.38 (d, *J* = 14.5 Hz, 1H), 6.18 (d, *J* = 11.1 Hz, 1H), 5.91 (d, *J* = 15.6 Hz, 1H), 5.64-5.57 (2H), 5.30 (m, 1H), 4.81-4.67 (2H), 4.28 (m, 1H), 4.26 (m, 1H), 4.06 (m, 1H), 4.02-3.90 (2H), 3.69 (m, 1H), 2.51 (m, 1H), 2.32 (m, 1H), 2.12-2.08 (2H), 2.06 (s, 3H), 1.97 (s, 3H), 1.95-1.92 (2H), 1.90 (s, 3H), 1.80-1.75 (4H), 1.70-1.62 (2H), 1.54-1.49 (2H), 1.13 (d, *J* = 6.1 Hz, 3H), 0.92 (s, 3H), 0.90 (s, 3H), 0.87 (s, 3H).

**<sup>13</sup>C NMR (Acetone-d<sub>6</sub>, 75 MHz)** δ 173.9, 167.8, 152.2, 144.1, 141.3, 138.3, 136.5, 135.6, 134.2, 133.1, 128.0, 126.1, 120.6, 118.4, 80.2, 77.3, 76.8, 73.3, 68.7, 42.8, 39.7, 37.9, 37.0, 36.1, 34.1, 25.2, 22.0, 21.7, 20.9, 19.9, 19.4, 18.6, 15.3, 14.4.

**HRMS-ESI** calculated for C<sub>34</sub>H<sub>52</sub>O<sub>7</sub>Na : *m/z* 595.3605 ([M+Na]<sup>+</sup>), found: *m/z* 595.3588 ([M+Na]<sup>+</sup>).

## 2.2 Synthesis of monodeoxy series



### (2E,4E)-Ethyl 2-methylocta-2,4-dienoate (19)

To a solution of (1-ethoxycarbonyl ethylidene)triphenylphosphorane (11.25 g, 31.0 mmol, 1.2 eq.) in dichloromethane (84 mL) at 0 °C was added *trans*-hexenal **SI-10** (3.0 mL, 25.9 mmol) in solution in dichloromethane (6 mL). The reaction mixture was stirred at room temperature for 48 h. After being concentrated under reduced pressure, the crude product was purified by flash chromatography (cyclohexane/ethyl acetate 100:1 to 10:1) to give **19** (4.63 g, 25.4 mmol, 98 %) as a yellow oil.

**<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)** δ 7.16 (d, *J* = 11.2 Hz, 1H), 6.34 (dd, *J* = 11.2, 14.7 Hz, 1H), 6.08 (dd, *J* = 7.3, 14.7 Hz, 1H), 4.20 (q, *J* = 7.2 Hz, 2H), 2.17 (dt ap. q, *J* = 7.3 Hz, 2H), 1.92 (s, 3H), 1.46 (dq ap. td, *J* = 7.2, 14.7 Hz, 2H), 1.30 (t, *J* = 7.2 Hz, 3H), 0.93 (t, *J* = 7.2 Hz, 3H).

**<sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz)** δ 168.5, 142.7, 138.4, 126.1, 125.0, 60.3, 35.2, 22.1, 14.2, 13.6, 12.4.

The spectral data are in agreement with those reported in the literature.<sup>4</sup>

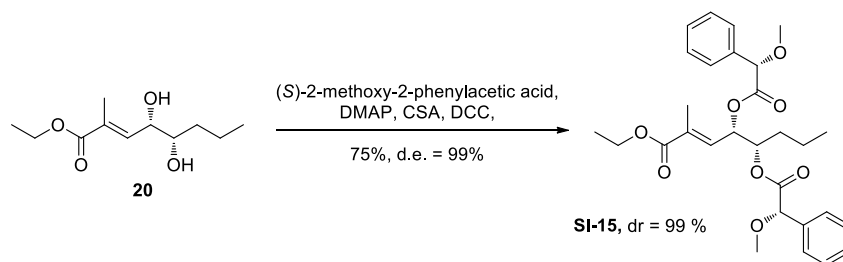
### Ethyl (2E,4S,5S)-4,5-dihydroxy-2-methyloct-2-enoate (20)

To a solution of AD-mix α (19.25 g) in a mixture of *t*-BuOH and water (68:68 mL) were added methanesulfonamide (1.3 g, 13.7 mmol) and potassium osmate dihydrate (30 mg, 0.082 mmol, 0.6 %). The reaction mixture was stirred at room temperature until both phases were clear, and then cooled at 0 °C whereupon the inorganic salts partially precipitate. **19** (2.5 g, 13.7 mmol) was then added and the reaction mixture was stirred at 0 °C for 15 h. Sodium sulfite (20.5 g) was then added at 0 °C. The reaction mixture was stirred at room temperature for 15 min and the aqueous phase was extracted 3 times with ethyl acetate. The combined organic layers were washed with an aqueous solution of potassium hydroxide (2N), with brine and dried over magnesium sulfate. After being filtered and concentrated under reduced pressure, the crude product was purified by flash chromatography (cyclohexane/ethyl acetate 8:2) to give **20** (2.83 g, 13.1 mmol, 95 %) as a yellow oil.

**<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)** δ 6.64 (qd, *J* = 1.3, 9.3 Hz, 1H), 4.26-4.17 (3H), 3.54 (m, 1H), 2.74 (br s, 2H), 1.91 (d, *J* = 1.3 Hz, 3H), 1.54 (m, 1H), 1.44-1.36 (3H), 1.30 (t, *J* = 7.2 Hz, 3H), 0.92 (t, *J* = 6.8 Hz, 3H).

**<sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz)** δ 167.8, 139.0, 131.1, 74.2, 71.8, 60.9, 34.8, 18.8, 14.2, 14.0, 13.3.

**HRMS-ESI** calculated for C<sub>11</sub>H<sub>20</sub>O<sub>4</sub>: *m/z* 239.1254 ([M+Na]<sup>+</sup>), found: *m/z* 239.1256 ([M+Na]<sup>+</sup>).



#### Ethyl (2*E*,4*S*,5*S*)-4,5-bis([(2*S*)-2-methoxy-2-phenylacetyl]oxy)-2-methyloct-2-enoate (SI-15)

To a solution of **20** (18 mg, 0.083 mmol) were added (*S*)-2-methoxy-2-phenylacetic acid (54 mg, 0.32 mmol, 3.9 eq.), DMAP (10 mg, 0.084 mmol, 1 eq.), CSA (15 mg, 0.065 mmol, 0.8 eq.) and DCC (69 mg, 0.33 mmol, 3.9 eq.). The reaction mixture was stirred at room temperature for 15 h, before being filtered, concentrated under reduced pressure. <sup>1</sup>H NMR analysis of the crude material indicates a d.r. of 99%. The product was purified by preparative TLC (heptane/ethyl acetate 70:30). **SI-15** (32 mg, 0.062 mmol, 75 %) was obtained as a colorless oil.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 7.40-7.35 (10H), 6.26 (dd, *J* = 1.4, 9.1 Hz, 1H), 5.56 (dd, *J* = 4.7, 9.1 Hz, 1H), 5.00 (td, *J* = 4.7, 9.2 Hz, 1H), 4.66 (s, 1H), 4.61 (s, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 3.33 (s, 3H), 3.29 (s, 3H), 1.79 (d, *J* = 1.4 Hz, 3H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.23-1.12 (2H), 1.08-0.94 (2H), 0.66 (t, *J* = 7.1 Hz, 3H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz) δ 169.9, 169.5, 166.9, 136.0, 133.2, 132.9 (2C), 128.8, 128.7, 128.6 (2C), 128.5 (2C), 127.3 (2C), 127.1 (2C), 82.5, 82.1, 73.9, 71.1, 60.9, 57.3, 57.2, 31.8, 18.1, 14.2, 13.5, 13.1.

#### (2*E*,4*S*,5*S*)-Ethyl 4,5-bis[(*tert*-butyldimethylsilyl)oxy]-2-methyloct-2-enoate (SI-11)

To a solution of **20** (2.8 g, 12.95 mmol) in DMF (70 mL) were added *tert*-butyldimethylsilyl chloride (13.08 g, 86.8 mmol, 6.7 eq.), imidazole (5.8 g, 85.5 mmol, 6.6 eq.) and DMAP (395 mg, 3.23 mmol, 0.25 eq.). The reaction mixture was stirred at room temperature for 24 h, and then hydrolysed with water. The aqueous layer was extracted three times with a cyclohexane/dichloromethane mixture (9:1). The combined organic layers were washed with brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel (eluting with cyclohexane/ethyl acetate 20:1) to give **SI-11** as a colorless oil (5.62 g, 12.6 mmol, 97 %).

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 6.69 (qd, *J* = 1.4, 8.9 Hz, 1H), 4.40 (dd, *J* = 4.1, 8.9 Hz, 1H), 4.20 (qd, *J* = 0.7, 7.0 Hz, 2H), 3.65 (td, *J* = 4.1, 7.1 Hz, 1H), 1.88 (d, *J* = 1.4 Hz, 3H), 1.63 (m, 1H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.28-1.23 (3H), 0.91 (t, *J* = 7.0 Hz, 3H), 0.88 (s, 18H), 0.06 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H), 0.00 (s, 3H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz) δ 168.1, 141.5, 127.9, 76.0, 72.1, 60.5, 34.5, 25.9 (3C), 25.8 (3C), 19.2, 18.1 (2C), 14.3, 14.2, 13.3, -4.2, -4.4, -4.6, -4.7.

[α]<sub>D</sub><sup>20</sup> = - 34.8 (c 2.9, CHCl<sub>3</sub>).

HRMS-ESI calculated for C<sub>23</sub>H<sub>48</sub>O<sub>4</sub>Si<sub>2</sub>: *m/z* 467.2983 ([M+Na]<sup>+</sup>), found: *m/z* 467.2978 ([M+Na]<sup>+</sup>).

#### (2*E*,4*S*,5*S*)-4,5-bis[(*tert*-Butyldimethylsilyl)oxy]-2-methyloct-2-en-1-ol (SI-12)

To a solution of **SI-11** (3.0 g, 6.75 mmol) in dichloromethane (35 mL) was added DIBAL-H (9.9 mL, 1.5 M in toluene, 2.2 eq.). The reaction mixture was stirred at 0 °C for 1 h and a saturated aqueous solution of Rochelle salts was added. After being stirred for 12h, the aqueous layer was extracted three times with diethyl ether. The combined organic layers were washed with brine, dried over magnesium

sulfate, filtered and concentrated under reduced pressure to give **SI-12** as a colorless oil (2.67 g, 6.64 mmol, 98 %).

**<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)** δ 5.44 (qd, *J* = 0.9, 9.1 Hz, 1H), 4.34 (dd, *J* = 4.1 Hz, 9.1 Hz, 1H), 4.02 (s, 2H), 3.59 (td, *J* = 4.1, 7.6 Hz, 1H), 1.71 (d, *J* = 0.9 Hz, 3H), 1.55-1.25 (4H), 0.91 (d, *J* = 6.9 Hz, 3H), 0.88 (s, 18H), 0.07 (s, 3H), 0.06 (s, 3H), 0.04 (s, 3H), 0.00 (s, 3H).

**<sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz)** δ 136.3, 125.8, 76.1, 71.5, 68.8, 34.1, 25.9 (3C), 25.8 (3C), 19.4, 18.1 (2C), 14.5, 14.4, -4.1, -4.3, -4.6, -4.7.

**HRMS-ESI** calculated for C<sub>21</sub>H<sub>46</sub>NaO<sub>3</sub>Si<sub>2</sub>: *m/z* 425.2878 ([M+Na]<sup>+</sup>), found: *m/z* 425.2875 ([M+Na]<sup>+</sup>).

#### **(2*E*,4*S*,5*S*)-4,5-bis[(*tert*-Butyldimethylsilyl)oxy]-2-methyloct-2-enal (SI-13)**

To a solution of **SI-12** (210 mg, 0.52 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (4 mL) was added activated MnO<sub>2</sub> (970 mg, 11.2 mmol, 21 eq.). After being refluxed for 20 h the reaction mixture was filtered over a bed of Celite and washed with CH<sub>2</sub>Cl<sub>2</sub>. Solvent was removed under reduced pressure to give **SI-13** (196 mg, 0.49 mmol, 94 %) as a yellow oil.

**<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)** δ 9.46 (s, 1H), 6.43 (qd, *J* = 1.0, 8.3 Hz, 1H), 4.57 (dd, *J* = 4.0, 8.3 Hz, 1H), 3.70 (td, *J* = 4.0, 7.7 Hz, 1H), 1.81 (d, *J* = 1.0 Hz, 3H), 1.75 (m, 1H), 1.35-1.25 (3H), 0.93 (d, *J* = 7.0 Hz, 3H), 0.89 (s, 9H), 0.87 (s, 9H), 0.0 (s, 9H), 0.01 (s, 3H).

**<sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz)** δ 195.6, 153.2, 127.2, 76.0, 72.1, 34.4, 25.7 (6C), 19.3, 18.1 (2C), 14.3, 13.1, -4.0, -4.4, -4.6, -4.7.

#### **(1*E*,3*E*)-(5*S*,6*S*)-bis-(*tert*-Butyldimethylsilyloxy)-1-iodo-3-methyl-nona-1,3-diene (SI-14)**

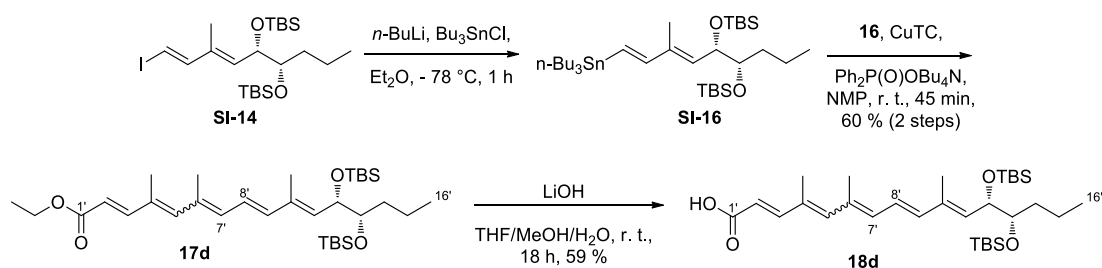
To a suspension of CrCl<sub>2</sub> (6.51 g, 52.9 mmol, 10 eq.) in THF (40 mL) was added dropwise a solution of **SI-13** (2.12 g, 5.3 mmol) and CHI<sub>3</sub> (6.25 g, 15.8 mmol, 3 eq.) in THF (35 mL). The reaction mixture was stirred at room temperature for 12 h before being diluted with diethyl ether. The aqueous phase was extracted three times, and the combined organic phases were washed with water and brine. After being dried over magnesium sulfate, filtered and concentrated under reduced pressure, the crude product was purified by flash chromatography eluting with cyclohexane/toluene (100:1) to give **SI-14** (1.87 g, 3.56 mmol, 67 %) as a colorless oil.

**<sup>1</sup>H NMR (C<sub>6</sub>D<sub>6</sub>, 300 MHz)** δ 7.02 (d, *J* = 14.7 Hz, 1H), 5.99 (d, *J* = 14.7 Hz, 1H), 5.44 (d, *J* = 9.1 Hz, 1H), 4.46 (dd, *J* = 4.1, 9.1 Hz, 1H), 3.71 (td, *J* = 4.1, 7.7 Hz, 1H), 1.76 (m, 1H), 1.54 (d, *J* = 0.9 Hz, 3H), 1.48-1.30 (3H), 0.96 (s, 9H), 0.95 (s, 9H), 0.95 (t, *J* = 7.1 Hz, 3H), 0.11 (s, 3H), 0.07 (s, 6H), 0.02 (s, 3H).

**<sup>13</sup>C NMR (C<sub>6</sub>D<sub>6</sub>, 75 MHz)** δ 149.9, 135.6, 134.4, 77.0, 76.5, 72.5, 35.1, 26.5 (6C), 20.1, 18.6 (2C), 14.9, 13.3, -3.5, -3.7, -4.1, -4.2.

**[α]<sup>20</sup><sub>D</sub>** = - 25.4 (c 0.5, CHCl<sub>3</sub>).

**HRMS-ESI** calculated for C<sub>22</sub>H<sub>45</sub>INaO<sub>2</sub>Si<sub>2</sub>: *m/z* 547.1895 ([M+Na]<sup>+</sup>), found: *m/z* 547.1888 ([M+Na]<sup>+</sup>).



**(1*E*,3*E*)-(5*S*,6*S*)-bis-(*tert*-Butyldimethylsilyloxy)-1-tributylstannyl-3-methyl-nona-1,3-diene (SI-16)**

To a solution of **SI-14** (290 mg, 0.55 mmol) in Et<sub>2</sub>O (2.9 mL) at -78 °C was added *n*-BuLi (566 μL, 1.6 M in hexane, 0.91 mmol, 1.6 eq.) and the reaction mixture was stirred for 20 min. Bu<sub>3</sub>SnCl (320 μL, 1.2 mmol, 2.0 eq.) was then added to the solution and the reaction mixture was allowed to warm to room temperature for 1 h. The reaction mixture was hydrolyzed with saturated aqueous NaHCO<sub>3</sub> solution. The aqueous phase was extracted twice with Et<sub>2</sub>O. The combined organic phases were washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude **SI-16** was used without further purification.

**Ethyl (2*E*,4*E*,6*E*,8*E*,10*E*,12*S*,13*S*)-12,13-bis[(*tert*-butyldimethylsilyl)oxy]-4,6,10-trimethylhexadeca-2,4,6,8,10-pentaenoate (**17d**)**

To a solution of **SI-16** and tetrabutylammonium diphenylphosphate (472 mg, 1.02 mmol) in NMP (3 mL) was added 0.17 mL of the following solution: 340 mg of **16** (1.1 mmol, 2.1 eq.) in NMP (2.1 mL). After the addition of CuTc (211 mg, 1.11 mmol, 2 eq.), the remaining solution of **16** was added dropwise for 5 min. The reaction mixture was stirred at room temperature for 40 min, and then diluted with Et<sub>2</sub>O. The mixture was filtered through a pad of neutral alumina. The filtrate was then washed with water, with brine, dried over MgSO<sub>4</sub>, filtered, and concentrated. The crude product was purified by preparative TLC eluting with heptane/ethyl acetate 90:10 to give **17d** (193 mg, 0.33 mmol, 60 % over 2 steps) as a yellow oil. A (4'*E*)/(4'*Z*) = 96:4 mixture could be detected by <sup>1</sup>H analysis.

**<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz, 4'*E* isomer)** δ 7.37 (d, *J* = 15.5 Hz, 1H), 6.49 (dd, *J* = 10.6, 15.0 Hz, 1H), 6.37 (d, *J* = 13.2 Hz, 1H), 6.35 (s, 1H), 6.26 (d, *J* = 10.6 Hz, 1H), 5.86 (d, *J* = 15.5 Hz, 1H), 5.55 (d, *J* = 9.0 Hz, 1H), 4.43 (dd, *J* = 4.1, 9.0 Hz, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 3.62 (td, *J* = 4.1, 7.1 Hz, 1H), 2.05 (s, 3H), 2.02 (s, 3H), 1.96-1.92 (2H), 1.85 (s, 3H), 1.62 (m, 1H), 1.41 (m, 1H), 1.31 (t, *J* = 7.1 Hz, 3H), 0.91 (d, *J* = 5.5 Hz, 3H), 0.87 (s, 9H), 0.86 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H), 0.03 (s, 3H), -0.02 (s, 3H).

**<sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz, 4'*E* isomer)** δ 167.6, 150.8, 143.7, 139.9, 135.2, 134.6, 134.3, 134.0, 132.1, 123.5, 116.1, 72.1, 65.7, 60.2, 34.5, 25.9 (3C), 25.8 (3C), 19.3, 18.1 (2C), 17.1, 14.4, 14.3, 14.2, 13.4, -4.1, -4.3, -4.5, -4.6, -4.7.

**HRMS-ESI** calculated for C<sub>33</sub>H<sub>60</sub>NaO<sub>4</sub>Si<sub>2</sub>: *m/z* 599.3922 ([M+Na]<sup>+</sup>), found: *m/z* 599.3926 ([M+Na]<sup>+</sup>).

**(2*E*,4*E*,6*E*,8*E*,10*E*,12*S*,13*S*)-12,13-bis[(*tert*-Butyldimethylsilyl)oxy]-4,6,10-trimethylhexadeca-2,4,6,8,10-pentaenoic acid (**18d**)**

To a solution of **17d** (169 mg, 0.29 mmol) in a mixture of THF/MeOH/H<sub>2</sub>O (5.3:1.4:1.4) was added a solution of LiOH (2.5 mL, 1M in water, 10 eq.) in H<sub>2</sub>O. The reaction mixture was stirred at room temperature for 18 h before being acidified with a saturated aqueous solution of NH<sub>4</sub>Cl. The aqueous



phase was extracted with ethyl acetate, and the combined organic phases were washed with brine and dried over  $\text{MgSO}_4$ . After being filtered and concentrated under reduced pressure, the crude product was purified by preparative TLC (elution with heptane/ethyl acetate 70:30, to give **18d** (95 mg, 0.17 mmol, 59 %) as a yellow oil. A (4'E)/(4'Z) = 89:11 mixture could be detected by  $^1\text{H}$  analysis.

**$^1\text{H}$  NMR (Acetone- $d_6$ , 300 MHz, 4'Z isomer)**  $\delta$  7.93 (d,  $J$  = 15.7 Hz, 1H), 6.6 (dd,  $J$  = 10.7, 15.0 Hz, 1H), 6.48 (d,  $J$  = 14.6 Hz, 1 H), 6.34 (s, 1H), 6.19 (d,  $J$  = 11.0 Hz, 1H), 5.93 (d,  $J$  = 15.5 Hz, 1H), 5.63 (d,  $J$  = 9.0 Hz, 1H), 4.56 (dd,  $J$  = 3.9, 9.1 Hz, 1H), 3.72 (td,  $J$  = 4.3, 6.8 Hz, 1H), 2.09 (s, 3H), 2.06 (s, 3H), 1.93 (s, 3H), 1.75-1.68 (2H), 1.42-1.30 (2H), 0.93 (d,  $J$  = 6.3 Hz, 3H), 0.90 (s, 18H), 0.11 (s, 3H), 0.08 (s, 6H), 0.03 (s, 3H).

**$^{13}\text{C}$  NMR (Acetone- $d_6$ , 75 MHz, 4'Z isomer)**  $\delta$  169.1, 152.6, 144.5, 141.1, 137.2, 136.2, 135.9, 132.9, 134.2, 126.0, 120.4, 78.0, 73.7, 36.5, 27.3 (3C), 27.2 (3C), 22.1, 20.9, 19.7, 19.6, 18.0, 15.7, 14.9, -2.8, -3.0, -3.4, -3.5.

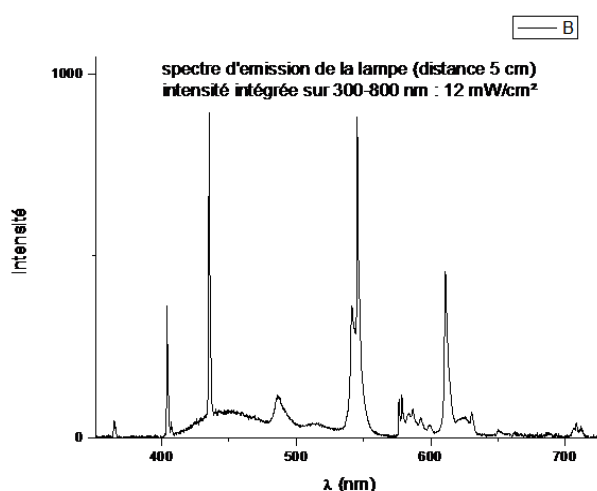
**$^1\text{H}$  NMR (Acetone- $d_6$ , 300 MHz, 4'E isomer)**  $\delta$  7.36 (d,  $J$  = 15.5 Hz, 1H), 6.66 (dd,  $J$  = 11.1, 14.8 Hz, 1H), 6.48 (d,  $J$  = 14.8 Hz, 1 H), 6.46 (s, 1H), 6.38 (d,  $J$  = 11.1 Hz, 1H), 5.87 (d,  $J$  = 15.5 Hz, 1H), 5.63 (d,  $J$  = 9.0 Hz, 1H), 4.56 (dd,  $J$  = 3.9, 9.1 Hz, 1H), 3.72 (td,  $J$  = 4.3, 6.8 Hz, 1H), 2.09 (s, 3H), 2.06 (s, 3H), 1.93 (s, 3H), 1.75-1.68 (2H), 1.42-1.30 (2H), 0.93 (d,  $J$  = 6.3 Hz, 3H), 0.90 (s, 18H), 0.11 (s, 3H), 0.08 (s, 6H), 0.03 (s, 3H).

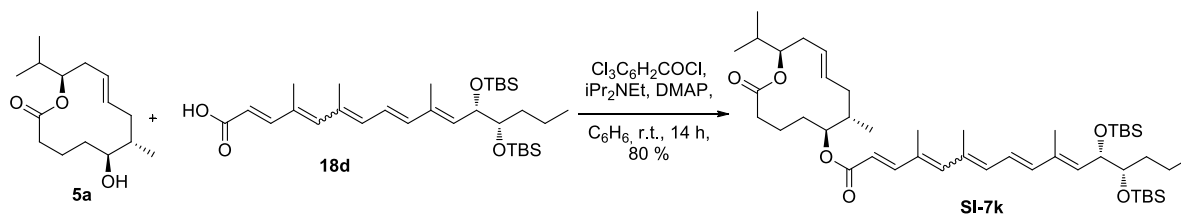
**$^{13}\text{C}$  NMR (Acetone- $d_6$ , 75 MHz, 4'E isomer)**  $\delta$  169.1, 152.6, 145.3, 142.9, 141.4, 137.2, 136.7, 136.0, 134.1, 126.0, 118.1, 78.0, 73.7, 36.4, 27.3 (3C), 27.2 (3C), 22.1, 20.9, 19.7, 19.6, 18.1, 15.3, 14.8, -2.8, -3.0, -3.4, -3.5.

**HRMS-ESI** calculated for  $\text{C}_{31}\text{H}_{55}\text{NaO}_4\text{Si}_2$ :  $m/z$  547.3644 ( $[\text{M}-\text{H}]^-$ ), found:  $m/z$  547.3647 ( $[\text{M}-\text{H}]^-$ ).

The acid **18d** was photoisomerized in acetone for 2 h, using a green fluorescent bulb, in order to obtain **18d** with a 4'E/ 4'Z = 60:40 ratio as detected by  $^1\text{H}$  NMR.

Spectrum emission of the fluorescent bulb at 5 cm: 365, 405, 435, 486, 541, 545, 576, 578, 610 nm. Intensity integrated on 300-800 nm: 12 mW/cm<sup>2</sup>.

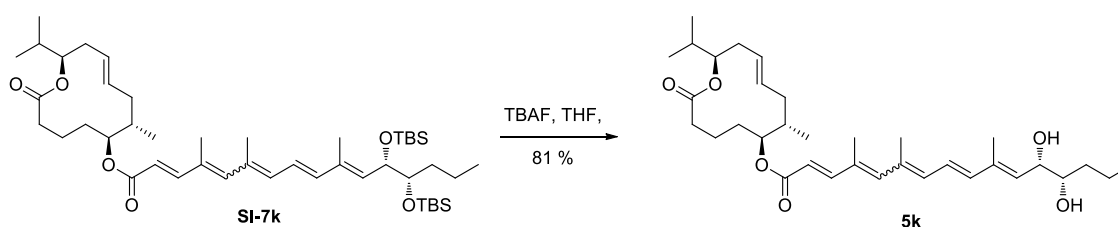




**(6*S*,7*S*,9*E*,12*R*)-7-Methyl-2-oxo-12-(propan-2-yl)-1-oxacyclododec-9-en-6-yl  
(2*E*,4*E*,6*E*,8*E*,10*E*,12*S*,13*S*)-12,13-bis[(*tert*-butyldimethylsilyl)oxy]-4,6,10-trimethylhexadeca-  
2,4,6,8,10-pentaenoate (SI-7k)**

To a solution of **18d** (21 mg, 0.04 mmol) in benzene (0.4 mL) were added diisopropylethyl amine (33  $\mu$ L, 0.17 mmol, 5.6 eq.), 2,4,6-trichlorobenzoyl chloride (17  $\mu$ L, 0.08 mmol, 3 eq.), and DMAP (33 mg). The reaction mixture was stirred at room temperature for 15 min and **5a** (6.5 mg, 0.025 mmol) was added. After being stirred at room temperature for 14 h, an aqueous saturated solution of sodium hydrogenocarbonate was added to the reaction mixture. The aqueous layer was extracted three times with benzene. The combined organic layers were washed with brine, dried over  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. The crude product was purified on preparative TLC eluting with heptane/ethyl acetate 90:10 to give **SI-7k** (16 mg, 0.020 mmol, 80 %) as a yellow oil. A (4'*E*)/(4'*Z*) = 36:64 mixture could be detected by  $^1\text{H}$  analysis.

**$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)**  $\delta$  7.94 (d,  $J$  = 15.6 Hz, 1H, *Z* isomer), 7.36 (d,  $J$  = 15.5 Hz, 1H, *E* isomer), 6.51 (dd,  $J$  = 14.8, 11.2 Hz, 1H), 6.37 (d,  $J$  = 14.8 Hz, 1H), 6.36 (s, 1H), 6.28 (d,  $J$  = 11.2 Hz, 1H), 5.85 (d,  $J$  = 15.5 Hz, 1H), 5.51 (m, 1H), 5.45 (m, 1H), 5.27 (m, 1H), 4.81-4.70 (2H), 4.45 (m, 1H), 3.60 (m, 1H), 2.49 (m, 1H), 2.30 (m, 1H), 2.15-2.06 (2H), 2.04 (s, 3H), 2.03 (s, 3H), 1.98-1.96 (4H), 1.85 (s, 3H), 1.87-1.61 (4H), 1.34-1.32 (4H), 0.95 (s, 3H), 0.93 (s, 3H), 0.92 (s, 3H), 0.90 (s, 3H), 0.87 (s, 9H), 0.86 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H), 0.03 (s, 3H), -0.02 (s, 3H).



**(6*S*,7*S*,9*E*,12*R*)-7-Methyl-2-oxo-12-(propan-2-yl)-1-oxacyclododec-9-en-6-yl  
(2*E*,4*E*,6*E*,8*E*,10*E*,12*S*,13*S*)-12,13-dihydroxy-4,6,10-trimethylhexadeca-2,4,6,8,10-pentaenoate (5k)**

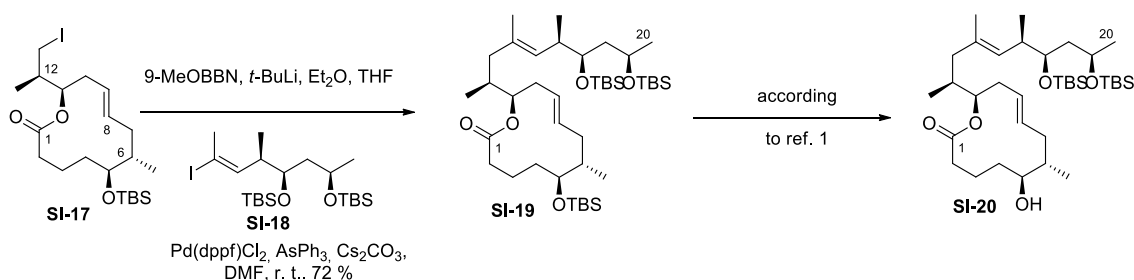
To a solution of **SI-7k** (16 mg, 0.020 mmol) in THF (0.2 mL) was added TBAF (0.15 mmol, 1M in THF, 8 eq.). The solution was stirred at room temperature for 4 h.  $\text{CaCO}_3$  (45 mg), Dowex 50WX8-400 (150 mg) and MeOH (0.3 mL) were added and the reaction mixture was stirred for 1 h. After being filtered and concentrated under reduced pressure, the crude product was purified by TLC preparative ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$  90:10) to give **5k** (9 mg, 0.016 mmol, 81 %). A (4'*E*)/(4'*Z*) = 47:53 mixture could be detected by  $^1\text{H}$  analysis.

**$^1\text{H}$  NMR (Acetone- $d_6$ , 400 MHz)**  $\delta$  7.76 (d,  $J$  = 15.6 Hz, 1H, *Z* isomer), 7.21 (d,  $J$  = 15.5 Hz, 1H, *E* isomer), 6.47 (dd,  $J$  = 11.1, 15.0 Hz, 1H), 6.30 (s, 1H), 6.29 (d,  $J$  = 15.0 Hz, 1H), 6.03 (d,  $J$  = 11.1 Hz, 1H), 5.76 (d,  $J$

= 15.5 Hz, 1H), 5.58 (m, 1H), 5.47 (m, 1H), 5.19 (m, 1H), 4.70-4.65 (2H), 4.10 (d,  $J = 7.1, 8.5$  Hz, 1H), 3.60-3.56 (2H), 3.40 (m, 1H), 2.50 (m, 1H), 2.32 (m, 1H), 2.12-2.08 (2H), 2.06 (s, 3H), 1.97 (s, 3H), 1.95-1.92 (2H), 1.90 (s, 3H), 1.80-1.75 (4H), 1.70-1.62 (2H), 1.54-1.49 (4H), 1.19 (s, 3H), 0.77 (s, 3H), 0.76 (s, 3H), 0.73 (s, 3H).

**$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz)**  $\delta$  173.0, 166.8, 150.7, 143.3, 142.7, 141.0, 138.2, 134.8, 133.7, 132.7, 131.4, 126.0, 125.1, 116.7, 78.7, 75.9, 74.9, 72.1, 38.0, 36.1, 35.5, 35.0, 34.4, 32.3, 29.6, 21.0, 20.4, 19.2, 18.9, 18.5, 18.2, 17.2, 14.0, 13.3.

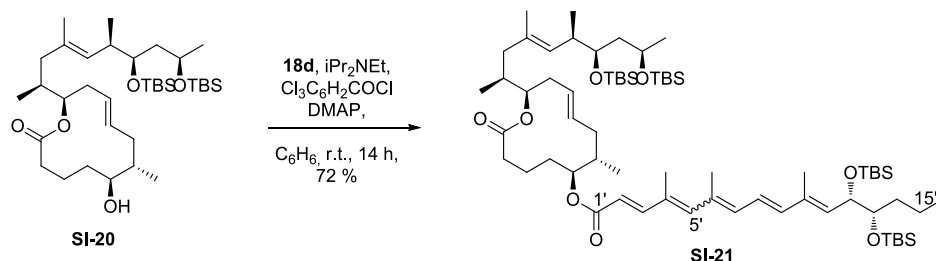
**HRMS-ESI** calculated for  $\text{C}_{34}\text{H}_{52}\text{O}_6\text{Na}$ :  $m/z$  579.3656 ( $[\text{M}+\text{Na}]^+$ ), found:  $m/z$  579.3649 ( $[\text{M}+\text{Na}]^+$ ).



**(6*S*,7*S*,12*R*,*E*)-12-((2*S*,6*R*,7*R*,9*R*,*E*)-7,9-bis((*tert*-Butyldimethylsilyl)oxy)-4,6-dimethyldec-4-en-2-yl)-6-((*tert*-butyldimethylsilyl)oxy)-7-methyloxacyclododec-9-en-2-one (SI-19)**

To a solution of **SI-17**<sup>1</sup> (65 mg, 0.13 mmol) and 9-MeO-BBN (1.0 M in hexane, 0.27 mL, 0.27 mmol) in  $\text{Et}_2\text{O}$  (1.3 mL) was added *tert*-butyllithium (1.6 M in pentane, 0.16 mL, 0.1 mmol) and THF (1.3 mL) slowly via syringe at  $-78^\circ\text{C}$ . The resulting mixture was stirred for 10 min at  $-78^\circ\text{C}$  and then allowed to warm to RT, thereby turning from a milky, slightly yellow suspension into a colorless solution, which was stirred at RT for additional 45 min. This solution was then transferred into a solution of vinyl iodide **SI-18** (67 mg, 0.13 mmol),  $\text{Pd}(\text{dppf})\text{Cl}_2$  (9 mg, 12  $\mu\text{mol}$ ),  $\text{AsPh}_3$  (13 mg, 42  $\mu\text{mol}$ ), and aq.  $\text{Cs}_2\text{CO}_3$ -solution (3.0 M in  $\text{H}_2\text{O}$ , 156  $\mu\text{L}$ , 0.47 mmol) in DMF (1.3 mL) via syringe. The yellow solution was stirred in the dark for 18 h at RT.  $\text{H}_2\text{O}$  and  $\text{Et}_2\text{O}$  were then added, the layers were separated, and the aqueous layer was extracted with  $\text{Et}_2\text{O}$ . The combined organic extracts were washed with brine, dried over  $\text{MgSO}_4$ , and the solvent was evaporated under reduced pressure. Purification of the residue by preparative TLC (elution: heptane:ethyl acetate 90:10) yielded 71 mg (72 %) of the coupling product **SI-19** as a slightly yellow oil.

The spectroscopic data are in agreement with those reported in the literature.<sup>1</sup>



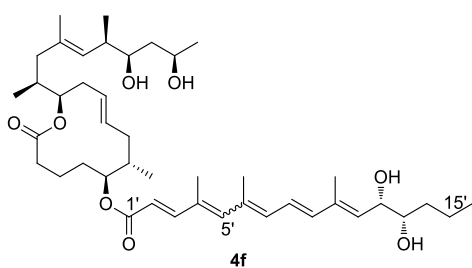
**(2*E*,8*E*,10*E*,12*S*,13*S*)-(6*S*,7*S*,12*R*,*E*)-12-((2*S*,6*R*,7*R*,9*R*,*E*)-7,9-bis((*tert*-Butyldimethylsilyl)oxy)-4,6-dimethyldec-4-en-2-yl)-7-methyl-2-oxooxacyclododec-9-en-6-yl-12,13-bis((*tert*-butyldimethylsilyl)oxy)-4,6,10-trimethylhexadeca-2,4,6,8,10-pentaenoate (SI-21)**

To a solution of **18d** (35 mg, 0.055 mmol) in benzene (0.3 mL) were added diisopropylethyl amine (30  $\mu$ L, 0.16 mmol, 5.6 eq.), 2,4,6-trichlorobenzoyl chloride (16  $\mu$ L, 0.1 mmol, 3 eq.), and DMAP (30 mg). The reaction mixture was stirred at room temperature for 15 min and **SI-20** (12 mg, 0.019 mmol) was added. After being stirred at room temperature for 14 h, an aqueous saturated solution of sodium hydrogenocarbonate was added to the reaction mixture. The aqueous layer was extracted three times with benzene. The combined organic layers were washed with brine, dried over  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. The crude product was purified on preparative TLC eluting with heptane/ethyl acetate 90:10 to give **SI21** (19 mg, 0.016 mmol, 84 %) as a yellow oil. A (4'*E*)/(4'*Z*) = 57:43 mixture could be detected by  $^1\text{H}$  analysis.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz, 4'*E* isomer)  $\delta$  7.34 (d,  $J$  = 15.5 Hz, 1H), 6.50 (dd,  $J$  = 10.6, 15.1 Hz, 1H), 6.38 (d,  $J$  = 15.1 Hz, 1H), 6.33 (s, 1H), 6.27 (d,  $J$  = 10.6 Hz, 1H), 5.82 (d,  $J$  = 15.5 Hz, 1H), 5.52 (d,  $J$  = 9.0 Hz, 1H), 5.42 (m, 1H), 5.21-5.08 (2H), 5.04 (d,  $J$  = 9.5 Hz, 1H), 4.78 (m, 1H), 4.43 (dd,  $J$  = 4.05, 9.1 Hz, 1H), 3.64-3.54 (2H), 3.33 (dd,  $J$  = 4.5, 9.0 Hz, 1H), 2.53 (m, 1H), 2.46 (m, 1H), 2.24-2.22 (2H), 2.15-2.10 (2H), 2.04 (s, 3H), 2.01 (s, 3H), 1.97 (m, 1H), 1.94-1.92 (2H), 1.84 (s, 6H), 1.80-1.59 (12H), 1.53 (s, 3H), 1.25 (d,  $J$  = 5.8 Hz, 3H), 1.24-1.22 (2H), 0.94 (d,  $J$  = 6.7 Hz, 3H), 0.89 (s, 9H), 0.88 (s, 9H), 0.87 (s, 9H), 0.86 (s, 9H), 0.79 (d,  $J$  = 6.6 Hz, 3H), 0.07 (s, 6H), 0.06 (s, 6H), 0.04 (s, 6H), 0.02 (s, 6H).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz, 4'*E* isomer)  $\delta$  173.3, 166.9, 150.6, 141.4, 139.8, 139.6, 135.6, 135.2, 134.6, 134.2, 134.0, 132.2, 131.9, 130.6, 123.8, 116.5, 76.4, 75.0, 73.9, 72.9 (2C), 68.3, 42.9, 42.8, 41.7, 39.6, 38.0, 37.3, 36.3, 35.9, 35.6, 34.9, 32.7, 29.8, 25.9 (9C), 25.8 (3C), 21.2, 20.8, 19.3, 18.3 (2C), 18.1 (2C), 17.5, 15.9, 15.6, 14.5, 14.2, 13.4, -4.1, -4.2 (2C), -4.3, -4.5, -4.6, -4.7, -4.8.

HRMS-ESI calculated for  $\text{C}_{67}\text{H}_{124}\text{O}_8\text{Si}_4\text{Na}$ :  $m/z$  1192.8291 ( $[\text{M}+\text{Na}]^+$ ), found:  $m/z$  1192.8273 ( $[\text{M}+\text{Na}]^+$ ).



**(2*E*,8*E*,10*E*,12*S*,13*S*)-(6*S*,7*S*,12*R*,*E*)-12-((2*S*,6*R*,7*R*,9*R*,*E*)-7,9-Dihydroxy-4,6-dimethyldec-4-en-2-yl)-7-methyl-2-oxooxacyclododec-9-en-6-yl-12,13-dihydroxy-4,6,10-trimethylhexadeca-2,4,6,8,10-pentaenoate (4f)**

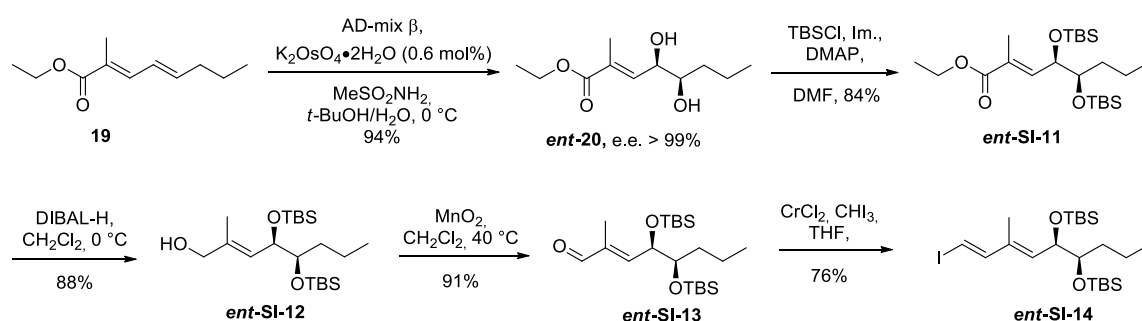
To a solution of **SI-21** (15 mg, 12.6  $\mu$ mol) in THF (3.0 mL) was added TBAF (0.24 mL, 20 eq.). The solution was stirred at room temperature for 12 h. For stabilities issues of **4f**, the reaction was quenched at 60 % of conversion.  $\text{CaCO}_3$  (50 mg), Dowex 50WX8-400 (140 mg) and MeOH (0.3 mL) were added and the reaction mixture was stirred for 20 min. After being filtered and concentrated under reduced pressure, the crude product was purified by preparative TLC ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$  90:10). The recovered triol was recycled. After one recycle, **4f** was obtained (1.5 mg). Due to the minute amount of **4f** obtained, clean

$^1\text{H}$  and  $^{13}\text{C}$  NMR could not be obtained. However, the NMR analyses are unambiguous. A (4'E)/(4'Z) = 43:57 mixture could be detected by  $^1\text{H}$  analysis.

**$^1\text{H}$  NMR (Acetone- $d_6$ , 400 MHz, 4'Z isomer)**  $\delta$  7.91 (d,  $J$  = 15.5 Hz, 1H), 6.64 (dd,  $J$  = 10.8, 14.7 Hz, 1H), 6.44 (d,  $J$  = 15.5 Hz, 1H), 6.33 (s, 1H), 6.17 (d,  $J$  = 10.8 Hz, 1H), 5.92 (d,  $J$  = 15.0 Hz, 1H), 5.61 (m, 1H), 5.45 (m, 1H), 5.22 (m, 1H), 5.20 (m, 1H), 5.06 (d,  $J$  = 15.6 Hz, 1H), 4.84 (m, 1H), 4.22 (m, 1H), 3.90 (m, 1H), 3.60 (m, 1H), 3.51 (m, 1H), 3.42-3.38 (3H), 2.42 (m, 1H), 2.40 (m, 1H), 2.30 (m, 1H), 2.12 (m, 1H), 2.10 (m, 1H), 2.02 (s, 3H), 1.96 (m, 1H), 1.95 (m, 1H), 1.92-1.84 (8H), 1.80 (m, 1H), 1.77 (m, 1H), 1.75-1.70 (4H), 1.65 (m, 1H), 1.62-1.56 (4H), 1.52-1.48 (2H), 1.48-1.42 (2H), 1.26 (m, 1H), 1.25 (d,  $J$  = 6.2 Hz, 3H), 1.00-0.96 (6H), 0.88-0.83 (6H).

**$^1\text{H}$  NMR (Acetone- $d_6$ , 400 MHz, 4'E isomer)**  $\delta$  7.34 (d,  $J$  = 15.6 Hz, 1H), 6.64 (dd,  $J$  = 10.8, 14.7 Hz, 1H), 6.47 (s, 1H), 6.38 (d,  $J$  = 10.8 Hz, 1H), 5.87 (d,  $J$  = 15.6 Hz, 1H), 5.61 (m, 1H), 5.45 (m, 1H), 5.22 (m, 1H), 5.20 (m, 1H), 5.06 (d,  $J$  = 9.4 Hz, 1H), 4.84 (m, 1H), 4.22 (m, 1H), 3.90 (m, 1H), 3.60 (m, 1H), 3.51 (m, 1H), 3.42-3.38 (3H), 2.42 (m, 1H), 2.40 (m, 1H), 2.30 (m, 1H), 2.12 (m, 1H), 2.10 (m, 1H), 2.02 (s, 3H), 1.96 (m, 1H), 1.95 (m, 1H), 1.92-1.84 (8H), 1.80 (m, 1H), 1.77 (m, 1H), 1.75-1.70 (4H), 1.65 (m, 1H), 1.62-1.56 (4H), 1.52-1.48 (2H), 1.48-1.42 (2H), 1.26 (m, 1H), 1.25 (d,  $J$  = 6.2 Hz, 3H), 1.00-0.96 (6H), 0.88-0.83 (6H).

**HRMS-ESI** calculated for  $\text{C}_{43}\text{H}_{68}\text{O}_8\text{Na}$  :  $m/z$  735.4806 ( $[\text{M}+\text{Na}]^+$ ), found:  $m/z$  735.4799 ( $[\text{M}+\text{Na}]^+$ ).



#### (4R,5R,E)-Ethyl 4,5-dihydroxy-2-methyloct-2-enoate (*ent*-20)

To a stirred solution of AD-mix  $\beta$  (7.7 g, 0.4 % osmium, 1 % (DHQD) $_2$ PHAL) in a mixture 1:1  $t$ -BuOH/ $\text{H}_2\text{O}$  (27:27 mL) were added successively methanesulfonamide (520 mg, 5.47 mmol, 1 eq.) and potassium osmate(VI) dihydrate (12 mg, 32.57  $\mu\text{mol}$ , 0.6 mol%). The mixture was stirred at room temperature until two clear phases were produced. The solution was cooled to 0  $^\circ\text{C}$ , whereupon the inorganic salts partially precipitate, and **19** (1 g, 5.49 mmol) was added. After stirring 48 h at 0  $^\circ\text{C}$ ,  $\text{Na}_2\text{SO}_3$  (8.2 g) was added and the reaction mixture was stirred for 30 min at room temperature. The mixture was extracted three times with EtOAc. The combined organic extracts were washed with an aqueous KOH solution (2M), brine, dried over  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. The crude product was purified by chromatography (cyclohexane/EtOAc 8:2) to give *ent*-**20** (1.12 g, 5.18 mmol, 94 %, e.e. > 99%) as a colorless oil.

**$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)**  $\delta$  6.64 (dq,  $J$  = 9.1, 1.4 Hz, 1H), 4.26-4.15 (3H), 3.54 (m, 1H), 2.63 (br s, 2H), 1.91 (d,  $J$  = 1.5 Hz, 3H), 1.53 (m, 1H), 1.44-1.35 (3H), 1.30 (t,  $J$  = 7.1 Hz, 3H), 0.92 (t,  $J$  = 6.8 Hz, 3H).

**(4*R*,5*R*,*E*)-Ethyl 4,5-bis((*tert*-butyldimethylsilyl)oxy)-2-methyloct-2-enoate (*ent*-SI-11)**

To a stirred solution of **ent-20** (1.12 g, 5.18 mmol) in dry DMF (15 mL), under a nitrogen atmosphere, were added *tert*-butyldimethylsilyl chloride (5.23 g, 34.7 mmol, 6.7 eq.), imidazole (2.32 g, 34.2 mmol, 6.6 eq.) and DMAP (158 mg, 1.31 mmol, 0.2 eq.). The reaction mixture was stirred at room temperature for 48 h. The resulting solution was hydrolyzed with water and the aqueous layer was extracted three times with a mixture of cyclohexane and DCM (9:1). The combined organic extracts were washed with water, brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude product was purified by chromatography (cyclohexane/EtOAc 20:1) to give **ent-SI-11** (1.94 g, 4.37 mmol, 84 %) as a colorless oil.

**<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)**  $\delta$  6.70 (dq, *J* = 8.9, 1.4 Hz, 1H), 4.41 (dd, *J* = 8.9, 3.8 Hz, 1H), 4.20 (qd, *J* = 7.1, 0.8 Hz, 2H), 3.64 (dt, *J* = 7.1, 4.1 Hz, 1H), 1.88 (d, *J* = 1.4 Hz, 3H), 1.67 (m, 1H), 1.42-1.26 (6H including 1.30 (t, *J* = 7.1 Hz, 3H)), 0.91-0.87 (21H including 0.89 (t, *J* = 7.0 Hz, 3H), 0.88 (s, 18H)), 0.06 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H), 0.00 (s, 3H).

**<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)**  $\delta$  168.0, 141.5, 128.0, 76.0, 72.1, 60.5, 34.5, 25.9 (3C), 25.8 (3C), 19.2, 18.1 (2C), 14.3, 14.2, 13.3, -4.2, -4.4, -4.6, -4.8.

**HRMS-ESI** calculated for C<sub>23</sub>H<sub>48</sub>O<sub>4</sub>NaSi<sub>2</sub> : *m/z* 467.2983 ([M+Na]<sup>+</sup>), found : *m/z* 467.2971 ([M+Na]<sup>+</sup>).

**[ $\alpha$ ]<sup>20</sup><sub>D</sub>** = + 33.2 (c 2.1, CHCl<sub>3</sub>).

**(4*R*,5*R*,*E*)-4,5-bis((*tert*-Butyldimethylsilyl)oxy)-2-methyloct-2-en-1-ol (*ent*-SI-12)**

To a stirred solution of **ent-SI-11** (1.80 g, 4.05 mmol) in dry DCM (21 mL), under a nitrogen atmosphere, was added DIBAL-H (6 mL, 1.5 M in toluene, 8.91 mmol, 2.2 eq.) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h. Saturated aqueous Rochelle salt solution was then added, and the resulting mixture warmed to room temperature and vigorously stirred overnight. The aqueous layer was extracted with Et<sub>2</sub>O and the combined organic extracts were washed with water, brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude alcohol was purified by chromatography (cyclohexane/EtOAc 9:1) to afford **ent-SI-12** (1.44 g, 3.58 mmol, 88 %) as a colorless oil.

**<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)**  $\delta$  5.45 (dq, *J* = 9.1, 1.4 Hz, 1H), 4.35 (dd, *J* = 9.1, 4.1 Hz, 1H), 4.02 (s, 2H), 3.61 (dt, *J* = 7.8, 4.1 Hz, 1H), 1.72 (d, *J* = 1.4 Hz, 3H), 1.65 (m, 1H), 1.46-1.27 (3H), 0.93-0.87 (21H including 0.91 (t, *J* = 7.0 Hz, 3H), 0.88 (s, 9H), 0.88 (s, 9H)), 0.07 (s, 3H), 0.06 (s, 3H), 0.04 (s, 3H), 0.00 (s, 3H).

**<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)**  $\delta$  136.3, 125.8, 76.1, 71.5, 68.8, 34.1, 25.9 (3C), 25.8 (3C), 19.4, 18.1 (2C), 14.5, 14.4, -4.1, -4.2, -4.6, -4.7.

**HRMS-ESI** calculated for C<sub>21</sub>H<sub>46</sub>O<sub>3</sub>NaSi<sub>2</sub> : *m/z* 425.2878 ([M+Na]<sup>+</sup>), found : *m/z* 425.2874 ([M+Na]<sup>+</sup>).

**[ $\alpha$ ]<sup>20</sup><sub>D</sub>** = + 25.2 (c 2.1, CHCl<sub>3</sub>).

**(4*R*,5*R*,*E*)-4,5-bis((*tert*-Butyldimethylsilyl)oxy)-2-methyloct-2-enal (*ent*-SI-13)**

To a stirred solution of **ent-SI-12** (1.33 g, 3.31 mmol) in dry DCM (25.4 mL), under a nitrogen atmosphere, was added MnO<sub>2</sub> (5.75 g, 66.1 mmol, 20 eq.) at room temperature. The reaction mixture was warmed to 40 °C and vigorously stirred for 48 h. The resulting mixture was cooled to room temperature and filtered through celite with DCM. The solvent was then removed under reduced pressure to give **ent-SI-13** (1.21 g, 3.02 mmol, 91 %) as a colorless oil which was used in the next step without further purification.

**<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)**  $\delta$  9.46 (s, 1H), 6.44, (dq,  $J$  = 8.4, 1.4 Hz, 1H), 4.59 (dd,  $J$  = 8.4, 4.0 Hz, 1H), 3.71 (dt,  $J$  = 7.6, 3.8 Hz, 1H), 1.81 (d,  $J$  = 1.4 Hz, 3H), 1.72 (m, 1H), 1.50-1.26 (3H), 0.95-0.87 (21H including 0.93 (t,  $J$  = 7.0 Hz, 3H), 0.89 (s, 9H), 0.87 (s, 9H)), 0.07 (s, 9H), 0.01 (s, 3H).

**(1*E*,3*E*)-(5*R*,6*R*)-bis-(*tert*-Butyldimethylsilyloxy)-1-iodo-3-methyl-nona-1,3-diene (*ent*-SI-14)**

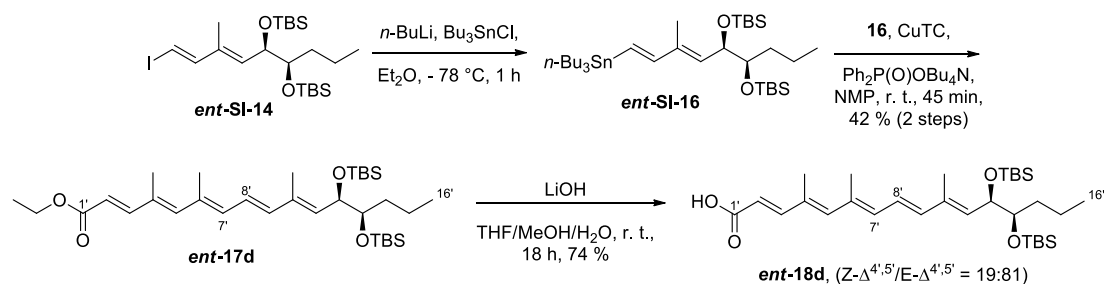
To a stirred solution of CrCl<sub>2</sub> (3.53 g, 28.7 mmol, 10 eq.) in dry THF (21.7 mL), under a nitrogen atmosphere, was added a solution of *ent*-SI-13 (1.15 g, 2.87 mmol) and CHI<sub>3</sub> (3.39 g, 8.62 mmol, 3 eq.) in dry THF (18.9 mL) dropwise. The reaction mixture was stirred at room temperature for 12 h. The resulting mixture was hydrolyzed with water and diluted with Et<sub>2</sub>O. The aqueous layer was extracted three times with Et<sub>2</sub>O and the combined organic extracts were washed with water, brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude product was then purified by chromatography (cyclohexane/toluene 100:1) to afford *ent*-SI-14 (1.15 g, 2.19 mmol, 76 %) as a pale yellow oil.

**<sup>1</sup>H NMR (C<sub>6</sub>D<sub>6</sub>, 300 MHz)**  $\delta$  7.02 (d,  $J$  = 14.8 Hz, 1H), 6.00 (d,  $J$  = 14.8 Hz, 1H), 5.44 (dq,  $J$  = 9.0, 1.2 Hz, 1H), 4.47 (dd,  $J$  = 9.1, 4.0 Hz, 1H), 3.72 (dt,  $J$  = 7.4, 3.8 Hz, 1H), 1.77 (m, 1H), 1.56 (d,  $J$  = 1.2 Hz, 3H), 1.51-1.36 (3H), 1.00-0.92 (21H including 0.96 (s, 9H), 0.96 (s, 9H), 0.94 (t,  $J$  = 7.2 Hz, 3H)), 0.11 (s, 3H), 0.08 (s, 3H), 0.07 (s, 3H), 0.02 (s, 3H).

**<sup>13</sup>C NMR (C<sub>6</sub>D<sub>6</sub>, 100 MHz)**  $\delta$  149.9, 135.6, 134.4, 77.0, 76.5, 72.5, 35.2, 26.5 (3C), 26.4 (3C), 20.1, 18.7, 18.6, 15.0, 13.3, -3.5, -3.8, -4.1, -4.2.

**HRMS-ESI** calculated for C<sub>22</sub>H<sub>45</sub>O<sub>2</sub>NaSi<sub>2</sub> :  $m/z$  547.1895 ([M+Na]<sup>+</sup>), found :  $m/z$  547.1871 ([M+Na]<sup>+</sup>).

**[ $\alpha$ ]<sup>20</sup><sub>D</sub>** = + 28.1 (c 2.2, CHCl<sub>3</sub>).



**(1*E*,3*E*)-(5*R*,6*R*)-bis-(*tert*-Butyldimethylsilyloxy)-1-tributylstannyl-3-methyl-nona-1,3-diene (*ent*-SI-16)**

To a stirred solution of *ent*-SI-14 (300 mg, 0.57 mmol) in dry Et<sub>2</sub>O (3 mL), under a nitrogen atmosphere, was added *n*-BuLi (0.78 mL, 1.1 M in hexane, 0.86 mmol, 1.5 eq.) at -78 °C. The reaction mixture was stirred for 20 min at -78 °C and Bu<sub>3</sub>SnCl (0.24 mL, 0.86 mmol, 1.5 eq.) was added. The resulting solution was stirred at -78 °C for another 20 min and allowed to warm to room temperature for 1 h. Saturated aqueous NaHCO<sub>3</sub> solution was then added and the aqueous layer was extracted three times with Et<sub>2</sub>O. The combined organic extracts were washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude *ent*-SI-16 was used in the next step without further purification.

**(2E,4E,6E,8E,10E,12R,13R)-Ethyl 12,13-bis((tert-butyltrimethylsilyl)oxy)-4,6,10-trimethylhexadeca-2,4,6,8,10-pentaenoate (*ent*-17d)**

To a stirred solution of crude *ent*-SI-16 and tetra-*n*-butylammonium diphenylphosphinate (605 mg, 1.31 mmol, 2.3 eq.) in dry NMP (3.9 mL), under a nitrogen atmosphere, was added 0.2 mL of a solution of **16** in NMP (418 mg, 1.37 mmol, 2.4 eq., 2.6 mL). After addition of CuTC (217 mg, 1.14 mmol, 2 eq.), the rest of the **16** solution was added dropwise and the resulting mixture was stirred at room temperature for 40 min. The reaction mixture was then diluted with Et<sub>2</sub>O and filtered through neutral alumina oxide. The filtrate was washed with water, brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude product was then purified by preparative TLC (cyclohexane/EtOAc 9:1) to afford *ent*-17d (137 mg, 0.24 mmol, 42 % for two steps) as a yellow oil. NMR analysis showed the presence of mixture of isomers 4'E/4'Z = 92:8.

**<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz, 4'E isomer)** δ 7.95 (d, *J* = 15.5 Hz, 1H, *Z* isomer), 7.38 (d, *J* = 15.5 Hz, 1H, *E* isomer), 6.50 (dd, *J* = 15.0, 10.8 Hz, 1H), 6.38 (d, *J* = 15.0 Hz, 1H), 6.36 (s, 1H), 6.27 (d, *J* = 10.8 Hz, 1H), 5.87 (d, *J* = 15.5 Hz, 1H), 5.56 (d, *J* = 9.2 Hz, 1H), 4.45 (dd, *J* = 9.1, 4.1 Hz, 1H), 4.23 (q, *J* = 7.1 Hz, 2H), 3.63 (dt, *J* = 7.0, 4.2 Hz, 1H), 2.05 (s, 3H), 2.03 (s, 3H), 1.86 (s, 3H), 1.64 (m, 1H), 1.47-1.27 (6H including 1.32 (t, *J* = 7.1 Hz, 3H)), 0.93-0.87 (21H including 0.91 (t, *J* = 6.8 Hz, 3H), 0.88 (s, 9H), 0.88 (s, 9H)), 0.07 (s, 3H), 0.06 (s, 3H), 0.04 (s, 3H), -0.01 (s, 3H).

**<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)** δ 167.5, 150.8, 143.7, 139.9, 135.2, 134.6 (2C), 134.0, 132.1, 123.5, 116.1, 76.4, 72.1, 60.2, 34.5, 25.9 (3C), 25.8 (3C), 19.3, 18.1 (2C), 17.1, 14.4, 14.3, 14.2, 13.4, -4.1, -4.3, -4.6, -4.7.

**HRMS-ESI** calculated for C<sub>33</sub>H<sub>60</sub>O<sub>4</sub>NaSi<sub>2</sub> : *m/z* 599.3922 ([M+Na]<sup>+</sup>), found : *m/z* 599.3910 ([M+Na]<sup>+</sup>).

**(2E,4E,6E,8E,10E,12R,13R)-12,13-bis((tert-Butyltrimethylsilyl)oxy)-4,6,10-trimethylhexadeca-2,4,6,8,10-pentaenoic acid (*ent*-18d)**

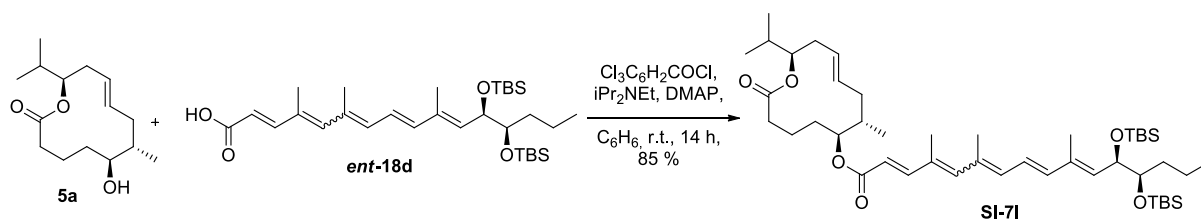
To a stirred solution of *ent*-17d (106 mg, 0.18 mmol) in a mixture THF/MeOH/H<sub>2</sub>O (4/1/1 mL) was added LiOH (45 mg, 1.85 mmol, 10 eq.). The resulting mixture was stirred at room temperature for 18 h. After addition of saturated aqueous NH<sub>4</sub>Cl solution, the mixture was extracted three times with EtOAc and the combined organic extracts were washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude material was purified by preparative TLC (cyclohexane/EtOAc 7:3) to afford *ent*-18d (75 mg, 0.14 mmol, 74 %) as a yellow oil. NMR analysis showed the presence of mixture of isomers 4'E/4'Z = 81:19, as well as another isomer.

**<sup>1</sup>H NMR (d<sub>6</sub>-Acetone, 300 MHz, 4'E isomer)** δ 7.93 (d, *J* = 15.5 Hz, 1H, *Z* isomer), 7.36 (d, *J* = 15.5 Hz, 1H, *E* isomer), 6.66 (dd, *J* = 15.0, 11.0 Hz, 1H), 6.50-6.18 (3H including 6.48 (d, *J* = 15.0 Hz, 1H), 6.45 (s, 1H), 6.38 (d, *J* = 11.0 Hz, 1H)), 5.87 (d, *J* = 15.5 Hz, 1H), 5.64 (d, *J* = 9.0 Hz, 1H), 4.56 (dd, *J* = 9.1, 3.9 Hz, 1H), 3.72 (m, 1H), 2.09 (s, 3H), 2.06 (s, 3H), 1.92 (s, 3H), 1.75-1.66 (1H), 1.49-1.29 (3H), 0.94-0.86 (21H including 0.92 (t, *J* = 7.0 Hz, 3H), 0.90 (s, 18H)), 0.11 (s, 3H), 0.08 (s, 6H), 0.03 (s, 3H).

**<sup>13</sup>C NMR (d<sub>6</sub>-Acetone, 100 MHz, 4'E isomer)** δ 168.3, 151.7, 144.3, 141.9, 140.5, 136.2, 135.8, 135.2, 133.2, 125.1, 117.3, 77.1, 72.9, 35.6, 26.4 (3C), 26.3 (3C), 20.0, 18.8, 18.7, 17.3, 14.8, 14.4, 13.8, -3.7, -3.9, -4.2, -4.3.

**HRMS-ESI** calculated for C<sub>31</sub>H<sub>56</sub>O<sub>4</sub>NaSi<sub>2</sub> : *m/z* 571.3609 ([M+Na]<sup>+</sup>), found : *m/z* 571.3603 ([M+Na]<sup>+</sup>).



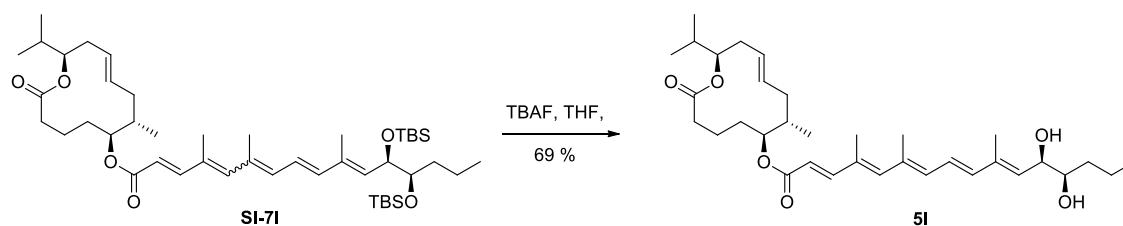


**(6*S*,7*S*,9*E*,12*R*)-7-Methyl-2-oxo-12-(propan-2-yl)-1-oxacyclododec-9-en-6-yl-  
(2*E*,4*E*,6*E*,8*E*,10*E*,12*R*,13*R*)-12,13-bis[[(*tert*-butyldimethylsilyl)oxy]-4,6,10-trimethylhexadeca-  
2,4,6,8,10-pentaenoate SI-7I**

To a solution of **ent-18d** (22 mg, 0.040 mmol) in benzene (0.4 mL) were added diisopropylethyl amine (33  $\mu$ L, 0.18 mmol, 5.6 eq.), 2,4,6-trichlorobenzoyl chloride (17  $\mu$ L, 0.09 mmol, 3 eq.), and DMAP (33 mg). The reaction mixture was stirred at room temperature for 15 min and **5a** (7 mg, 0.027 mmol) was added. After being stirred at room temperature for 14 h, an aqueous saturated solution of sodium hydrogenocarbonate was added to the reaction mixture. The aqueous layer was extracted three times with benzene. The combined organic layers were washed with brine, dried over  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. The crude product was purified on preparative TLC eluting with heptane/ethyl acetate 90:10 to give **SI-7I** (18 mg, 0.023 mmol, 85 %) as a yellow oil. A (4'*E*)/(4'*Z*) = 59:41 mixture could be detected by  $^1\text{H}$  analysis.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  7.94 (d,  $J$  = 15.5 Hz, 1H, *Z* isomer), 7.37 (d,  $J$  = 15.5 Hz, 1H, *E* isomer), 6.51 (dd,  $J$  = 14.8, 11.2 Hz, 1H), 6.37 (d,  $J$  = 14.8 Hz, 1H), 6.35 (s, 1H), 6.26 (d,  $J$  = 11.2 Hz, 1H), 5.86 (d,  $J$  = 15.52 Hz, 1H), 5.59 (d,  $J$  = 8.8 Hz, 1H), 5.51 (m, 1H), 5.30 (m, 1H), 4.83-4.74 (2H), 4.44 (dd,  $J$  = 9.1, 3.9 Hz, 1H), 3.61 (m, 1H), 2.49 (m, 1H), 2.30 (m, 1H), 2.15-2.06 (2H), 2.04 (s, 3H), 2.02 (s, 3H), 1.98-1.96 (2H), 1.85 (s, 3H), 1.87-1.61 (6H), 1.34-1.26 (4H), 0.95 (s, 3H), 0.93 (s, 3H), 0.92 (s, 3H), 0.90 (s, 3H), 0.87 (s, 9H), 0.86 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H), 0.03 (s, 3H), -0.02 (s, 3H).

**HRMS-ESI** calculated for  $\text{C}_{46}\text{H}_{80}\text{O}_6\text{Si}_2\text{Na}$ :  $m/z$  807.5385 ( $[\text{M}+\text{Na}]^+$ ), found:  $m/z$  807.5379 ( $[\text{M}+\text{Na}]^+$ ).



**(6*S*,7*S*,9*E*,12*R*)-7-Methyl-2-oxo-12-(propan-2-yl)-1-oxacyclododec-9-en-6-yl  
(2*E*,4*E*,6*E*,8*E*,10*E*,12*R*,13*R*)-12,13-dihydroxy-4,6,10-trimethylhexadeca-2,4,6,8,10-pentaenoate (5I)**

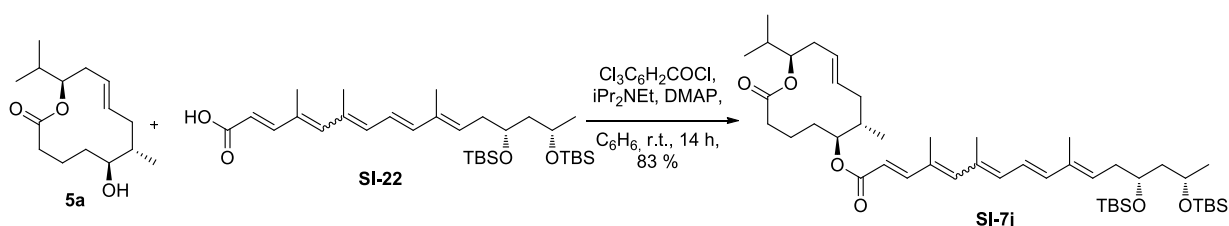
To a solution of **SI-7I** (18 mg, 0.023 mmol) in THF (0.2 mL) was added TBAF (0.14 mmol, 1M in THF, 6 eq.). The solution was stirred at room temperature for 4 h.  $\text{CaCO}_3$  (50 mg), Dowex 50WX8-400 (140 mg) and MeOH (0.4 mL) were added and the reaction mixture was stirred for 1 h. After being filtered and concentrated under reduced pressure, the crude product was purified by TLC preparative

(CH<sub>2</sub>Cl<sub>2</sub>/MeOH 90:10) to give **5I** (9 mg, 0.016 mmol, 69 %). A (4'E)/(4'Z) = 52:48 mixture could be detected by <sup>1</sup>H analysis.

**<sup>1</sup>H NMR (Acetone-d<sub>6</sub>, 300 MHz)** δ 7.93 (d, *J* = 15.6 Hz, 1H, *Z* isomer), 7.37 (d, *J* = 15.5 Hz, 1H, *E* isomer), 6.63 (dd, *J* = 11.1, 15.0 Hz, 1H), 6.47 (s, 1H), 6.36 (d, *J* = 15.0 Hz, 1H), 6.15 (d, *J* = 11.1 Hz, 1H), 5.89 (d, *J* = 15.5 Hz, 1H), 5.56 (d, *J* = 8.5 Hz, 1H), 5.50 (m, 1H), 5.30 (m, 1H), 4.78-4.67 (2H), 4.22 (d, *J* = 6.9, 8.9 Hz, 1H), 3.90 (m, 1H), 3.60 (m, 1H), 3.40 (m, 1H), 2.50 (m, 1H), 2.32 (m, 1H), 2.12-2.08 (2H), 2.06 (s, 3H), 1.97 (s, 3H), 1.95-1.92 (2H), 1.90 (s, 3H), 1.80-1.75 (4H), 1.70-1.62 (2H), 1.54-1.49 (4H), 1.19 (s, 3H), 0.92 (s, 3H), 0.90 (s, 3H), 0.87 (s, 3H).

**<sup>13</sup>C NMR (Acetone-d<sub>6</sub>, 75 MHz)** δ 173.9, 167.8, 152.2, 144.1, 141.3, 138.1, 136.5, 135.9, 134.2, 133.1, 128.0, 126.1, 120.6, 118.4, 80.2, 77.3, 76.2, 73.4, 39.7, 37.9, 37.0, 36.8, 36.1, 34.1, 22.0, 21.7, 20.9, 20.7, 19.9, 19.4, 18.6, 15.5, 15.3, 14.4.

**HRMS-ESI** calculated for C<sub>34</sub>H<sub>52</sub>O<sub>6</sub>Na : *m/z* 579.3656 ([M+Na]<sup>+</sup>), found: *m/z* 579.3655 ([M+Na]<sup>+</sup>).

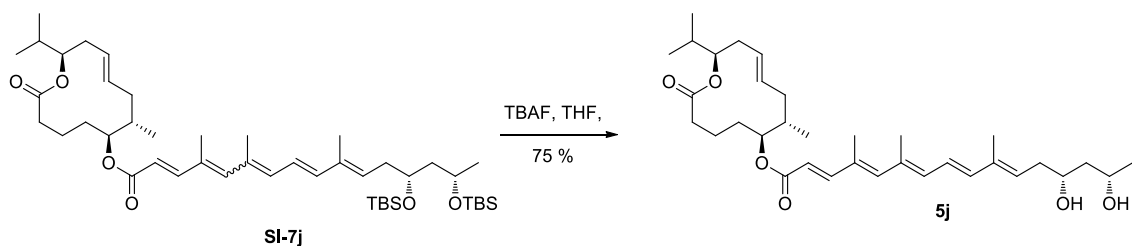


**(6*S*,7*S*,9*E*,12*R*)-7-Methyl-2-oxo-12-(propan-2-yl)-1-oxacyclododec-9-en-6-yl  
(2*E*,4*E*,6*E*,8*E*,10*E*,13*R*,15*S*)-13,15-bis[(*tert*-butyldimethylsilyl)oxy]-4,6,10-trimethylhexadeca-  
2,4,6,8,10-pentaenoate (**SI-7j**)**

To a solution of **SI-22**<sup>1</sup> (20 mg, 0.04 mmol) in benzene (0.7 mL) were added diisopropylethyl amine (33 μL, 0.17 mmol, 5.6 eq.), 2,4,6-trichlorobenzoyl chloride (17 μL ; 0.09 mmol, 3 eq.), and DMAP (33 mg). The reaction mixture was stirred at room temperature for 15 min and **5a** (7 mg, 0.03 mmol) was added. After being stirred at room temperature for 14 h, an aqueous saturated solution of sodium hydrogenocarbonate was added to the reaction mixture. The aqueous layer was extracted three times with benzene. The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude product was purified on preparative TLC eluting with heptane/ethyl acetate 90:10 to give **SI-7j** (20 mg, 0.024 mmol, 83 %) as a yellow oil. A (4'E)/(4'Z) = 58:42 mixture could be detected by <sup>1</sup>H analysis.

**<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)** δ 7.95 (d, *J* = 15.5 Hz, 1H, *Z* isomer), 7.36 (d, *J* = 15.6 Hz, 1H, *E* isomer), 6.49 (dd, *J* = 14.8, 11.2 Hz, 1H), 6.37 (d, *J* = 14.8 Hz, 1H), 6.36 (s, 1H), 6.28 (d, *J* = 11.2 Hz, 1H), 5.85 (d, *J* = 15.5 Hz, 1H), 5.59 (d, *J* = 8.8 Hz, 1H), 5.51 (m, 1H), 5.30 (m, 1H), 4.82-4.70 (2H), 3.89 (m, 1H), 3.82 (m, 1H), 2.49 (m, 1H), 2.30 (m, 1H), 2.15-2.06 (2H), 2.04 (s, 3H), 2.03 (s, 3H), 1.98-1.96 (3H), 1.85 (s, 3H), 1.87-1.61 (6H), 1.13 (d, *J* = 6.0 Hz, 3H), 0.95 (s, 3H), 0.93 (s, 3H), 0.92 (s, 3H), 0.90 (s, 3H), 0.87 (s, 9H), 0.85 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H), 0.02 (s, 3H), -0.02 (s, 3H).

**HRMS-ESI** calculated for C<sub>46</sub>H<sub>80</sub>O<sub>6</sub>NaSi<sub>2</sub> : *m/z* 807.5385 ([M+Na]<sup>+</sup>), found : *m/z* 807.5377 ([M+Na]<sup>+</sup>).



**(6S,7S,9E,12R)-7-Methyl-2-oxo-12-(propan-2-yl)-1-oxacyclododec-9-en-6-yl**

**(2E,4E,6E,8E,10E,13S,15S)-13,15-dihydroxy-4,6,10-trimethylhexadeca-2,4,6,8,10-pentaenoate (**5j**)**

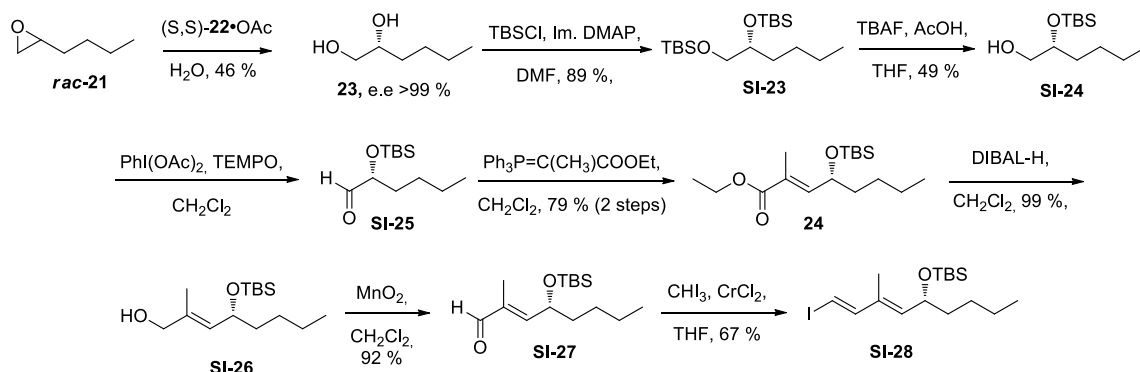
To a solution of **SI-7j** (20 mg, 0.024 mmol) in THF (0.2 mL) was added TBAF (0.23 mmol, 1M in THF, 9 eq.). The solution was stirred at room temperature for 4 h.  $\text{CaCO}_3$  (40 mg), Dowex 50WX8-400 (120 mg) and MeOH (0.3 mL) were added and the reaction mixture was stirred for 1 h. After being filtered and concentrated under reduced pressure, the crude product was purified by TLC preparative ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$  90:10) to give **5j** (10 mg, 0.018 mmol, 75 %). A (4'E)/(4'Z) = 41:59 mixture could be detected by  $^1\text{H}$  analysis.

**NMR  $^1\text{H}$  (Acetone- $d_6$ , 300 MHz)**  $\delta$  7.93 (d,  $J$  = 15.5 Hz, 1H, Z isomer), 7.36 (d,  $J$  = 15.5 Hz, 1H, E isomer), 6.63 (dd,  $J$  = 11.1, 14.5 Hz, 1H), 6.48 (s, 1H), 6.38 (d,  $J$  = 14.5 Hz, 1H), 6.17 (d,  $J$  = 11.1 Hz, 1H), 5.89 (d,  $J$  = 15.5 Hz, 1H), 5.71 (m, 1H), 5.50 (m, 1H), 5.28 (m, 1H), 4.78-4.63 (2H), 4.27 (m, 1H), 4.11 (m, 1H), 3.97 (m, 1H), 3.85 (m, 1H), 2.51 (m, 1H), 2.32 (m, 1H), 2.12-2.08 (2H), 2.06 (s, 3H), 1.97 (s, 3H), 1.95-1.92 (2H), 1.90 (s, 3H), 1.80-1.75 (4H), 1.70-1.62 (2H), 1.54-1.49 (2H), 1.13 (d,  $J$  = 6.1 Hz, 3H), 0.92 (s, 3H), 0.90 (s, 3H), 0.87 (s, 3H).

**NMR  $^{13}\text{C}$  (Acetone- $d_6$ , 75 MHz)**  $\delta$  173.9, 167.8, 152.2, 144.1, 141.6, 137.7, 136.5, 135.6, 134.0, 133.2, 128.0, 126.9, 120.4, 118.2, 80.2, 77.3, 73.2, 69.2, 46.7, 39.7, 39.0, 37.9, 37.0, 36.1, 34.1, 25.4, 22.0, 21.7, 20.9, 19.9, 19.4, 18.6, 15.3, 14.4.

**HRMS-ESI** calculated for  $\text{C}_{34}\text{H}_{52}\text{O}_6\text{Na}$ :  $m/z$  579.3656 ( $[\text{M}+\text{Na}]^+$ ), found:  $m/z$  579.3659 ( $[\text{M}+\text{Na}]^+$ ).

### 2.3 Synthesis of dideoxy series



### (2R)-Hexane-1,2-diol (**23**)

To (*S,S*)-**22**•OAc (124 mg, 0.205 mmol, 0.05 %) were added 2-butyloxirane *rac*-**21** (5 mL, 41 mmol), acetic acid (47  $\mu$ L, 0.82 mmol, 0.02 eq.) and THF (0.41 mL). The reaction mixture was cold to 0 °C, and water was added (0.33 mL, 18.45 mmol, 0.45 eq.). After being stirred at room temperature for 16 h, the reaction mixture was filtered over a pad of silica (eluant: cyclohexane/ethyl acetate 5:5) and concentrated under reduced pressure. The crude product was purified by distillation with Kugelrohr to give **23** (2.3 g, 19 mmol, 46 %) as a colorless oil.

**NMR**  $^1\text{H}$  ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  3.70 (m, 1H), 3.65 (dd,  $J$  = 3.5, 11.1 Hz, 1H), 3.41 (dd,  $J$  = 7.6, 11.1 Hz, 1H), 1.96-1.94 (large s, 2H), 1.42-1.40 (2H), 1.35-1.29 (2H), 0.89 (t,  $J$  = 7.1 Hz, 3H).

**HRMS-ESI** calculated for  $\text{C}_6\text{H}_{14}\text{O}_2\text{Na}$  :  $m/z$  141.0886 ( $[\text{M}+\text{Na}]^+$ ), found:  $m/z$  141.0883 ( $[\text{M}+\text{Na}]^+$ ).

$[\alpha]^{20}_{\text{D}}$  = + 18.1 (c 1.7,  $\text{CHCl}_3$ ) [Lit.,<sup>5</sup> + 15.2 (c 13.1, EtOH)].

The spectroscopic data are in agreement with those reported in the literature.<sup>5</sup>

### (5R)-5-Butyl-2,2,3,3,8,8,9,9-octamethyl-4,7-dioxa-3,8-disiladecane (**SI-23**)

To a solution of **23** (2.2 g, 19 mmol) in DMF (100 mL) were added *tert*-butyldimethylsilyl chloride (8.6 g, 57 mmol, 3 eq.), imidazole (3 g, 44 mmol, 2.3 eq.) and DMAP (450 mg, 3.7 mmol, 0.2 eq.). The reaction mixture was stirred at room temperature for 48 h and was then hydrolysed with water. The aqueous layer was extracted with a mixture of cyclohexane/dichloromethane (90:10). The combined organic phases were washed with water, brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (elution with cyclohexane/ethyl acetate 25:1) to give **SI-23** (5.85 g, 17 mmol, 89 %) as a colorless oil.

**NMR**  $^1\text{H}$  ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  3.68-3.63 (m, 1H), 3.52 (dd,  $J$  = 5.5, 9.9 Hz, 1H), 3.41 (dd,  $J$  = 6.3, 9.9 Hz, 1H), 1.58-1.41 (m, 1H), 1.39-1.25 (5H), 0.91 (t,  $J$  = 7.1 Hz, 3H), 0.90 (s, 9H), 0.89 (s, 9H), 0.06 (s, 6H), 0.05 (s, 6H).

**NMR**  $^{13}\text{C}$  ( $\text{CDCl}_3$ , 75 MHz)  $\delta$  73.2, 67.5, 37.3, 34.1, 26.0 (3C), 25.9 (3C), 22.9, 18.4, 18.2, 14.1, -4.2, -4.7, -5.3, -5.4.

$[\alpha]^{20}_{\text{D}}$  = + 13.9 (c 1.5,  $\text{CHCl}_3$ ).

**HRMS-ESI** calculated for  $\text{C}_{18}\text{H}_{43}\text{O}_2\text{Si}_2$  :  $m/z$  347.2796 ( $[\text{M}+\text{H}]^+$ ), found:  $m/z$  347.2788 ( $[\text{M}+\text{H}]^+$ ).

### (2R)-2-[(*tert*-Butyldimethylsilyl)oxy]hexan-1-ol (**SI-24**)

To a solution of **SI-23** (400 mg, 1.15 mmol) in THF (10 mL) were added acetic acid (0.3 mL) and TBAF (1.26 mL, 1.26 mmol, 1.1 eq.). The solution was stirred at room temperature for 3 h, before being hydrolyzed with an aqueous saturated solution of ammonium chloride. The aqueous phase was extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried over  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography eluting with cyclohexane/AcOEt (90:10) to give **SI-24** (130 mg, 0.56 mmol, 49 %) as a colorless oil.

$^1\text{H}$  **NMR** ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  3.73 (dddd ap. dq,  $J$  = 3.6, 6.3 Hz, 1 H), 3.57 (dd,  $J$  = 3.6, 11.0 Hz), 3.44 (dd,  $J$  = 5.4, 11.0 Hz), 1.81 (s large. 1H), 1.52-1.45 (2H), 1.35-1.22 (4H), 0.91-0.89 (12H), 0.06 (s, 6H).

$[\alpha]^{20}_{\text{D}}$  = + 14.5 (c 1.1,  $\text{CHCl}_3$ ).

#### **(2R)-2-[(*tert*-Butyldimethylsilyl)oxy]hexanal (SI-25)**

To a solution of **SI-24** (260 mg, 1.12 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) at 0 °C were added diacetate iodosobenzene (433 mg, 1.34 mmol, 1.2 eq.) and TEMPO (17.5 mg, 0.11 mmol, 0.1 eq.). The solution was stirred and allowed to warm up to room temperature. After 2.5 hour, water was added to the reaction mixture and the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic extracts were dried over MgSO<sub>4</sub>, filtered and concentrated to yield aldehyde **SI-25** (580 mg) which was used without further purification.

#### **Ethyl (2E,4R)-4-[(*tert*-butyldimethylsilyl)oxy]-2-methyloct-2-enoate (**24**)**

To a solution of **SI-25** in dichloromethane (8 mL) was added ethyl 2-(triphenyl-λ<sup>5</sup>-phosphoranylidene)propionate (607 g, 1.67 mmol, 1.5 eq.) at 0 °C during 10 min. The reaction mixture was heated under reflux during 24 h. After being concentrated under reduced pressure, the crude product was purified by flash chromatography eluting with cyclohexane/AcOEt (20:1) to give **24** (280 mg, 0.89 mmol, 79 %) as a colorless oil.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 6.64 (qd, *J* = 1.4, 8.5 Hz, 1H), 4.42 (ddd, *J* = 5.2, 7.4, 8.4 Hz, 1H), 4.20 (dq, *J* = 2.0, 7.1 Hz, 2H), 1.84 (d, *J* = 1.4 Hz, 3H), 1.63-1.25 (9H including 1.31 (t, *J* = 7.1 Hz, 3H)), 0.90 (t, *J* = 6.8 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 3H), 0.02 (s, 3H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz) δ 168.1, 145.0, 125.9, 69.6, 60.6, 37.0, 27.3, 25.8 (3C), 22.6, 18.2, 14.2, 14.0, 12.8, -4.4, -4.9.

[α]<sub>D</sub><sup>20</sup> = + 4.8 (c 0.6, CHCl<sub>3</sub>).

HRMS-ESI calculated for C<sub>17</sub>H<sub>35</sub>O<sub>3</sub>Si : *m/z* 315.2350 ([M+H]<sup>+</sup>), found: *m/z* 315.2349 ([M+H]<sup>+</sup>).

#### **(2E,4R)-4-[(*tert*-Butyldimethylsilyl)oxy]-2-methyloct-2-en-1-ol (SI-26)**

To a solution of **24** (272 mg, 0.86 mmol) in dichloromethane (4.5 mL) was added DIBAL-H (1.3 mL, 1.5 M in toluene, 2.2 eq.). The reaction mixture was stirred at 0 °C for 1 h and a saturated aqueous solution of Rochelle salts was added. After being stirred for 12 h, the aqueous layer was extracted three times with diethyl ether. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure to give **SI-26** as a colorless oil (235 mg, 0.86 mmol, 99 %).

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 5.37 (dd, *J* = 1.1, 8.6 Hz 1H), 4.33 (ddd, *J* = 5.6, 7.0, 8.5 Hz, 1H), 3.98 (s, 2H), 1.65 (d, *J* = 1.1 Hz, 3H), 1.56-1.49 (2H), 1.32-1.23 (4H), 0.86 (t, *J* = 6.8 Hz, 3H), 0.85 (s, 9H), 0.02 (s, 3H), -0.01 (s, 3H).

#### **(2E,4R)-4-[(*tert*-Butyldimethylsilyl)oxy]-2-methyloct-2-enal (SI-27)**

To a solution of **SI-26** (235 mg, 0.86 mmol) in dichloromethane (6 mL) was added activated MnO<sub>2</sub> (1.5 g, 17.2 mmol, 20 eq.). After being refluxed for 18 h the reaction mixture was filtered over a bed of Celite and washed with CH<sub>2</sub>Cl<sub>2</sub>. Solvent was removed under reduced pressure to give **SI-27** (215 mg, 0.79 mmol, 92%), directly engaged in the next step.

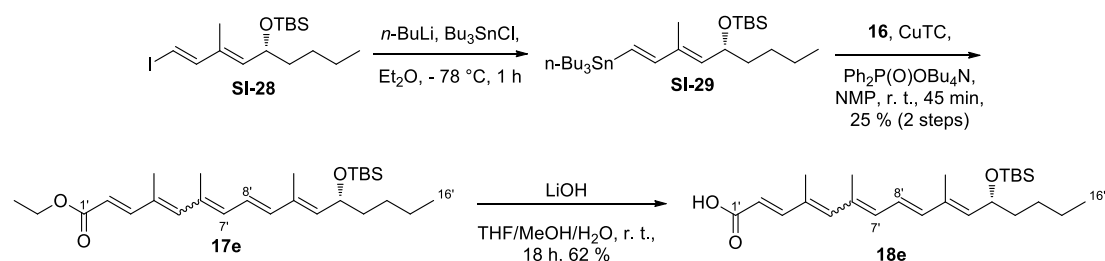
**<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)** δ 9.39 (s, 1H), 6.35 (dd, *J* = 1.3, 8.0 Hz, 1H), 4.55 (td, *J* = 5.3, 8.0 Hz, 1H), 1.72 (d, *J* = 1.3 Hz, 3H), 1.60 (m, 1H), 1.45 (m, 1H), 1.35-1.27 (4H), 0.87 (t, *J* = 6.9 Hz, 3H), 0.86 (s, 9H), 0.03 (s, 3H), -0.02 (s, 3H).

**(1*E*,3*E*)-(5*S*)-*tert*-Butyldimethylsilyloxy-1-iodo-3-methyl-nona-1,3-diene (SI-28)**

To a suspension of CrCl<sub>2</sub> (1 g, 7.96 mmol, 10 eq.) in THF (6 mL) was added dropwise a solution of **SI-27** (215 mg, 0.79 mmol) and CHI<sub>3</sub> (940 mg, 2.39 mmol, 3 eq.) in THF (5 mL). The reaction mixture was stirred at room temperature for 12 h before being diluted with diethyl ether. The aqueous phase was extracted three times, and the combined organic phases were washed with water and brine. After being dried over magnesium sulfate, filtered and concentrated under reduced pressure, the crude product was purified by flash chromatography eluting with cyclohexane/toluene (100:1) to give **SI-28** (210 mg, 0.53 mmol, 67 %) as a colorless oil.

**<sup>1</sup>H NMR (C<sub>6</sub>D<sub>6</sub>, 300 MHz)** δ 6.93 (d, *J* = 14.7 Hz, 1H), 5.93 (d, *J* = 14.7 Hz, 1H), 5.30 (d, *J* = 8.7 Hz, 1H), 4.34 (ddd, *J* = 5.3, 7.1, 8.7 Hz, 1H), 1.58 (m, 1H), 1.35 (s, 3H), 1.42-1.10 (5H), 0.97 (s, 9H), 0.87 (t, *J* = 6.9 Hz, 3H), 0.05 (s, 3H), 0.01 (s, 3H).

**<sup>13</sup>C NMR (C<sub>6</sub>D<sub>6</sub>, 75 MHz)** δ 149.3, 138.0, 133.1, 75.7, 69.4, 38.3, 27.7, 26.0 (3C), 23.0, 18.4, 14.3, 12.2, -4.1, -4.7.



**(1*E*,3*E*)-(5*S*)-*tert*-Butyldimethylsilyloxy-1-tributylstannyl-3-methyl-nona-1,3-diene (SI-29)**

To a solution of **SI-28** (160 mg, 0.41 mmol) in Et<sub>2</sub>O (2.1 mL) at - 78 °C was added *n*-BuLi (435 μL, 1.6 M in hexane, 0.70 mmol, 1.7 eq.) and the reaction mixture was stirred for 20 min. Bu<sub>3</sub>SnCl (237 μL, 0.87 mmol, 2.1 eq.) was then added to the solution and the reaction mixture was allowed to warm to room temperature for 1 h. The reaction mixture was hydrolyzed with saturated aqueous NaHCO<sub>3</sub> solution. The aqueous phase was extracted twice with Et<sub>2</sub>O. The combined organic phases were washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude **SI-29** was used without further purification.

**Ethyl (2*E*,4*E*,6*E*,8*E*,10*E*,12*R*)-12-[(*tert*-butyldimethylsilyl)oxy]-4,6,10-trimethylhexadeca-2,4,6,8,10-pentaenoate (17e)**

To a solution of **SI-29** and tetrabutylammonium diphenylphosphate (263 mg, 0.57 mmol) in NMP (2.3 mL) was added 0.1 mL of the following solution: 260 mg of **16** (0.85 mmol, 2.1 eq.) in NMP (1.6 mL). After the addition of CuTc (160 mg, 0.85 mmol, 2 eq.), the remaining solution of **16** (1.5 mL) was added dropwise for 5 min. The reaction mixture was stirred at room temperature for 40 min, and then diluted with Et<sub>2</sub>O. The mixture was filtered through a pad of neutral alumina. The filtrate was then washed

with water, with brine, dried over  $\text{MgSO}_4$ , filtered, and concentrated under reduced pressure. The crude product was purified by preparative TLC eluting with heptane/ethyl acetate 90:10 to give **17e** (45 mg, 0.1 mmol, 25 % over 2 steps) as a yellow oil. A (4'E)/(4'Z) = 83:17 mixture could be detected by  $^1\text{H}$  analysis.

**$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz, 4'E isomer)**  $\delta$  7.36 (d,  $J$  = 15.6 Hz, 1H), 6.53 (dd,  $J$  = 10.8, 15.0 Hz, 1H), 6.34 (s, 1H), 6.33 (d,  $J$  = 15.1 Hz, 1H), 6.25 (d,  $J$  = 10.5 Hz, 1H), 5.86 (d,  $J$  = 15.6 Hz, 1H), 5.51 (d,  $J$  = 8.5 Hz, 1H), 4.45 (m, 1H), 4.21 (q,  $J$  = 7.1 Hz, 2H), 2.04 (s, 3H), 2.01 (s, 3H), 1.96-1.92 (2H), 1.85 (s, 3H), 1.62 (m, 1H), 1.41 (m, 1H), 1.31 (t,  $J$  = 7.1 Hz, 3H), 1.30-1.27 (2H), 0.89 (s, 3H), 0.87 (s, 9H), 0.03 (s, 3H), -0.01 (s, 3H).

**HRMS-ESI** calculated for  $\text{C}_{27}\text{H}_{46}\text{O}_3\text{NaSi}$  :  $m/z$  469.3108 ( $[\text{M}+\text{Na}]^+$ ), found :  $m/z$  469.3125 ( $[\text{M}+\text{Na}]^+$ ).

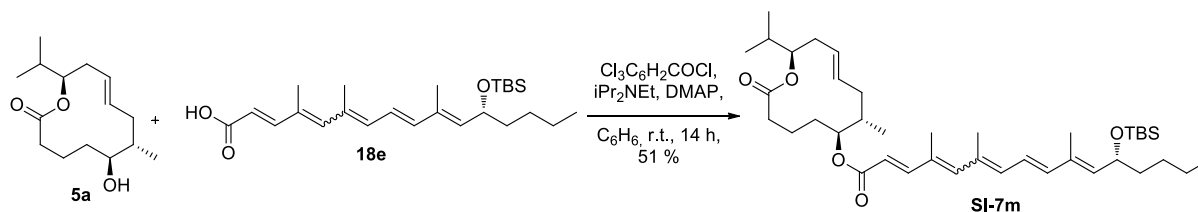
**(2E,4E,6E,8E,10E,12R)-12-[(tert-butyldimethylsilyl)oxy]-4,6,10-trimethylhexadeca-2,4,6,8,10-pentaenoic acid (18e)**

To a solution of **17e** (45 mg, 0.1 mmol) in a mixture of THF/MeOH/ $\text{H}_2\text{O}$  (1.7:0.5:0.5) was added a solution of LiOH (47 mg, 1 mmol, 10 eq.) in  $\text{H}_2\text{O}$  (1mL). The reaction mixture was stirred at room temperature for 18 h before being acidified with a saturated aqueous solution of  $\text{NH}_4\text{Cl}$ . The aqueous phase was extracted with ethyl acetate, and the combined organic phases were washed with brine and dried over  $\text{MgSO}_4$ . After being filtered and concentrated under reduced pressure, the crude product was purified by preparative TLC (elution with heptane/ethyl acetate 70:30, to give **18e** (26 mg, 0.06 mmol, 62 %) as a yellow oil. A (4'E)/(4'Z) = 79:21 mixture could be detected by  $^1\text{H}$  analysis.

**$^1\text{H}$  NMR (Acetone- $d_6$ , 300 MHz, 4'E isomer)**  $\delta$  7.32 (d,  $J$  = 15.5 Hz, 1H), 6.51 (dd,  $J$  = 10.8, 15.0 Hz, 1H), 6.37 (d,  $J$  = 15.0 Hz, 1H), 6.36 (s, 1H), 6.28 (d,  $J$  = 10.8 Hz, 1H), 5.84 (d,  $J$  = 15.5 Hz, 1H), 5.47 (d,  $J$  = 8.4 Hz, 1H), 4.51 (m, 1H), 2.05 (s, 3H), 2.03 (s, 3H), 1.82 (s, 3H), 1.58-1.52 (2H), 1.36-1.24 (4H), 0.91 (s, 3H), 0.83 (s, 9H), 0.01 (s, 3H), -0.04 (s, 3H).

**$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz, 4'E isomer)**  $\delta$  172.7, 153.2, 145.0, 140.0, 138.8, 135.6, 133.9, 132.5, 123.5, 115.0, 69.7, 38.0, 27.5, 25.8 (3C), 25.6, 22.7, 18.2, 17.0, 14.2, 12.9, -4.3, -4.8.

**HRMS-ESI** calculated for  $\text{C}_{25}\text{H}_{41}\text{O}_3\text{Si}$  :  $m/z$  417.2830 ( $[\text{M}-\text{H}]^-$ ), found :  $m/z$  417.2836 ( $[\text{M}-\text{H}]^-$ ).



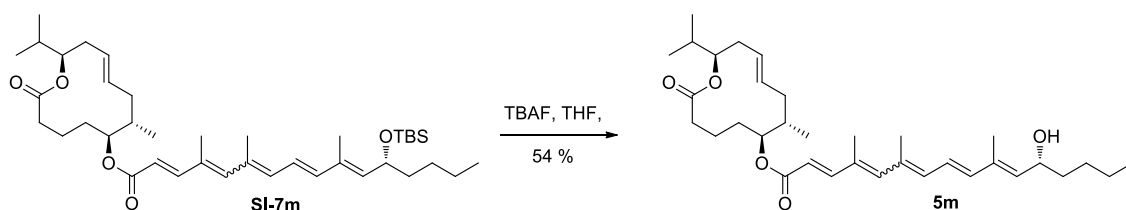
**(6S,7S,9E,12R)-7-Methyl-2-oxo-12-(propan-2-yl)-1-oxacyclododec-9-en-6-yl (2E,4E,6E,8E,10E,12R)-12-[(tert-butyldimethylsilyl)oxy]-4,6,10-trimethylhexadeca-2,4,6,8,10-pentaenoate (SI-7m)**

To a solution of **18e** (38 mg, 0.089 mmol) in benzene (1.1 mL) were added diisopropylethyl amine (72  $\mu\text{L}$ , 0.39 mmol, 6.6 eq.), 2,4,6-trichlorobenzoyl chloride (36  $\mu\text{L}$ , 0.22 mmol, 3.7 eq.), and DMAP (72 mg). The reaction mixture was stirred at room temperature for 15 min and **5a** (12mg, 0.047 mmol) was added. After being stirred at room temperature for 14 h, an aqueous saturated solution of sodium hydrogenocarbonate was added to the reaction mixture. The aqueous layer was extracted three times with benzene. The combined organic layers were washed with brine, dried over  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. The crude product was purified on preparative TLC eluting with benzene/heptane 60:40 to give **SI-7m** (16 mg, 0.024 mmol, 51%) as a yellow oil. In contrast to the

previously described analogues, several other isomers are clearly apparent, thus resulting in complicated  $^1\text{H}$  NMR spectra. For the sake of clarity, only the major isomer is described. A (4'E)/(4'Z) = 71:29 mixture could be detected by  $^1\text{H}$  analysis.

**$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)**  $\delta$  7.95 (d,  $J$  = 15.5 Hz, 1H, Z isomer), 7.37 (d,  $J$  = 15.5 Hz, 1H, E isomer), 6.51 (dd,  $J$  = 14.8, 11.2 Hz, 1H), 6.37 (d,  $J$  = 14.8 Hz, 1H), 6.36 (s, 1H), 6.28 (d,  $J$  = 11.2 Hz, 1H), 5.85 (d,  $J$  = 15.5 Hz, 1H), 5.51 (m, 1H), 5.45 (m, 1H), 5.27 (m, 1H), 4.81-4.70 (2H), 4.45 (m, 1H), 2.49 (m, 1H), 2.30 (m, 1H), 2.15-2.06 (2H), 2.04 (s, 3H), 2.03 (s, 3H), 1.98-1.96 (4H), 1.85 (s, 3H), 1.87-1.61 (6H), 1.34-1.32 (4H), 0.95 (s, 3H), 0.93 (s, 3H), 0.92 (s, 3H), 0.90 (s, 3H), 0.87 (s, 9H), 0.07 (s, 3H), 0.03 (s, 3H).

**HRMS-ESI** calculated for  $\text{C}_{40}\text{H}_{66}\text{O}_5\text{SiNa}$  :  $m/z$  677.4571 ( $[\text{M}+\text{Na}]^+$ ), found:  $m/z$  677.4570 ( $[\text{M}+\text{Na}]^+$ ).



**(6S,7S,9E,12R)-7-Methyl-2-oxo-12-(propan-2-yl)-1-oxacyclododec-9-en-6-yl (2E,4E,6E,8E,10E,12S)-12-hydroxy-4,6,10-trimethylhexadeca-2,4,6,8,10-pentaenoate (5m)**

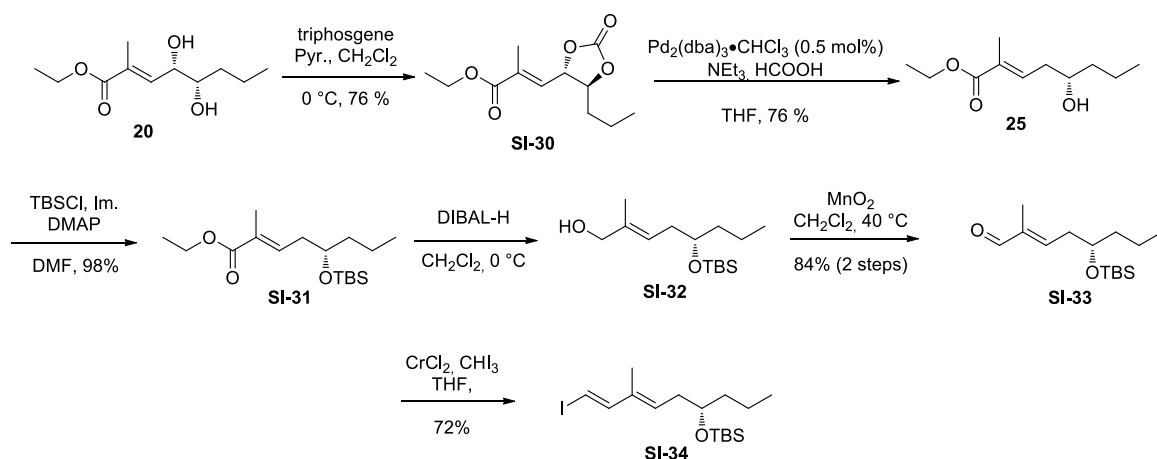
To a solution of **SI-7m** (16 mg, 0.024 mmol) in THF (0.2 mL) was added TBAF (0.2 mmol, 1M in THF, 10 eq.). The solution was stirred at room temperature for 4 h.  $\text{CaCO}_3$  (50 mg), Dowex 50WX8-400 (150mg) and MeOH (0.4 mL) were added and the reaction mixture was stirred for 1 h. After being filtered and concentrated under reduced pressure, the crude product was purified by TLC preparative ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$  90:10) to give **5m** (7 mg, 0.013 mmol, 54 %). In contrast to the previously described analogues, several other isomers are clearly apparent, thus resulting in complicated  $^1\text{H}$  NMR spectra. For the sake of clarity, only the major isomer is described. A (4'E)/(4'Z) = 54:46 mixture could be detected by  $^1\text{H}$  analysis.

**$^1\text{H}$  NMR (Acetone- $d_6$ , 300 MHz)**  $\delta$  7.93 (d,  $J$  = 15.6 Hz, 1H, Z isomer), 7.37 (d,  $J$  = 15.5 Hz, 1H, E isomer), 6.63 (dd,  $J$  = 11.3, 15.0 Hz, 1H), 6.47 (s, 1H), 6.36 (d,  $J$  = 15.0 Hz, 1H), 6.17 (d,  $J$  = 11.3 Hz, 1H), 5.89 (d,  $J$  = 15.5 Hz, 1H), 5.58-5.50 (2H), 5.29 (m, 1H), 4.79-4.66 (2H), 4.46 (m, 1H), 3.60 (m, 1H), 2.49 (m, 1H), 2.32 (m, 1H), 2.12-2.08 (2H), 2.06 (s, 3H), 1.97 (s, 3H), 1.95-1.92 (2H), 1.90 (s, 3H), 1.80-1.75 (4H), 1.70-1.62 (4H), 1.54-1.49 (4H), 1.28 (s, 3H), 0.92 (s, 3H), 0.90 (s, 3H), 0.87 (s, 3H).

**$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz)**  $\delta$  173.9, 167.8, 152.2, 145.4, 141.6, 137.3, 136.5, 136.0, 134.1, 133.0, 128.1, 125.7, 120.6, 118.4, 80.2, 77.3, 69.4, 68.3, 39.8, 39.4, 37.9, 37.1, 36.1, 34.1, 28.5, 24.4, 22.0, 21.6, 20.9, 19.9, 19.4, 18.1, 15.3, 14.0.

**HRMS-ESI** calculated for  $\text{C}_{34}\text{H}_{52}\text{O}_5\text{Na}$  :  $m/z$  563.3707 ( $[\text{M}+\text{Na}]^+$ ), found:  $m/z$  563.3700 ( $[\text{M}+\text{Na}]^+$ ).





### (*E*)-Ethyl 2-methyl-3-((4*S*,5*S*)-2-oxo-5-propyl-1,3-dioxolan-4-yl)acrylate (SI-30)

To a stirred solution of **20**<sup>1</sup> (1 g, 4.62 mmol) and pyridine (1.5 mL) in dichloromethane (7.2 mL) at 0 °C, was added slowly a solution of triphosgene (686 mg, 2.31 mmol, 0.5 eq., 1.7 M in dichloromethane). The resulting mixture was stirred at 0 °C for 3 h. The reaction mixture was then hydrolyzed at 0 °C with a saturated aqueous NH<sub>4</sub>Cl solution and the aqueous layer was extracted three times with Et<sub>2</sub>O. The combined organic extracts were washed with a saturated aqueous NaHCO<sub>3</sub> solution, brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude product was purified by chromatography (cyclohexane/EtOAc 20:1) to afford **SI-30** (851 mg, 3.51 mmol, 76 %) as colorless oil.

**<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)** δ 6.66 (dq, *J* = 8.9, 1.5 Hz, 1H), 5.02 (dd, *J* = 8.9, 7.4 Hz, 1H), 4.39 (ddd, *J* = 7.9, 7.4, 4.4 Hz, 1H), 4.25 (qd, *J* = 7.1, 0.8 Hz, 2H), 1.97 (d, *J* = 1.5 Hz, 3H), 1.87-1.40 (4H), 1.33 (t, *J* = 7.1 Hz, 3H), 0.99 (t, *J* = 7.2 Hz, 3H).

**<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)** δ 166.4, 154.0, 135.1, 132.6, 81.7, 77.9, 61.4, 35.0, 18.1, 14.1, 13.6, 13.3.

**HRMS-ESI** calculated for C<sub>12</sub>H<sub>22</sub>NO<sub>5</sub> : *m/z* 260.1492 ([M+NH<sub>4</sub>]<sup>+</sup>), found : *m/z* 260.1494 ([M+NH<sub>4</sub>]<sup>+</sup>).

[α]<sub>D</sub><sup>20</sup> = - 87.4 (c 2.1, CHCl<sub>3</sub>).

### (*S,E*)-Ethyl 5-hydroxy-2-methyloct-2-enoate (**25**)

To a stirred solution of **SI-30** (550 mg, 2.27 mmol) in dry THF (5.1 mL) were added Pd<sub>2</sub>(dba)<sub>3</sub>•CHCl<sub>3</sub> (11.7 mg, 11.35 μmol, 0.5 mol%), triethylamine (0.61 mL, 4.54 mmol, 2 eq.) and formic acid (171 μL, 4.54 mmol, 2 eq.). The reaction mixture was stirred for 72 h at room temperature, then diluted with Et<sub>2</sub>O, hydrolyzed with water and the aqueous layer was extracted. The combined organic extracts were washed with a saturated aqueous Na<sub>2</sub>CO<sub>3</sub> solution, brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude product was purified by chromatography (cyclohexane/EtOAc 9:1) to give **25** (347 mg, 1.73 mmol, 76 %) as a colorless oil.

**<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)** δ 6.83 (tq, *J* = 7.6, 1.4 Hz, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.79 (m, 1H), 2.36 (m, 2H), 1.87 (d, *J* = 1.4 Hz, 3H), 1.54-1.38 (4H), 1.31 (t, *J* = 7.1 Hz, 3H), 0.95 (t, *J* = 7.0 Hz, 3H).

**<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)** δ 168.0, 137.9, 130.0, 70.8, 60.5, 39.3, 36.7, 18.8, 14.3, 14.0, 12.6.

**HRMS-ESI** calculated for C<sub>11</sub>H<sub>19</sub>O<sub>2</sub> : *m/z* 183.1379 ([M+H]<sup>+</sup>+[- H<sub>2</sub>O]), found : *m/z* 183.1381 ([M+H]<sup>+</sup>+[- H<sub>2</sub>O]).

[α]<sub>D</sub><sup>20</sup> = - 5.5 (c 0.6, CHCl<sub>3</sub>)

#### **(*S,E*)-Ethyl 5-((*tert*-butyldimethylsilyl)oxy)-2-methyloct-2-enoate (SI-31)**

To a stirred solution of **24** (1.0 g, 5.2 mmol) in dry DMF (33 mL), under a nitrogen atmosphere, were added *tert*-butyldimethylsilyl chloride (4.70 g, 31.2 mmol, 6 eq.), imidazole (1.41 g, 20.7 mmol, 4 eq.) and DMAP (317 mg, 2.59 mmol, 0.5 eq.). The reaction mixture was stirred at room temperature for 48 h. The resulting solution was hydrolyzed with water and the aqueous layer was extracted three times with a mixture of cyclohexane and DCM (9:1). The combined organic extracts were washed with water, brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude product was purified by chromatography (cyclohexane/EtOAc 20:1) to give **SI-31** (1.6 g, 5.09 mmol, 98 %) as a colorless oil.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 6.83 (tq, *J* = 7.3, 1.5 Hz, 1H), 4.20 (q, *J* = 7.2 Hz, 2H), 3.78 (m, 1H), 2.32 (m, 2H), 1.84 (d, *J* = 1.5 Hz, 3H), 1.47-1.32 (4H), 1.30 (t, *J* = 7.3 Hz, 3H), 0.91-0.87 (12H including 0.89 (t, *J* = 7.1 Hz, 3H), 0.89 (s, 9H)), 0.05 (s, 6H).

#### **(*S,E*)-5-((*tert*-Butyldimethylsilyl)oxy)-2-methyloct-2-en-1-ol (SI-32)**

To a stirred solution of **SI-31** (1.6 g, 5.1 mmol) in dry DCM (22 mL), under a nitrogen atmosphere, was added DIBAL-H (7.5 mL, 1.5 M in toluene, 11.2 mmol, 2.2 eq.) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h. Saturated aqueous Rochelle salt solution was then added, and the resulting mixture warmed to room temperature and vigorously stirred overnight. The aqueous layer was extracted with Et<sub>2</sub>O and the combined organic extracts were washed with water, brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure to give **SI-32** as a pale yellow oil which was used in the next step without further purification.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 5.46 (tq, *J* = 7.3, 1.4 Hz, 1H), 4.03 (s, 2H), 3.69 (m, 1H), 2.20 (m, 2H), 1.68 (d, *J* = 1.4 Hz, 3H), 1.43-1.27 (4H), 0.93-0.88 (12H including 0.90 (s, 9H), 0.90 (t, *J* = 7.1 Hz, 3H)), 0.05 (s, 6H).

#### **(*S,E*)-5-((*tert*-Butyldimethylsilyl)oxy)-2-methyloct-2-enal (SI-33)**

To a stirred solution of crude alcohol **SI-32** in dry DCM (40 mL), under a nitrogen atmosphere, was added MnO<sub>2</sub> (8.24 g, 94.8 mmol, 20 eq.) at room temperature. The reaction mixture was warmed to 40 °C and vigorously stirred for 48 h. The resulting mixture was cooled to room temperature and filtered through celite with DCM. The solvent was then removed under reduced pressure to give **SI-33** (1.17 g, 4.3 mmol, 84 % over two steps) as a pale yellow oil which was used in the next step without further purification.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 9.43 (s, 1H), 6.61 (tq, *J* = 7.3, 1.3 Hz, 1H), 3.87 (m, 1H), 2.51 (m, 2H), 1.76 (d, *J* = 1.4 Hz, 3H), 1.51-1.27 (4H), 0.92-0.87 (12H including 0.91 (t, *J* = 7.1 Hz, 3H), 0.89 (s, 9H)), 0.07 (s, 3H), 0.05 (s, 3H).

#### **(1*E*,3*E*)-(6*S*)-*tert*-Butyldimethylsilyloxy-1-iodo-3-methyl-nona-1,3-diene (SI-34)**

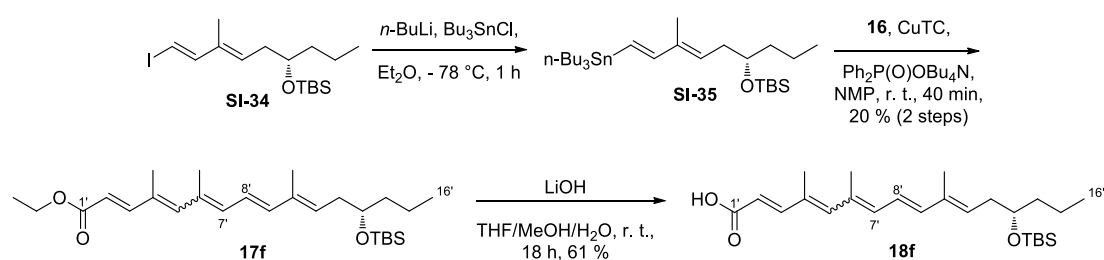
To a stirred solution of CrCl<sub>2</sub> (1.5 g, 12.2 mmol, 10 eq.) in dry THF (9.4 mL), under a nitrogen atmosphere, was added a solution of **SI-33** (331 mg, 1.22 mmol) and CHI<sub>3</sub> (1.45 g, 3.67 mmol, 3 eq.) in dry THF (7.5 mL) dropwise. The reaction mixture was stirred at room temperature for 12 h. The

resulting mixture was hydrolyzed with water and diluted with Et<sub>2</sub>O. The aqueous layer was extracted three times with Et<sub>2</sub>O and the combined organic extracts were washed with water, brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude product was then purified by chromatography (cyclohexane/toluene 100:1) to afford **SI-34** (350 g, 0.88 mmol, 72 %) as a pale yellow oil.

<sup>1</sup>H NMR (C<sub>6</sub>D<sub>6</sub>, 300 MHz) δ 7.06 (d, *J* = 14.5 Hz, 1H), 5.93 (d, *J* = 14.5 Hz, 1H), 5.34 (t, *J* = 7.5 Hz, 1H), 3.57 (m, 1H), 2.12 (m, 2H), 1.4 (s, 3H), 1.38-1.25 (4H), 0.97 (s, 9H), 0.87 (t, *J* = 7.1 Hz, 3H), 0.05 (s, 3H), 0.02 (s, 3H).

<sup>13</sup>C NMR (C<sub>6</sub>D<sub>6</sub>, 100 MHz) δ 150.2, 136.2, 131.2, 74.3, 72.3, 40.0, 36.8, 26.4 (3C), 19.4, 18.6, 14.8, 12.3, -3.9, -4.1.

[α]<sub>D</sub><sup>20</sup> = - 8.8 (c 1.1, CHCl<sub>3</sub>).



#### (1*E*,3*E*)-(6*S*)-*tert*-Butyldimethylsilyloxy-1-tributylstannyl-3-methyl-nona-1,3-diene (SI-35)

To a stirred solution of **SI-34** (300 mg, 0.76 mmol) in dry Et<sub>2</sub>O (4 mL), under a nitrogen atmosphere, was added *n*-BuLi (0.45 mL, 2.5 M in hexane, 1.14 mmol, 1.5 eq.) at -78 °C. The reaction mixture was stirred for 20 min at -78 °C and Bu<sub>3</sub>SnCl (0.33 mL, 1.14 mmol, 1.5 eq.) was added. The resulting solution was stirred at -78 °C for another 20 min and allowed to warm to room temperature for 1 h. Saturated aqueous NaHCO<sub>3</sub> solution was then added and the aqueous layer was extracted three times with Et<sub>2</sub>O. The combined organic extracts were washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude **SI-35** was used in the next step without further purification.

#### (*S*,2*E*,4*E*,6*E*,8*E*,10*E*)-Ethyl-13-((*tert*-butyldimethylsilyl)oxy)-4,6,10-trimethylhexadeca-2,4,6,8,10-pentaenoate (**17f**)

To a stirred solution of crude **SI-35** and tetra-*n*-butylammonium diphenylphosphinate (810 mg, 1.75 mmol, 2.3 eq.) in dry NMP (5 mL), under a nitrogen atmosphere, was added 0.2 mL of a solution of **16** in NMP (466 mg, 1.52 mmol, 2 eq., 3 mL). After addition of CuTC (290 mg, 1.52 mmol, 2 eq.), the rest of the **16** solution was added dropwise and the resulting mixture was stirred at room temperature for 40 min. The reaction mixture was then diluted with Et<sub>2</sub>O and filtered through neutral alumina oxide. The filtrate was washed with water, brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude product was then purified by preparative TLC (cyclohexane/EtOAc 9:1) to afford **17f** (69 mg, 0.15 mmol, 20 % for two steps) as a yellow oil. NMR analysis showed the presence of mixture of isomers 4'*E*/4'*Z* = 81:19, as well as other isomers.

**<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz, 4'E isomer)** δ 7.95 (d, *J* = 15.6 Hz, 1H, *Z* isomer), 7.38 (d, *J* = 15.6 Hz, 1H, *E* isomer), 6.50 (dd, *J* = 15.1, 11.3 Hz, 1H), 6.38 (d, *J* = 15.6 Hz, 1H), 6.36 (s, 1H), 6.26 (d, *J* = 11.3 Hz, 1H), 5.85 (d, *J* = 15.5 Hz, 1H), 5.64 (m, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 3.72 (m, 1H), 2.34 (m, 2H), 2.05 (s, 3H), 2.03 (s, 3H), 1.82 (s, 3H), 1.37-1.22 (7H including 1.31 (t, *J* = 7.1 Hz, 3H)), 0.92-0.87 (12H including 0.90 (t, *J* = 6.8 Hz, 3H), 0.89 (s, 9H)), 0.05 (s, 6H).

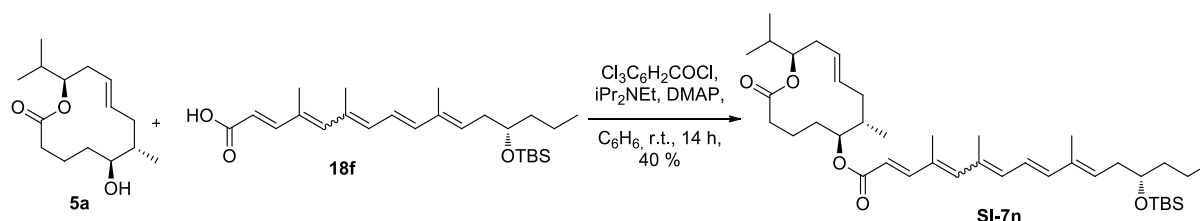
**(*S*,2*E*,4*E*,6*E*,8*E*,10*E*)-13-((*tert*-Butyldimethylsilyl)oxy)-4,6,10-trimethylhexadeca-2,4,6,8,10-pentaenoic acid (**18f**)**

To a stirred solution of **17f** (69 mg, 0.15 mmol) in a mixture THF/MeOH/H<sub>2</sub>O (3.7/1/1 mL) was added LiOH (37 mg, 1.56 mmol, 10 eq.). The resulting mixture was stirred at room temperature for 18 h. After addition of saturated aqueous NH<sub>4</sub>Cl solution, the mixture was extracted three times with EtOAc and the combined organic extracts were washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude material was purified by preparative TLC (cyclohexane/EtOAc 7:3) to afford **18f** (40 mg, 95.63 μmol, 61 %) as a yellow oil. NMR analysis showed the presence of mixture of isomers 4'E/4'Z = 74:26, as well as two other isomers.

**<sup>1</sup>H NMR (d<sub>6</sub>-Acetone, 300 MHz, 4'E isomer)** δ 7.93 (d, *J* = 15.5 Hz, 1H, *Z* isomer), 7.35 (d, *J* = 15.5 Hz, 1H, *E* isomer), 6.65 (dd, *J* = 15.3, 11.2 Hz, 1H), 6.51-6.17 (3H including 6.46 (d, *J* = 14.8 Hz, 1H), 6.45 (s, 1H), 6.36 (d, *J* = 11.0 Hz, 1H)), 5.86 (d, *J* = 15.6 Hz, 1H), 5.68 (m, 1H), 3.82 (m, 1H), 2.36 (m, 2H), 2.08-1.84 (9H including 2.08 (s, 3H), 1.96 (s, 3H)), 1.47-1.29 (4H), 0.92-0.88 (12H including 0.89 (s, 9H)), 0.07 (s, 6H).

**<sup>13</sup>C NMR (d<sub>6</sub>-Acetone, 100 MHz, 4'E isomer)** δ 168.3, 151.8, 144.5, 141.0, 139.0, 136.7, 136.6, 132.6, 132.2, 123.6, 117.0, 72.8, 40.4, 37.3, 26.3 (3C), 19.4, 18.2, 17.2, 14.6, 14.4, 12.9, -4.1, -4.3.

**HRMS-ESI** calculated for C<sub>25</sub>H<sub>42</sub>O<sub>3</sub>NaSi : *m/z* 441.2795 ([M+Na]<sup>+</sup>), found : *m/z* 441.2807 ([M+Na]<sup>+</sup>).

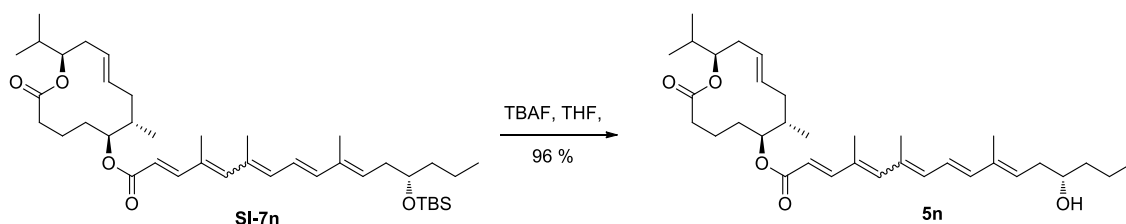


**(6*S*,7*S*,9*E*,12*R*)-7-Methyl-2-oxo-12-(propan-2-yl)-1-oxacyclododec-9-en-6-yl (2*E*,4*E*,6*E*,8*E*,10*E*,13*S*)-13-((*tert*-butyldimethylsilyl)oxy)-4,6,10-trimethylhexadeca-2,4,6,8,10-pentaenoate (**SI-7n**)**

To a solution of **18f** (17 mg, 0.04 mmol) in benzene (0.8 mL) were added diisopropylethyl amine (33 μL, 0.18 mmol, 5.6 eq.), 2,4,6-trichlorobenzoyl chloride (17 μL, 0.09 mmol, 3 eq.), and DMAP (33 mg). The reaction mixture was stirred at room temperature for 15 min and **5a** (7 mg, 0.03 mmol) was added. After being stirred at room temperature for 14 h, an aqueous saturated solution of sodium hydrogenocarbonate was added to the reaction mixture. The aqueous layer was extracted three times with benzene. The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude product was purified on preparative TLC eluting with heptane/ethyl acetate 70:30 to give **SI-7n** (7 mg, 0.011 mmol, 40 %) as a yellow oil. Compound **SI-7n**

exists as a mixture of three isomers in a 32:20:48 ratio and a few diagnostic chemical shifts of the first (32 %) and third (48 %) isomers could be identified in proton NMR.

**<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)** δ 7.94 (d, *J* = 15.5 Hz, 1H, diagnostic chemical shift of the first isomer), 7.42 (d, *J* = 15.5 Hz, 1H), 7.36 (d, *J* = 15.8 Hz, 1H, diagnostic chemical shift of the third isomer), 6.51 (dd, *J* = 14.8, 11.2 Hz, 1H), 6.37 (d, *J* = 14.8 Hz, 1H), 6.36 (s, 1H), 6.28 (d, *J* = 11.2 Hz, 1H), 5.86 (d, *J* = 15.5 Hz, 1H), 5.59 (m, 1H), 5.51 (m, 1H), 5.30 (m, 1H), 4.83-4.74 (2H), 3.70 (m, 1H), 2.49 (m, 1H), 2.30 (m, 1H), 2.15-2.06 (2H), 2.06 (s, 3H), 2.03 (s, 3H), 1.95 (s, 3H), 1.81 (s, 3H), 1.87-1.61 (10H), 1.39-1.36 (4H), 0.95 (s, 3H), 0.93 (s, 3H), 0.92 (s, 3H), 0.88 (s, 9H), 0.04 (s, 6H).



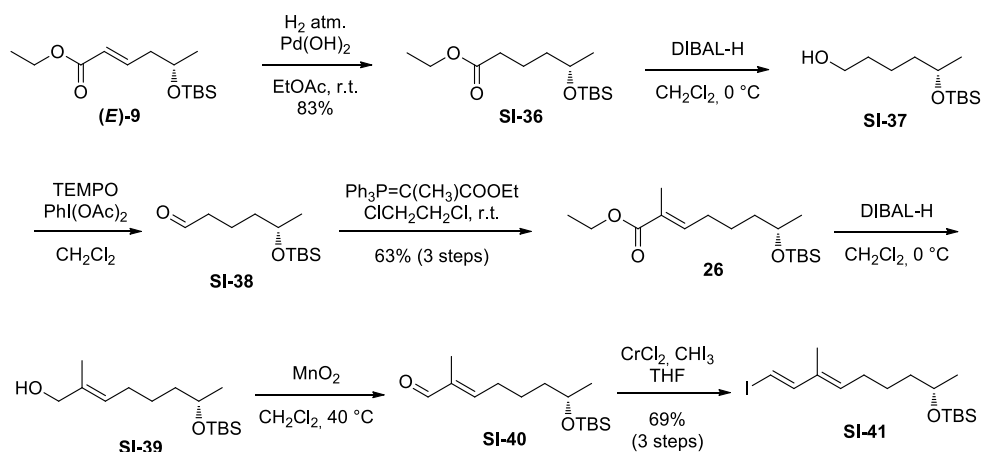
**(6*S*,7*S*,9*E*,12*R*)-7-Methyl-2-oxo-12-(propan-2-yl)-1-oxacyclododec-9-en-6-yl (2*E*,4*E*,6*E*,8*E*,10*E*,13*S*)-13-hydroxy-4,6,10-trimethylhexadeca-2,4,6,8,10-pentaenoate (5n)**

To a solution of **SI-7n** (7 mg, 0.01 mmol) in THF (0.2 mL) was added TBAF (0.04 mmol, 1M in THF, 4 eq.). The solution was stirred at room temperature for 4 h. CaCO<sub>3</sub> (50 mg), Dowex 50WX8-400 (150 mg) and MeOH (0.4 mL) were added and the reaction mixture was stirred for 1 h. After being filtered and concentrated under reduced pressure, the crude product was purified by TLC preparative (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 90:10) to give **5n** (5 mg, 0.009 mmol, 96%). Compound **5n** exists as a mixture of three isomers in a 44:25:31 ratio and a few diagnostic chemical shifts of the first (44%) and third (31%) isomers could be identified in proton NMR.

**<sup>1</sup>H NMR (Acetone-d<sub>6</sub>, 400 MHz)** δ 7.93 (d, *J* = 15.8 Hz, 1H, diagnostic chemical shift of the first isomer), 7.44 (d, *J* = 15.5 Hz, 1H), 7.37 (d, *J* = 15.6 Hz, 1H, diagnostic chemical shift of the third isomer), 6.63 (dd, *J* = 11.1, 15.0 Hz, 1H), 6.47 (s, 1H), 6.36 (d, *J* = 15.0 Hz, 1H), 6.17 (d, *J* = 11.1 Hz, 1H), 5.89 (d, *J* = 15.5 Hz, 1H), 5.74 (m, 1H), 5.50 (m, 1H), 5.30 (m, 1H), 4.78-4.67 (2H), 3.68-3.65 (2H), 2.50 (m, 1H), 2.32 (m, 1H), 2.12-2.08 (2H), 2.06 (s, 3H), 1.97 (s, 3H), 1.95-1.92 (2H), 1.90 (s, 3H), 1.80-1.75 (4H), 1.70-1.62 (4H), 1.54-1.49 (4H), 1.19 (s, 3H), 0.92 (s, 3H), 0.90 (s, 3H), 0.87 (s, 3H).

**<sup>13</sup>C NMR (Acetone-d<sub>6</sub>, 100 MHz)** δ 173.9, 167.8, 152.3, 144.1, 141.7, 137.7, 136.5, 133.9, 132.8, 128.0, 126.8, 125.4, 120.4, 118.1, 80.2, 77.3, 77.2, 41.3, 39.7, 39.6, 38.8, 37.9, 37.0, 36.1, 34.1, 22.0, 21.6, 20.9, 20.6, 19.9, 19.4, 18.6, 15.5, 13.8.

**HRMS-ESI** calculated for C<sub>34</sub>H<sub>52</sub>O<sub>5</sub>Na : *m/z* 563.3707 ([M+Na]<sup>+</sup>), found: *m/z* 563.3704 ([M+Na]<sup>+</sup>).



### (S)-Ethyl 5-((*tert*-butyldimethylsilyl)oxy)hexanoate (SI-36)

To a stirred solution of (*E*)-**9**<sup>3</sup> (1.89 g, 6.94 mmol) in EtOAc (130 mL, 0.05 M), was added Pd(OH)<sub>2</sub>. The round-bottom flask was evacuated and then refilled with H<sub>2</sub> three times and the reaction mixture was stirred at room temperature for 12 h. The crude mixture was then filtered through celite with EtOAc. The solvent was removed under reduced pressure. The crude product was then purified by chromatography (cyclohexane/EtOAc 95:5) to afford **SI-36** (1.58 g, 5.76 mmol, 83 %) as a colorless oil.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  4.13 (q, *J* = 7.1 Hz, 2H), 3.80 (tq ap. sextet, *J* = 6.1 Hz, 1H), 2.30 (t, *J* = 7.4 Hz, 2H), 1.77-1.56 (2H), 1.50-1.39 (2H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.13 (d, *J* = 6.1 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 6H).

### (S)-5-((*tert*-Butyldimethylsilyl)oxy)hexan-1-ol (SI-37)

To a stirred solution of **SI-36** (1.58 g, 5.76 mmol) in dry DCM (35 mL), under a nitrogen atmosphere, was added DIBAL-H (8.45 mL, 1.5 M in toluene, 12.7 mmol, 2.2 eq.) at 0 °C. The reaction mixture was stirred at 0 °C for 3 h. Saturated aqueous Rochelle salt solution was then added, and the resulting mixture warmed to room temperature and vigorously stirred overnight. The aqueous layer was extracted with Et<sub>2</sub>O and the combined organic extracts were washed with water, brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure to give **SI-37** as a colorless oil which was used in the next step without further purification.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  3.81 (tq ap. sextet, *J* = 6.2 Hz, 1H), 3.66 (t, *J* = 6.5 Hz, 2H), 1.63-1.34 (6H), 1.14 (d, *J* = 6.1 Hz, 3H), 0.90 (s, 9H), 0.07 (s, 6H).

### (S)-5-((*tert*-Butyldimethylsilyl)oxy)hexanal (SI-38)

To a stirred solution of crude alcohol **SI-37** in dry DCM (10 mL), under a nitrogen atmosphere, were added iodosobenzene diacetate (2.08 g, 6.46 mmol, 1.2 eq.) and TEMPO (84 mg, 0.54 mmol, 0.1 eq.) at 0 °C. The reaction mixture was stirred at room temperature for 5 h. Water was then added to the reaction mixture which was extracted three times with DCM. The combined organic extracts were washed with water, brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude aldehyde **SI-38** was used in the next step without further purification.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  9.78 (t, *J* = 1.8 Hz, 1H), 3.83 (tq ap. sextet, *J* = 6.0 Hz, 1H), 2.45 (td, *J* = 7.3, 1.8 Hz, 2H), 1.78-1.60 (2H), 1.49-1.41 (2H), 1.15 (d, *J* = 6.1 Hz, 3H), 0.91 (s, 9H), 0.07 (s, 6H).

### **(*S,E*)-Ethyl 7-((*tert*-butyldimethylsilyl)oxy)-2-methyloct-2-enoate (**26**)**

To a stirred solution of crude aldehyde **SI-38** in DCM (38 mL), under a nitrogen atmosphere, was added (1-ethoxycarbonyl ethylidene)triphenyl phosphorane (292 mg, 8.07 mmol, 1.5 eq.) at room temperature. The reaction mixture was stirred at room temperature for 48 h. The solvent was then removed under reduced pressure and the residue purified by chromatography (cyclohexane/EtOAc 95:5) to give **26** (1.15 g, 3.66 mmol, 63 % over three steps) as a colorless oil.

**<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)**  $\delta$  6.76 (tq,  $J$  = 7.2, 1.4 Hz, 1H), 4.19 (q,  $J$  = 7.1 Hz, 2H), 3.79 (m, 1H), 2.17 (m, 2H), 1.83 (d,  $J$  = 1.4 Hz, 3H), 1.56-1.40 (4H), 1.30 (t,  $J$  = 7.1 Hz, 3H), 1.13 (d,  $J$  = 6.3 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 6H).

**<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)**  $\delta$  168.3, 142.2, 127.8, 68.3, 60.4, 39.3, 28.7, 25.9 (3C), 24.7, 23.8, 18.1, 14.3, 12.4, -4.4, -4.7.

**HRMS-ESI** calculated for C<sub>17</sub>H<sub>35</sub>O<sub>3</sub>Si :  $m/z$  315.2355 ([M+H]<sup>+</sup>), found :  $m/z$  315.2357 ([M+H]<sup>+</sup>).

**[ $\alpha$ ]<sup>20</sup><sub>D</sub>** = + 10.7 (c 0.3, CHCl<sub>3</sub>).

### **(*S,E*)-7-((*tert*-Butyldimethylsilyl)oxy)-2-methyloct-2-en-1-ol (**SI-39**)**

To a stirred solution of **26** (1.15 g, 3.66 mmol) in dry DCM (60 mL), under a nitrogen atmosphere, was added DIBAL-H (5.37 mL, 1.5 M in toluene, 8.05 mmol, 2.2 eq.) at 0 °C. The reaction mixture was stirred at 0 °C for 3 h. Saturated aqueous Rochelle salt solution was then added, and the resulting mixture warmed to room temperature and vigorously stirred overnight. The aqueous layer was extracted with Et<sub>2</sub>O and the combined organic extracts were washed with water, brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure to give **SI-39** as a colorless oil which was used in the next step without further purification.

**<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)**  $\delta$  5.41 (tq,  $J$  = 7.1, 1.3 Hz, 1H), 4.01 (s, 2H), 3.79 (m, 1H), 2.04 (m, 2H), 1.67 (d,  $J$  = 1.3 Hz, 3H), 1.49-1.36 (4H), 1.12 (d,  $J$  = 6.1 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 6H).

### **(*S,E*)-7-((*tert*-Butyldimethylsilyl)oxy)-2-methyloct-2-enal (**SI-40**)**

To a stirred solution of crude alcohol **SI-39** in dry DCM (25 mL), under a nitrogen atmosphere, was added MnO<sub>2</sub> (6.06 g, 69.8 mmol, 20 eq.) at room temperature. The reaction mixture was warmed to 40 °C and vigorously stirred for 48 h. The resulting mixture was cooled to room temperature and filtered through celite with DCM. The solvent was then removed under reduced pressure to give **SI-40** as a pale yellow oil which was used in the next step without further purification.

**<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)**  $\delta$  9.41 (s, 1H), 6.49 (tq,  $J$  = 7.4, 1.3 Hz, 1H), 3.82 (m, 1H), 2.36 (m, 2H), 1.75 (d,  $J$  = 1.2 Hz, 3H), 1.65-1.41 (4H), 1.14 (d,  $J$  = 6.1 Hz, 3H), 0.89 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H).

### **(1*E*,3*E*)-(8*S*)-*tert*-Butyldimethylsilyloxy-1-iodo-3-methyl-nona-1,3-diene (**SI-41**)**

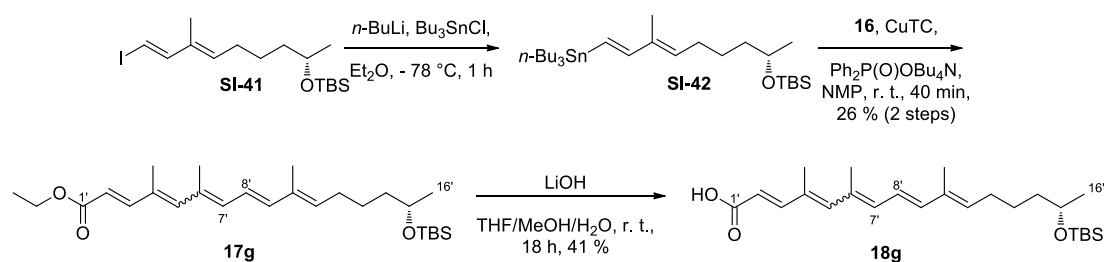
To a stirred solution of CrCl<sub>2</sub> (4.10 g, 33.4 mmol, 10 eq.) in dry THF (25 mL), under a nitrogen atmosphere, was added a solution of crude aldehyde **SI-40** and CHI<sub>3</sub> (3.94 g, 10 mmol, 3 eq.) in dry THF (20 mL) dropwise. The reaction mixture was stirred at room temperature for 12 h. The resulting mixture was hydrolyzed with water and diluted with Et<sub>2</sub>O. The aqueous layer was extracted three times

with Et<sub>2</sub>O and the combined organic extracts were washed with water, brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude product was then purified by chromatography (cyclohexane/toluene 100:1) to afford **SI-41** (1 g, 2.54 mmol, 69 % over three steps) as a pale yellow oil.

<sup>1</sup>H NMR (C<sub>6</sub>D<sub>6</sub>, 300 MHz) δ 6.99 (d, *J* = 14.6 Hz, 1H), 5.89 (d, *J* = 14.6 Hz, 1H), 5.20 (tq, *J* = 7.4, 1.1 Hz, 1H), 3.65 (m, 1H), 1.87 (m, 2H), 1.49-1.41 (2H), 1.37 (d, *J* = 1.1 Hz, 3H), 1.31-1.23 (2H), 1.07 (d, *J* = 6.1 Hz, 3H), 1.00 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H).

<sup>13</sup>C NMR (C<sub>6</sub>D<sub>6</sub>, 100 MHz) δ 150.3, 135.1, 134.9, 73.8, 69.0, 39.9, 28.6, 26.5 (3C), 26.1, 24.5, 18.6, 12.0, -3.8, -4.2.

[α]<sub>D</sub><sup>20</sup> = + 6.9 (c 1.2, CHCl<sub>3</sub>).



#### (1*E*,3*E*)-(8*S*)-*tert*-Butyldimethylsilyloxy-1-tributylstannyl-3-methyl-nona-1,3-diene (SI-42)

To a stirred solution of **SI-41** (300 mg, 0.76 mmol) in dry Et<sub>2</sub>O (4 mL), under a nitrogen atmosphere, was added *n*-BuLi (0.45 mL, 2.5 M in hexane, 1.14 mmol, 1.5 eq.) at -78 °C. The reaction mixture was stirred for 20 min at -78 °C and Bu<sub>3</sub>SnCl (0.33 mL, 1.14 mmol, 1.5 eq.) was added. The resulting solution was stirred at -78 °C for another 20 min and allowed to warm to room temperature for 1 h. Saturated aqueous NaHCO<sub>3</sub> solution was then added and the aqueous layer was extracted three times with Et<sub>2</sub>O. The combined organic extracts were washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude **SI-42** was used in the next step without further purification.

#### (*S*,2*E*,4*E*,6*E*,8*E*,10*E*)-Ethyl 15-((*tert*-butyldimethylsilyl)oxy)-4,6,10-trimethylhexadeca-2,4,6,8,10-pentaenoate (**17g**)

To a stirred solution of crude **SI-42** and tetra-*n*-butylammonium diphenylphosphinate (810 mg, 1.75 mmol, 2.3 eq.) in dry NMP (5 mL), under a nitrogen atmosphere, was added 0.2 mL of a solution of **16** in NMP (466 mg, 1.52 mmol, 2 eq., 3 mL). After addition of CuTC (290 mg, 1.52 mmol, 2 eq.), the rest of the **16** solution was added dropwise and the resulting mixture was stirred at room temperature for 40 min. The reaction mixture was then diluted with Et<sub>2</sub>O and filtered through neutral alumina oxide. The filtrate was washed with water, brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude product was then purified by preparative TLC (cyclohexane/EtOAc 9:1) to afford **17g** (89 mg, 0.2 mmol, 26 % for two steps) as a yellow oil. NMR analysis showed the presence of mixture of isomers 4'*E*/4'*Z* = 82:18.

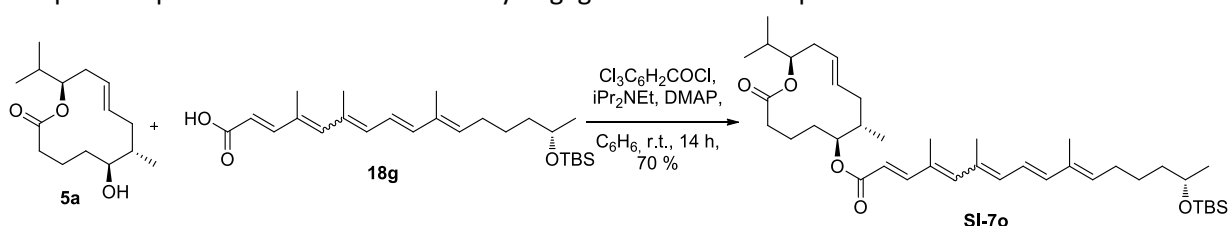


**(*S*,2*E*,4*E*,6*E*,8*E*,10*E*)-15-((*tert*-Butyldimethylsilyl)oxy)-4,6,10-trimethylhexadeca-2,4,6,8,10-pentaenoic acid (**18g**)**

To a stirred solution of **17g** (89 mg, 0.2 mmol) in a mixture THF/MeOH/H<sub>2</sub>O (4/1/1 mL) was added LiOH (47.5 mg, 2 mmol, 10 eq.). The resulting mixture was stirred at room temperature for 18 h. After addition of saturated aqueous NH<sub>4</sub>Cl solution, the mixture was extracted three times with EtOAc and the combined organic extracts were washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude material was purified by preparative TLC (cyclohexane/EtOAc 7:3) to afford **010** (35 mg, 83.67 μmol, 41 %) as a yellow oil.

**HRMS-ESI** calculated for C<sub>25</sub>H<sub>41</sub>O<sub>3</sub>Si : *m/z* 417.2830 ([M-H]<sup>-</sup>), found : *m/z* 417.2847 ([M-H]<sup>-</sup>).

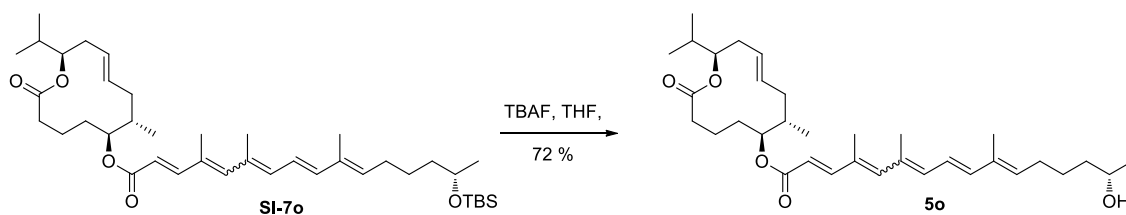
Due to the very limited stability of this carboxylic acid, only a HRMS has been performed on this sample. The purified acid was immediately engaged in the next step.



**(6*S*,7*S*,9*E*,12*R*)-7-Methyl-2-oxo-12-(propan-2-yl)-1-oxacyclododec-9-en-6-yl (2*E*,4*E*,6*E*,8*E*,10*E*,15*S*)-15-[(*tert*-butyldimethylsilyl)oxy]-4,6,10-trimethylhexadeca-2,4,6,8,10-pentaenoate (**SI-7o**)**

To a solution of **18g** (20 mg, 0.048 mmol) in benzene (0.4 mL) were added diisopropylethyl amine (33 μL, 0.18 mmol, 3.7 eq.), 2,4,6-trichlorobenzoyl chloride (17 μL ; 0.11 mmol, 2 eq.), and DMAP (33 mg). The reaction mixture was stirred at room temperature for 15 min and **5a** (6.5 mg, 0.026 mmol) was added. After being stirred at room temperature for 14 h, an aqueous saturated solution of sodium hydrogenocarbonate was added to the reaction mixture. The aqueous layer was extracted three times with benzene. The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude product was purified on preparative TLC eluting with heptane/ethyl acetate 90:10 to give **SI-7o** (12 mg, 0.018 mmol, 70 %) as a yellow oil. Compound **SI-7o** exists as a mixture of three isomers in a 29:28:43 ratio and a few diagnostic chemical shifts of the first (29%) and third (43%) isomers could be identified in proton NMR.

**<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)** δ 7.93 (d, *J* = 15.6 Hz, 1H, diagnostic chemical shift of the first isomer), 7.42 (d, *J* = 15.6 Hz, 1H), 7.36 (d, *J* = 15.6 Hz, 1H, diagnostic chemical shift of the third isomer), 6.51 (dd, *J* = 14.8, 11.2 Hz, 1H), 6.37 (d, *J* = 14.8 Hz, 1H), 6.36 (s, 1H), 6.28 (d, *J* = 11.2 Hz, 1H), 5.86 (d, *J* = 15.5 Hz, 1H), 5.59 (m, 1H), 5.51 (m, 1H), 5.30 (m, 1H), 4.80-4.71 (2H), 3.77 (m, 1H), 2.49 (m, 1H), 2.30 (m, 1H), 2.15-2.06 (4H), 2.04 (s, 3H), 2.02 (s, 3H), 1.98-1.96 (2H), 1.94 (s, 3H), 1.87-1.61 (6H), 1.80 (s, 3H), 1.43-1.38 (4H), 1.11 (d, *J* = 5.9 Hz, 3H), 0.93 (s, 3H), 0.91 (s, 3H), 0.88 (s, 9H), 0.04 (s, 6H).



**(6S,7S,9E,12R)-7-Methyl-2-oxo-12-(propan-2-yl)-1-oxacyclododec-9-en-6-yl (2E,4E,6E,8E,10E,15S)-15-dihydroxy-4,6,10-trimethylhexadeca-2,4,6,8,10-pentaenoate (5o)**

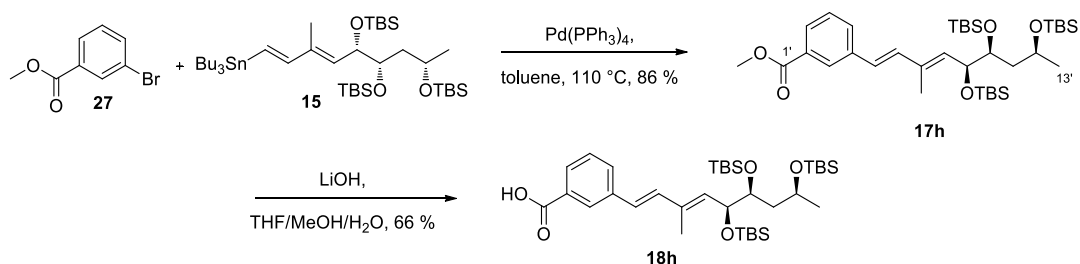
To a solution of **SI-7o** (12 mg, 0.018 mmol) in THF (0.2 mL) was added TBAF (70  $\mu$ L, 1M in THF, 4 eq.). The solution was stirred at room temperature for 4 h.  $\text{CaCO}_3$  (50 mg), Dowex 50WX8-400 (150 mg) and MeOH (0.4 mL) were added and the reaction mixture was stirred for 1 h. After being filtered and concentrated under reduced pressure, the crude product was purified by TLC preparative ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$  90:10) to give **5o** (7 mg, 0.013 mmol, 72 %). Compound **22j** exists as a mixture of three isomers in a 42:27:31 ratio and a few diagnostic chemical shifts of the first (42%) and third (31%) isomers could be identified in proton NMR.

**$^1\text{H}$  NMR (Acetone- $d_6$ , 400 MHz)**  $\delta$  7.93 (d,  $J$  = 15.8 Hz, 1H, diagnostic chemical shift of the first isomer), 7.44 (d,  $J$  = 15.5 Hz, 1H), 7.37 (d,  $J$  = 15.6 Hz, 1H, diagnostic chemical shift of the third isomer), 6.63 (dd,  $J$  = 11.1, 15.0 Hz, 1H), 6.47 (s, 1H), 6.36 (d,  $J$  = 15.0 Hz, 1H), 6.17 (d,  $J$  = 11.1 Hz, 1H), 5.89 (d,  $J$  = 15.5 Hz, 1H), 5.74 (m, 1H), 5.50 (m, 1H), 5.30 (m, 1H), 4.78-4.67 (2H), 3.71 (m, 1H), 3.58 (m, 1H), 2.50 (m, 1H), 2.32 (m, 1H), 2.12-2.08 (2H), 2.06 (s, 3H), 1.97 (s, 3H), 1.95-1.92 (2H), 1.90 (s, 3H), 1.80-1.75 (4H), 1.70-1.62 (4H), 1.54-1.49 (4H), 1.19 (s, 3H), 0.92 (s, 3H), 0.90 (s, 3H), 0.87 (s, 3H).

**$^{13}\text{C}$  NMR (Acetone- $d_6$ , 75 MHz)**  $\delta$  173.9, 167.8, 152.3, 144.1, 141.7, 137.7, 136.5, 133.9, 132.8, 128.0, 126.7, 125.4, 120.4, 118.1, 80.1, 77.3, 68.4, 40.9, 39.7, 39.6, 37.9, 37.0, 36.1, 34.1, 27.6, 25.1, 22.0, 21.6, 20.9, 19.9, 19.4, 18.6, 15.3, 13.5.

**HRMS-ESI** calculated for  $\text{C}_{34}\text{H}_{52}\text{O}_5\text{Na}$ :  $m/z$  563.3707 ( $[\text{M}+\text{Na}]^+$ ), found:  $m/z$  563.3679 ( $[\text{M}+\text{Na}]^+$ ).

## 2.4 Synthesis of aromatic series



**Methyl-3-[(1E,3E,5S,6S,8S)-5,6,8-tris[(*tert*-butyldimethylsilyl)oxy]-3-methylnona-1,3-dien-1-yl]benzoate (17h)**

To a solution of **27** (34 mg, 0.15 mmol) in toluene (0.8 mL) was added  $\text{Pd}(\text{PPh}_3)_4$  (9 mg, 0.008 mmol, 0.05 eq.) and a solution of **15**<sup>1</sup> (0.25 mmol) in toluene (0.4 mL). The reaction mixture was heated at

110 °C for 3 h. The solvent was then evaporated and the crude product was purified on TLC preparative eluting with heptane/ethyl acetate 9:1 to give **17h** (84 mg, 0.13 mmol, 86 %) as a colorless oil.

**<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)** δ 8.09 (s, 1H), 7.88 (d, *J* = 7.9 Hz, 1H), 7.62 (d, *J* = 7.9 Hz, 1H), 7.39 (dd ap. t, *J* = 7.8 Hz, 1H), 6.88 (d, *J* = 16.1 Hz, 1H), 6.54 (d, *J* = 16.1 Hz, 1H), 5.67 (d, *J* = 9.3 Hz, 1H), 4.47 (dd, *J* = 3.8, 9.3 Hz, 1H), 3.93 (s, 3H), 3.91 (m, 1H), 3.66 (m, 1H), 1.91 (s, 3H), 1.68-1.58 (2H), 1.15 (d, *J* = 6.0 Hz, 1H), 0.89 (s, 9H), 0.88 (s, 9H), 0.87 (s, 9H), 0.07 (s, 3H), 0.06 (s, 6H), 0.05 (s, 3H), 0.03 (s, 3H), -0.01 (s, 3H).

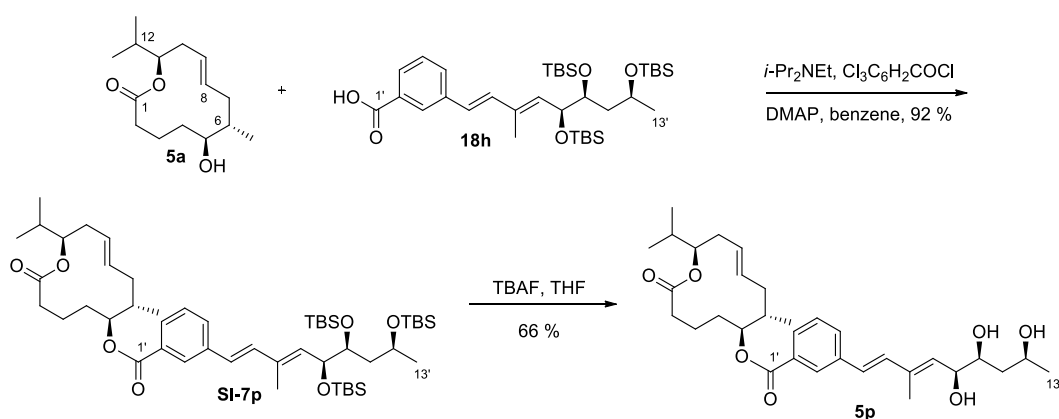
### 3-[(1*E*,3*E*,5*S*,6*S*,8*S*)-5,6,8-tris[(*tert*-Butyldimethylsilyl)oxy]-3-methylnona-1,3-dien-1-yl]benzoic acid (**18h**)

To a solution of **17h** (78 mg, 0.12 mmol) in a mixture of THF/MeOH/H<sub>2</sub>O (2.8:0.7:0.7) was added LiOH (61 mg). The reaction mixture was stirred at room temperature for 18 h before being acidified with a saturated aqueous solution of NH<sub>4</sub>Cl. The aqueous phase was extracted with ethyl acetate, and the combined organic phases were washed with brine and dried over MgSO<sub>4</sub>. After being filtered and concentrated under reduced pressure, the crude product was purified by preparative TLC (elution with heptane/ethyl acetate 70:30), to give **18h** (50 mg, 0.08 mmol, 66 %) as a colorless oil.

**<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)** δ 8.15 (s, 1H), 7.95 (d, *J* = 7.9 Hz, 1H), 7.67 (d, *J* = 7.9 Hz, 1H), 7.43 (dd ap. t, *J* = 7.8 Hz, 1H), 6.89 (d, *J* = 16.1 Hz, 1H), 6.56 (d, *J* = 16.1 Hz, 1H), 5.67 (d, *J* = 9.0 Hz, 1H), 4.48 (dd, *J* = 3.8, 9.0 Hz, 1H), 3.92 (m, 1H), 3.67 (m, 1H), 1.91 (s, 3H), 1.68-1.58 (2H), 1.15 (d, *J* = 6.0 Hz, 1H), 0.89 (s, 9H), 0.88 (s, 9H), 0.87 (s, 9H), 0.07 (s, 3H), 0.06 (s, 6H), 0.05 (s, 3H), 0.03 (s, 3H), -0.01 (s, 3H).

**<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)** δ 170.6, 143.1, 138.2, 135.2, 134.5, 131.2, 130.9, 128.8, 128.7, 128.1, 126.0, 73.7, 71.4, 66.1, 42.6, 29.4, 27.9, 27.0, 26.8, 25.9 (2C), 25.8, 23.4, 18.2 (3C), 17.5, 16.6, 13.5, -4.1, -4.2, -4.3, -4.5, -4.6, -4.7.

**HRMS-ESI** calculated for C<sub>35</sub>H<sub>64</sub>O<sub>5</sub>Si<sub>3</sub>Na : *m/z* 671.3953 ([M+Na]<sup>+</sup>), found: *m/z* 671.3949 ([M+Na]<sup>+</sup>).



### (6*S*,7*S*,9*E*,12*R*)-7-Methyl-2-oxo-12-(propan-2-yl)-1-oxacyclododec-9-en-6-yl-3-[(1*E*,3*E*,5*S*,6*S*,8*S*)-5,6,8-tris[(*tert*-butyldimethylsilyl)oxy]-3-methylnona-1,3-dien-1-yl]benzoate (**SI-7p**)

To a solution of **18h** (27 mg, 0.042 mmol) in benzene (0.4 mL) were added diisopropylethyl amine (29 μL, 0.17 mmol, 5.6 eq.), 2,4,6-trichlorobenzoyl chloride (14 μL, 0.09 mmol, 3 eq.), and DMAP (26 mg). The reaction mixture was stirred at room temperature for 15 min and **5a** (7 mg, 0.028 mmol) was

added. After being stirred at room temperature for 14 h, an aqueous saturated solution of sodium hydrogenocarbonate was added to the reaction mixture. The aqueous layer was extracted three times with benzene. The combined organic layers were washed with brine, dried over  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. The crude product was purified on preparative TLC eluting with heptane/ethyl acetate 90:10 to give **SI-7p** (22 mg, 0.025 mmol, 92 %) as a colorless oil.

$^1\text{H NMR}$  ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  8.08 (s, 1H), 7.89 (d,  $J = 7.7$  Hz, 1H), 7.62 (d,  $J = 7.7$  Hz, 1H), 7.39 (dd ap. t,  $J = 7.7$  Hz, 1H), 6.87 (d,  $J = 16.0$  Hz, 1H), 6.54 (d,  $J = 16.0$  Hz, 1H), 5.67 (d,  $J = 8.9$  Hz, 1H), 5.51 (m, 1H), 5.30 (m, 1H), 4.92 (m, 1H), 4.82 (ddd,  $J = 2.3, 6.1, 11.5$  Hz, 1H), 4.47 (dd,  $J = 9.1, 3.7$  Hz, 1H), 3.91 (m, 1H), 3.65 (td,  $J = 7.5, 3.7$  Hz, 1H), 2.49 (m, 1H), 2.30 (m, 1H), 2.15-2.06 (2H), 1.98-1.92 (4H), 1.91 (s, 3H), 1.87-1.61 (6H), 1.15 (d,  $J = 6.1$  Hz, 3H), 0.95 (s, 3H), 0.93 (s, 3H), 0.90 (s, 3H), 0.89 (s, 9H), 0.88 (s, 9H), 0.87 (s, 9H), 0.09 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H), -0.01 (s, 3H).

HRMS-ESI calculated for  $\text{C}_{50}\text{H}_{88}\text{O}_7\text{Si}_3\text{Na}$ :  $m/z$  907.5730 ( $[\text{M}+\text{Na}]^+$ ), found:  $m/z$  907.5736 ( $[\text{M}+\text{Na}]^+$ ).

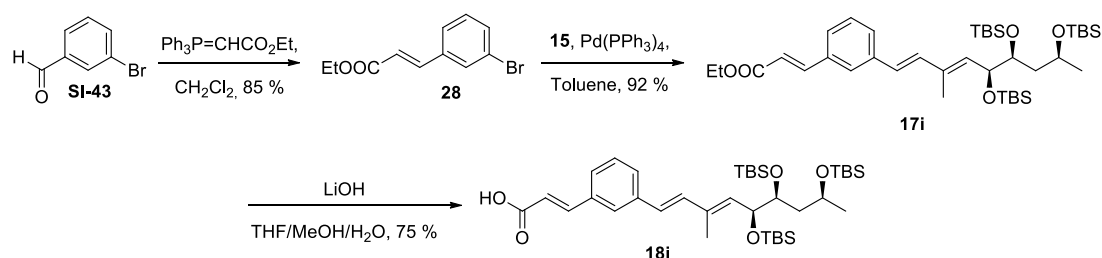
**(6S,7S,9E,12R)-7-Methyl-2-oxo-12-(propan-2-yl)-1-oxacyclododec-9-en-6-yl-3-[(1E,3E,5S,6S,8S)-5,6,8-trihydroxy-3-methylnona-1,3-dien-1-yl]benzoate (compound 22f) (5p)**

To a solution of **SI-7p** (22 mg, 0.025 mmol) in THF (0.2 mL) was added TBAF (0.225 mmol, 1M in THF, 9 eq.). The solution was stirred at room temperature for 4 h.  $\text{CaCO}_3$  (45 mg), Dowex 50WX8-400 (140 mg) and MeOH (0.3 mL) were added and the reaction mixture was stirred for 1 h. After being filtered and concentrated under reduced pressure, the crude product was purified by TLC preparative ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$  90:10) to give **5p** (9 mg, 0.017 mmol, 66 %).

$^1\text{H NMR}$  (Acetone- $d_6$ , 300 MHz)  $\delta$  8.12 (s, 1H), 7.90 (d,  $J = 7.7$  Hz, 1H), 7.79 (d,  $J = 7.7$  Hz, 1H), 7.48 (dd ap. t,  $J = 7.8$  Hz, 1H), 7.02 (d,  $J = 16.1$  Hz, 1H), 6.72 (d,  $J = 16.1$  Hz, 1H), 5.73 (d,  $J = 8.9$  Hz, 1H), 5.55 (m, 1H), 5.33 (m, 1H), 4.89 (m, 1H), 4.78 (ddd,  $J = 2.4, 6.2, 11.5$  Hz, 1H), 4.33 (dd,  $J = 6.2, 8.9$  Hz, 1H), 4.06 (s, 1H), 4.03 (s, 1H), 4.00 (m, 1H), 3.68 (m, 1H), 2.51 (m, 1H), 2.35 (m, 1H), 2.20-2.10 (2H), 2.06 (s, 3H), 1.94-1.92 (2H), 1.80-1.75 (2H), 1.82-1.76 (4H), 1.54-1.51 (2H), 1.12 (d,  $J = 6.1$  Hz, 3H), 0.96 (d,  $J = 5.6$  Hz, 3H), 0.94 (d,  $J = 7.0$  Hz, 3H), 0.90 (d,  $J = 7.0$  Hz, 3H).

$^{13}\text{C NMR}$  (Acetone- $d_6$ , 75 MHz)  $\delta$  173.9, 167.0, 140.1, 137.6, 136.5, 136.4, 136.2, 133.1, 132.2, 130.8, 129.8, 129.1, 128.4, 128.2, 81.3, 77.3, 76.7, 73.3, 68.7, 42.8, 39.7, 37.9, 36.9, 36.1, 34.1, 31.5, 25.2, 21.7, 21.1, 19.9, 19.4, 14.4.

HRMS-ESI calculated for  $\text{C}_{32}\text{H}_{46}\text{O}_7\text{Na}$ :  $m/z$  565.3135 ( $[\text{M}+\text{Na}]^+$ ), found:  $m/z$  565.3142 ( $[\text{M}+\text{Na}]^+$ ).



**Ethyl (2E)-3-(3-bromophenyl)prop-2-enoate (28)**

To a solution of 3-bromobenzaldehyde **SI-43** (315  $\mu\text{L}$ , 2.7 mmol) in dichloromethane (13.5 mL) was added at 0 °C 1-ethoxycarbonyl ethylidene)triphenylphosphorane (1.4 g, 4.05 mmol, 1.5 eq). The reaction mixture was stirred at room temperature for 18 h. After being concentrated under reduced

pressure, the crude product was purified by flash chromatography (cyclohexane/ethyl acetate 20:1) to give **28** (480 mg, 2.29 mmol, 85 %).

**<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)** δ 7.67 (s, 1H), 7.60 (d, *J* = 16.0 Hz, 1H), 7.50 (d, *J* = 7.9 Hz, 1H), 7.44 (d, *J* = 7.7 Hz, 1H), 7.26 (dd ap. t, *J* = 7.8 Hz, 1H), 6.43 (d, *J* = 16.0 Hz, 1H), 4.27 (q, *J* = 7.1 Hz, 2H), 1.34 (t, *J* = 7.1 Hz, 3H).

**Ethyl-(2*E*)-3-{3-[(1*E*,3*E*,5*S*,6*S*,8*S*)-5,6,8-tris[(*tert*-butyldimethylsilyl)oxy]-3-methylnona-1,3-dien-1-yl]phenyl}prop-2-enoate (**17i**)**

To a solution of **28** (34 mg, 0.13 mmol) in toluene (0.8 mL) was added Pd(PPh<sub>3</sub>)<sub>4</sub> (9 mg, 0.009 mmol, 0.06 eq.) and a solution of **15** (0.21 mmol) in toluene (0.8 mL). The reaction mixture was heated at 110 °C for 5 h. The solvent was then evaporated and the crude product was purified on TLC preparative eluting with heptane/ethyl acetate 9:1 to give **17i** (85 mg, 0.12 mmol, 92 %) as a colorless oil.

**<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)** δ 7.69 (d, *J* = 16.0 Hz, 1H), 7.56 (s, 1H), 7.46 (d, *J* = 7.1 Hz, 1H), 7.36 (d, *J* = 7.3 Hz, 1H), 7.34 (dd, *J* = 7.3, 7.1 Hz, 1H), 6.84 (d, *J* = 16.0 Hz, 1H), 6.51 (d, *J* = 16.0 Hz, 1H), 6.47 (d, *J* = 16.0 Hz, 1H), 5.66 (d, *J* = 9.2 Hz, 1H), 4.47 (dd, *J* = 3.9, 9.2 Hz, 1H), 4.27 (q, *J* = 7.1 Hz, 2H), 3.93 (m, 1H), 3.66 (m, 1H), 1.91 (d, *J* = 0.83 Hz, 3H), 1.66-1.61 (2H), 1.15 (d, *J* = 6.0 Hz, 3H), 0.92 (t, *J* = 7.1 Hz, 3H), 0.89 (s, 9H), 0.88 (s, 9H), 0.87 (s, 9H), 0.07 (s, 3H), 0.06 (s, 6H), 0.05 (s, 3H), 0.04 (s, 3H), -0.01 (s, 3H).

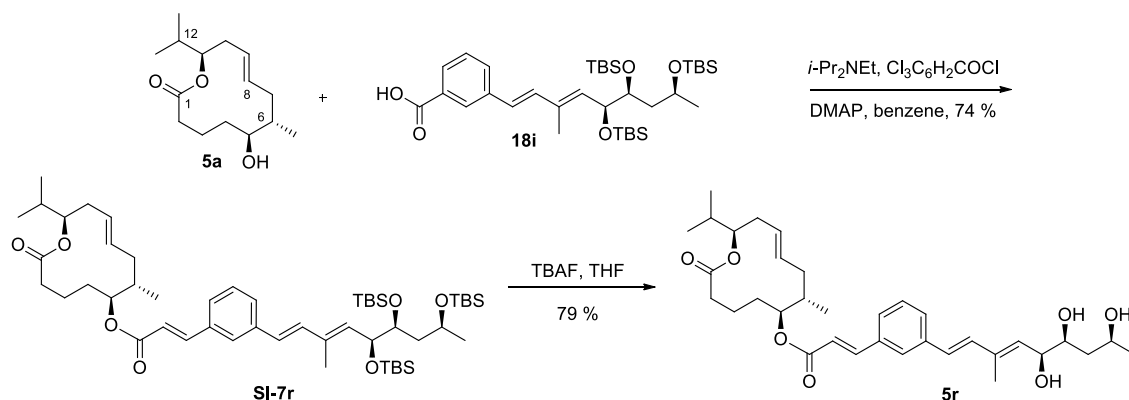
**(2*E*)-3-{3-[(1*E*,3*E*,5*S*,6*S*,8*S*)-5,6,8-tris[(*tert*-Butyldimethylsilyl)oxy]-3-methylnona-1,3-dien-1-yl]phenyl}prop-2-enoic acid (**18i**)**

To a solution of **17i** (85 mg, 0.12 mmol) in a mixture of THF/MeOH/H<sub>2</sub>O (2.9:0.8:0.8) was added LiOH (64 mg). The reaction mixture was stirred at room temperature for 18 h before being acidified with a saturated aqueous solution of NH<sub>4</sub>Cl. The aqueous phase was extracted with ethyl acetate, and the combined organic phases were washed with brine and dried over MgSO<sub>4</sub>. After being filtered and concentrated under reduced pressure, the crude product was purified by preparative TLC (elution with heptane/ethyl acetate 70:30), to give **18i** (60 mg, 0.09 mmol, 75 %) as a colorless oil.

**<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)** δ 7.79 (d, *J* = 15.9 Hz, 1H), 7.59 (s, 1H), 7.49 (d, *J* = 7.7 Hz, 1H), 7.39 (d, *J* = 7.4 Hz, 1H), 7.38 (dd, *J* = 7.4, 7.7 Hz, 1H), 6.85 (d, *J* = 15.9 Hz, 1H), 6.51 (d, *J* = 15.9 Hz, 1H), 6.48 (d, *J* = 15.9 Hz, 1H), 5.67 (d, *J* = 8.9 Hz, 1H), 4.47 (dd, *J* = 3.5, 8.9 Hz, 1H), 3.93 (m, 1H), 3.66 (m, 1H), 1.91 (s, 3H), 1.66-1.61 (2H), 1.15 (d, *J* = 6.0 Hz, 3H), 0.89 (s, 9H), 0.88 (s, 9H), 0.87 (s, 9H), 0.07 (s, 3H), 0.06 (s, 6H), 0.05 (s, 3H), 0.04 (s, 3H), -0.01 (s, 3H).

**<sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)** δ 171.4, 148.6, 146.9, 143.1, 138.4, 134.9, 134.3, 134.1, 129.2, 128.3, 126.9, 126.5, 117.3, 73.7, 71.4, 66.1, 42.7, 26.0 (3C), 25.9 (3C), 25.8 (3C), 23.5, 18.2, 18.1, 18.0, 13.5, -4.1 (2C), -4.3, -4.5, -4.6, -4.7.

**HRMS-ESI** calculated for C<sub>37</sub>H<sub>66</sub>O<sub>5</sub>Si<sub>3</sub>Na : *m/z* 697.4110 ([M+Na]<sup>+</sup>), found: *m/z* 697.4103 ([M+Na]<sup>+</sup>).



**(6*S*,7*S*,9*E*,12*R*)-7-Methyl-2-oxo-12-(propan-2-yl)-1-oxacyclododec-9-en-6-yl (2*E*)-3-{3-[(1*E*,3*E*,5*S*,6*S*,8*S*)-5,6,8-tris[(*tert*-butyldimethylsilyl)oxy]-3-methylnona-1,3-dien-1-yl]phenyl}prop-2-enoate (SI-7r)**

To a solution of **18i** (28 mg, 0.05 mmol) in benzene (0.4 mL) were added diisopropylethyl amine (33  $\mu$ L, 0.18 mmol, 5.6 eq.), 2,4,6-trichlorobenzoyl chloride (17  $\mu$ L, 0.09 mmol, 3 eq.), and DMAP (33 mg). The reaction mixture was stirred at room temperature for 15 min and **5a** (7 mg, 0.027 mmol) was added. After being stirred at room temperature for 14 h, an aqueous saturated solution of sodium hydrogenocarbonate was added to the reaction mixture. The aqueous layer was extracted three times with benzene. The combined organic layers were washed with brine, dried over  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. The crude product was purified on preparative TLC eluting with heptane/ethyl acetate 90:10 to give **SI-7r** (18 mg, 0.02 mmol, 74 %) as a yellow oil.

**$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)**  $\delta$  7.68 (d,  $J$  = 16.0 Hz, 1H), 7.57 (s, 1H), 7.45 (d,  $J$  = 7.2 Hz, 1H), 7.39 (d,  $J$  = 7.4 Hz, 1H), 7.38 (dd ap. t,  $J$  = 7.3 Hz, 1H), 6.84 (d,  $J$  = 16.0 Hz, 1H), 6.50 (d,  $J$  = 16.0 Hz, 1H), 6.46 (d,  $J$  = 16.0 Hz, 1H), 5.67 (d,  $J$  = 8.9 Hz, 1H), 5.66 (d,  $J$  = 9.1 Hz, 1H), 5.49 (m, 1H), 5.28 (m, 1H), 4.83-4.74 (2H), 4.47 (dd,  $J$  = 9.1, 3.8 Hz, 1H), 3.92 (m, 1H), 3.65 (m, 1H), 2.49 (m, 1H), 2.30 (m, 1H), 2.15-2.06 (2H), 1.97 (m, 1H), 1.91 (s, 3H), 1.87-1.61 (8H), 1.15 (d,  $J$  = 6.0 Hz, 3H), 0.95 (s, 3H), 0.93 (s, 3H), 0.92 (s, 3H), 0.89 (s, 9H), 0.88 (s, 9H), 0.87 (s, 9H), 0.07 (s, 3H), 0.06 (s, 6H), 0.05 (s, 3H), 0.04 (s, 3H), -0.01 (s, 3H).

**(6*S*,7*S*,9*E*,12*R*)-7-Methyl-2-oxo-12-(propan-2-yl)-1-oxacyclododec-9-en-6-yl (2*E*)-3-{3-[(1*E*,3*E*,5*S*,6*S*,8*S*)-5,6,8-trihydroxy-3-methylnona-1,3-dien-1-yl]phenyl}prop-2-enoate (5r)**

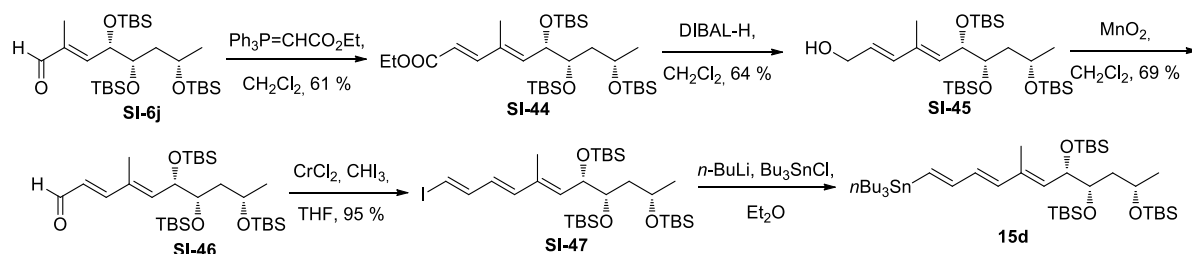
To a solution of **SI-7r** (18 mg, 0.02 mmol) in THF (0.15 mL) was added TBAF (0.2 mmol, 1M in THF, 10 eq). The solution was stirred at room temperature for 4 h.  $\text{CaCO}_3$  (50 mg), Dowex 50WX8-400 (150 mg) and MeOH (0.4 mL) were added and the reaction mixture was stirred for 1 h. After being filtered and concentrated under reduced pressure, the crude product was purified by TLC preparative ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$  90:10) to give **5r** (9 mg, 0.016 mmol, 79 %).

**$^1\text{H}$  NMR (Acetone- $d_6$ , 300 MHz)**  $\delta$  7.88 (s, 1H), 7.70 (d,  $J$  = 16.0 Hz, 1H), 7.56 (dd ap. t,  $J$  = 7.3 Hz, 1H), 7.53 (d,  $J$  = 7.3 Hz, 1H), 7.41 (d,  $J$  = 7.3 Hz, 1H), 7.07 (d,  $J$  = 16.3 Hz, 1H), 6.68 (d,  $J$  = 16.3 Hz, 1H), 6.63 (d,  $J$  = 16.0 Hz, 1H), 5.72 (d,  $J$  = 8.9 Hz, 1H), 5.53 (m, 1H), 5.30 (m, 1H), 4.80-4.72 (2H), 4.32 (dd,  $J$  = 6.3, 8.9 Hz, 1H), 4.06-3.94 (2H), 3.70 (ddd,  $J$  = 3.6, 6.3, 9.7 Hz, 1H), 2.49 (m, 1H), 2.32 (m, 1H), 2.20-2.10

(2H), 2.06 (s, 3H), 2.00-1.90 (2H), 1.96-1.94 (4H), 1.80-1.69 (4H), 1.57-1.50 (2H), 1.12 (d,  $J = 6.1$  Hz, 3H), 0.93 (s, 3H), 0.90 (s, 3H), 0.88 (s, 3H).

**$^{13}\text{C}$  NMR (Acetone- $d_6$ , 75 MHz)**  $\delta$  173.9, 167.5, 146.0, 140.4, 137.7, 136.8, 136.4, 136.2, 135.9, 131.1, 130.1, 128.9, 128.7, 128.1, 127.7, 120.9, 80.5, 77.3, 76.8, 73.3, 68.7, 42.8, 39.7, 37.9, 37.0, 36.0, 34.1, 31.6, 25.2, 21.6, 20.9, 19.9, 19.4, 14.3.

**HRMS-ESI** calculated for  $\text{C}_{34}\text{H}_{48}\text{O}_7\text{Na}$ :  $m/z$  591.3292 ( $[\text{M}+\text{Na}]^+$ ), found:  $m/z$  591.3289 ( $[\text{M}+\text{Na}]^+$ ).



#### Ethyl (2E,4E,6S,7S,9S)-6,7,9-tris[(*tert*-butyldimethylsilyl)oxy]-4-methyldeca-2,4-dienoate (SI-44)

To a solution of **SI-6j**<sup>1</sup> (400 mg, 0.75 mmol) in dichloromethane (4 mL) at 0 °C was added (1-ethoxycarbonyl ethylidene)triphenylphosphorane (400 mg, 1.15 mmol, 1.5 eq.). The reaction mixture was stirred at room temperature for 48 h. After being concentrated under reduced pressure, the crude product was purified by flash chromatography (cyclohexane/ethyl acetate 100:1 to 10:1) to give **SI-44** (275 mg, 0.46 mmol, 61 %) as a yellow oil.

#### (2E,4E,6S,7S,9S)-6,7,9-tris[(*tert*-Butyldimethylsilyl)oxy]-4-methyldeca-2,4-dien-1-ol (SI-45)

To a solution of **SI-44** (585 mg, 0.97 mmol) in dichloromethane (5 mL) was added DIBAL-H (1.4 mL, 1.5 M in toluene, 2.2 eq.). The reaction mixture was stirred at 0 °C for 1 h and a saturated aqueous solution of Rochelle salts was added. After being stirred for 12h, the aqueous layer was extracted three times with diethyl ether. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The crude product is purified by flash chromatography eluting with cyclohexane/ethyl acetate 15:1 to give **SI-45** as a colorless oil (345 mg, 0.62 mmol, 64 %).

**$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)**  $\delta$  6.27 (d,  $J = 15.8$  Hz, 1H), 5.79 (td,  $J = 6.2, 15.8$  Hz, 1H), 5.49 (d,  $J = 8.9$  Hz, 1H), 4.40 (dd,  $J = 3.80, 8.9$  Hz, 1H), 4.23 (d,  $J = 6.2$  Hz, 2H), 3.90 (m, 1H), 3.62 (m, 1H), 1.86 (m, 1H), 1.79 (s, 3H), 1.60 (m, 1H), 1.13 (d,  $J = 6.0$  Hz, 3H), 0.88 (s, 18H), 0.87 (s, 9H), 0.86 (s, 9H), 0.05 (18H).

#### (2E,4E,6S,7S,9S)-6,7,9-tris[(*tert*-Butyldimethylsilyl)oxy]-4-methyldeca-2,4-dienal (SI-46)

To a solution of **SI-45** (345 mg, 0.62 mmol) in dichloromethane (3 mL) was added  $\text{MnO}_2$  (1.06 g, 12.3 mmol, 20 eq.). The reaction mixture was heated under reflux for 24 h before being filtered on a bed of Celite. After being concentrated under reduced pressure, **SI-46** was obtained as a colorless oil (240 mg, 0.43 mmol, 69 %).

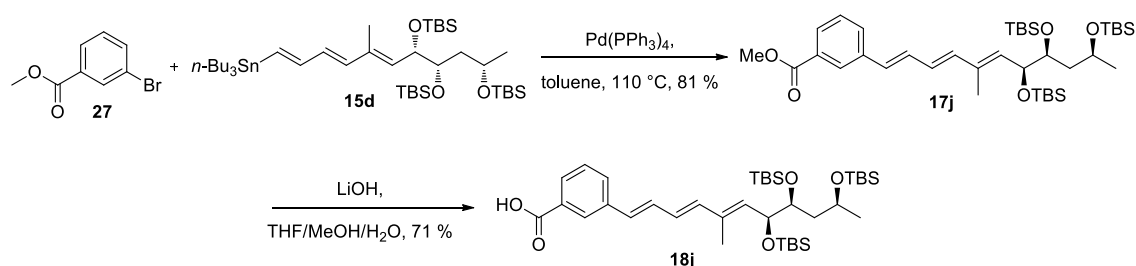
**<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)** δ 9.61 (d, *J* = 7.8 Hz, 1H), 7.13 (d, *J* = 15.9 Hz, 1H), 6.16 (dd, *J* = 7.8, 15.6 Hz, 1H), 5.99 (d, *J* = 8.8 Hz, 1H), 4.46 (dd, *J* = 3.7, 8.8 Hz, 1H), 3.91 (m, 1H), 3.68 (m, 1H), 1.87 (d, *J* = 1.1 Hz, 3H), 1.85 (m, 1H), 1.60 (m, 1H), 1.15 (d, *J* = 6.0 Hz, 3H), 0.88 (s, 18H), 0.87 (s, 9H), 0.86 (s, 9H), 0.05 (18H).

**(1*E*,3*E*,5*E*)-(7*S*,8*S*,10*S*)-tris-(*tert*-Butyldimethylsilyloxy)-1-iodo-5-methyl-undeca-1,3,5-triene (SI-47)**

To a suspension of CrCl<sub>2</sub> (329 mg, 2.68 mmol, 8 eq.) in THF (2.8 mL) was added dropwise a solution of **SI-46** (240 mg, 0.43 mmol) and CHI<sub>3</sub> (530 mg, 1.34 mmol, 3 eq.) in THF (1.8 mL). The reaction mixture was stirred at room temperature for 12 h before being diluted with diethyl ether and water. The aqueous phase was extracted three times, and the combined organic phases were washed with water and brine. After being dried over magnesium sulfate, filtered and concentrated under reduced pressure, the crude product was purified by Flash chromatography (eluting with cyclohexane/toluene 100:1) to give **SI-47** (280 g, 0.41 mmol, 95 %) as a colorless oil.

**(1*E*,3*E*,5*E*)-(7*S*,8*S*,10*S*)-tris-(*tert*-Butyldimethylsilyloxy)-1-tributylstannyl-5-methyl-undeca-1,3,5-triene (15d)**

To a solution of **SI-47** (280 mg, 0.41 mmol) in Et<sub>2</sub>O (2.0 mL) at -78 °C was added *n*-BuLi (380 μL, 1.6 M in hexane, 0.61 mmol, 1.5 eq.) and the reaction mixture was stirred for 20 min. Bu<sub>3</sub>SnCl (164 μL, 0.6 mmol, 1.5 eq.) was then added to the solution and the reaction mixture was allowed to warm to room temperature for 1 h. The reaction mixture was hydrolyzed with a saturated aqueous NaHCO<sub>3</sub> solution. The aqueous phase was extracted twice with Et<sub>2</sub>O. The combined organic phases were washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude material **15d** was used without further purification.



**Methyl 3-[(1*E*,3*E*,5*E*,7*S*,8*S*,10*S*)-7,8,10-tris[(*tert*-butyldimethylsilyl)oxy]-5-methylundeca-1,3,5-trien-1-yl]benzoate (17j)**

To a solution of **27** (55 mg, 0.26 mmol) in toluene (1.3 mL) was added Pd(PPh<sub>3</sub>)<sub>4</sub> (9 mg, 0.015 mmol, 0.06 eq.) and a solution of **15d** (0.41 mmol) in toluene (0.8 mL). The reaction mixture was heated at 110 °C for 5 h. The solvent was then evaporated and the crude product was purified on TLC preparative eluting with heptane/ethyl acetate 9:1 to give **17j** (140 mg, 0.21 mmol, 81 %) as a colorless oil.

**<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)** δ 8.06 (d, *J* = 7.1 Hz, 1H), 7.89 (dd, *J* = 7.1, 13.4 Hz, 1H), 7.54 (d, *J* = 7.6 Hz, 1H), 7.41 (dd, *J* = 7.6, 15.0 Hz, 1H), 6.94 (dd, *J* = 8.8, 15.3 Hz, 1H), 6.59 (d, *J* = 15.4 Hz, 1H), 6.44 (d, *J* = 14.7 Hz, 1H), 6.41 (s, 1H), 5.59 (d, *J* = 9.0 Hz, 1H), 4.44 (m, 1H), 3.92 (s, 3H), 3.93 (m, 1H), 3.64 (m, 1H),



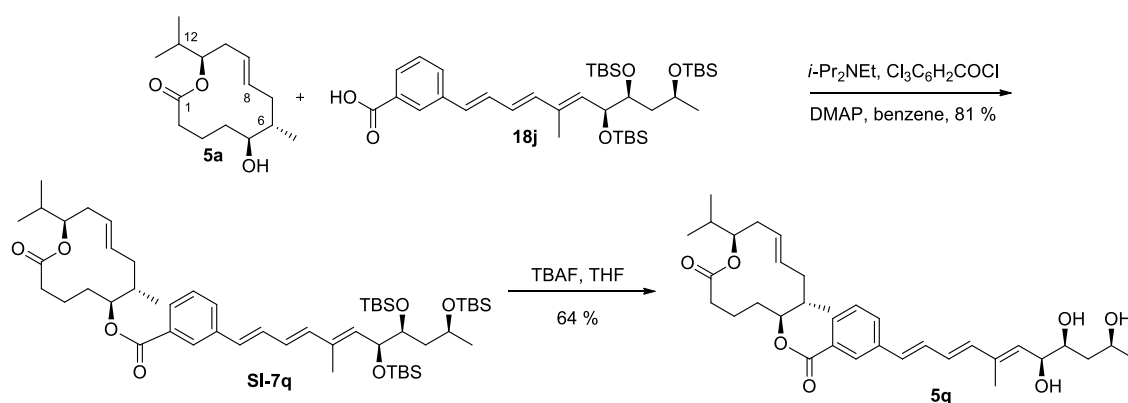
1.85 (s, 3H), 1.44 -1.32 (2H), 0.93 (d,  $J = 7.3$  Hz, 3H), 0.89 (s, 9H), 0.88 (s, 9H), 0.87 (s, 9H), 0.06-0.01 (18H).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz)  $\delta$  167.0, 141.0, 139.1, 138.0, 134.3, 133.1, 131.6, 130.5, 129.9, 128.4, 128.0, 127.4, 123.3, 73.6, 71.3, 66.0, 52.1, 42.7, 25.9 (6C), 25.8 (3C), 23.5, 18.1, 18.0, 17.9, 13.6, -4.2 (2C), -4.3, -4.5, -4.6, -4.7.

### 3-[(1*E*,3*E*,5*E*,7*S*,8*S*,10*S*)-7,8,10-tris[(*tert*-Butyldimethylsilyl)oxy]-5-methylundeca-1,3,5-trien-1-yl]benzoic acid (**18j**)

To a solution of **17j** (146 mg, 0.21 mmol) in a mixture of THF/MeOH/H<sub>2</sub>O (5:1.4:1.4 mL) was added LiOH (110 mg). The reaction mixture was stirred at room temperature for 18 h before being acidified with a saturated aqueous solution of NH<sub>4</sub>Cl. The aqueous phase was extracted with ethyl acetate, and the combined organic phases were washed with brine and dried over MgSO<sub>4</sub>. After being filtered and concentrated under reduced pressure, the crude product was purified by preparative TLC (elution with heptane/ethyl acetate 75:25, to give **18j** (100 mg, 0.15 mmol, 71 %) as a yellow oil.

HRMS-ESI calculated for C<sub>37</sub>H<sub>66</sub>O<sub>5</sub>Si<sub>3</sub>Na :  $m/z$  697.4110 ( $[\text{M}+\text{Na}]^+$ ), found:  $m/z$  697.4110 ( $[\text{M}+\text{Na}]^+$ ).



### (6*S*,7*S*,9*E*,12*R*)-7-Methyl-2-oxo-12-(propan-2-yl)-1-oxacyclododec-9-en-6-yl 3-[(1*E*,3*E*,5*E*,7*S*,8*S*,10*S*)-7,8,10-tris[(*tert*-butyldimethylsilyl)oxy]-5-methylundeca-1,3,5-trien-1-yl]benzoate (**SI-7q**)

To a solution of **18j** (27 mg, 0.041 mmol) in benzene (0.4 mL) were added diisopropylethyl amine (36  $\mu\text{L}$ , 0.17 mmol, 5.6 eq.), 2,4,6-trichlorobenzoyl chloride (14  $\mu\text{L}$ , 0.09 mmol, 3 eq.), and DMAP (27 mg). The reaction mixture was stirred at room temperature for 15 min and **5a** (7 mg, 0.027 mmol) was added. After being stirred at room temperature for 14 h, an aqueous saturated solution of sodium hydrogenocarbonate was added to the reaction mixture. The aqueous layer was extracted three times with benzene. The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude product was purified on preparative TLC eluting with heptane/ethyl acetate 90:10 to give **SI-7q** (20 mg, 0.022 mmol, 81 %) as a yellow oil.

HRMS-ESI calculated for C<sub>52</sub>H<sub>90</sub>O<sub>7</sub>Si<sub>3</sub>Na :  $m/z$  933.5886 ( $[\text{M}+\text{Na}]^+$ ), found:  $m/z$  933.5864 ( $[\text{M}+\text{Na}]^+$ ).

**(6*S*,7*S*,9*E*,12*R*)-7-Methyl-2-oxo-12-(propan-2-yl)-1-oxacyclododec-9-en-6-yl 3-[(1*E*,3*E*,5*E*,7*S*,8*S*,10*S*)-7,8,10-trihydroxy-5-methylundeca-1,3,5-trien-1-yl]benzoate (5q)**

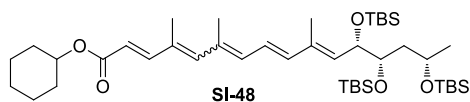
To a solution of **SI-7q** (20 mg, 0.022 mmol) in THF (0.4 mL) was added TBAF (0.20 mmol, 1M in THF, 9 eq.). The solution was stirred at room temperature for 4 h. CaCO<sub>3</sub> (50 mg), Dowex 50WX8-400 (150 mg) and MeOH (0.4 mL) were added and the reaction mixture was stirred for 1 h. After being filtered and concentrated under reduced pressure, the crude product was purified by TLC preparative (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 90:10) to give **5q** (8 mg, 0.014 mmol, 64 %).

**<sup>1</sup>H NMR (Acetone-d<sub>6</sub>, 300 MHz)** δ 8.09 (dd, *J* = 7.2, 8.0 Hz, 1H), 7.91 (dd, *J* = 7.8, 14.7 Hz, 1H), 7.74 (d, *J* = 7.7 Hz, 1H), 7.47 (dd ap. t, *J* = 7.7 Hz, 1H), 7.02 (d, *J* = 16.6 Hz, 1H), 6.78 (m, 1H), 6.57-6.39 (2H including 6.51 (s, 1H)), 5.60 (m, 1H), 5.52 (m, 1H), 5.32 (m, 1H), 4.89 (m, 1H), 4.74 (m, 1H), 4.29 (m, 1H), 4.04 (m, 1H), 3.94 (m, 1H), 3.68 (m, 1H), 2.51 (m, 1H), 2.35 (m, 1H), 2.07-2.04 (5H), 1.95-1.92 (2H), 1.80-1.75 (4H), 1.70-1.62 (4H), 1.54-1.49 (2H), 1.11 (d, *J* = 6.3 Hz, 3H), 0.96 (d, *J* = 5.7 Hz, 3H), 0.92 (d, *J* = 6.9 Hz, 3H), 0.90 (d, *J* = 6.9 Hz, 3H).

**<sup>13</sup>C NMR (Acetone-d<sub>6</sub>, 75 MHz)** δ 173.9, 166.9, 142.8, 140.6, 136.4, 135.5, 133.3, 132.7, 132.1, 131.2, 130.8, 130.1, 129.8, 128.9, 128.2, 125.4, 81.4, 77.4, 76.8, 73.3, 68.7, 42.8, 39.7, 38.0, 37.9, 37.0, 36.2, 34.1, 25.2, 21.6, 21.0, 19.9, 19.4, 14.3.

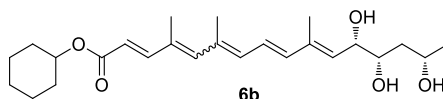
**HRMS-ESI** calculated for C<sub>34</sub>H<sub>48</sub>O<sub>7</sub>Na: *m/z* 591.3292 ([M+Na]<sup>+</sup>), found: *m/z* 591.3285 ([M+Na]<sup>+</sup>).

#### 4. Simplification of the core structure and inclusion of fluorescent motifs



**Cyclohexyl (2*E*,4*E*,6*E*,8*E*,10*E*,12*S*,13*S*,15*S*)-12,13,15-tris[(*tert*-butyldimethylsilyl)oxy]-4,6,10-trimethylhexadeca-2,4,6,8,10-pentaenoate (SI-48)**

To a solution of **18k**<sup>1</sup> (25 mg, 0.037 mmol) in benzene (0.7 mL) were added diisopropylethyl amine (25 μL, 0.14 mmol), 2,4,6-trichlorobenzoyl chloride (12 μL, 0.07 mmol), and DMAP (25 mg). The reaction mixture was stirred at room temperature for 15 min and cyclohexanol (10 μL) was added. After being stirred at room temperature for 14 h, an aqueous saturated solution of sodium hydrogenocarbonate was added to the reaction mixture. The aqueous layer was extracted three times with benzene. The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude product was purified on preparative TLC eluting with heptane/ethyl acetate 90:10 to give **SI-48** as a yellow oil. A (4'*E*)/(4'*Z*) = 84:16 mixture could be detected by <sup>1</sup>H analysis. **<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)** δ 7.87 (d, *J* = 15.6 Hz, 1H, *Z* isomer), 7.33 (d, *J* = 15.5 Hz, 1H, *E* isomer), 6.51 (dd, *J* = 14.8, 11.2 Hz, 1H), 6.37 (d, *J* = 14.8 Hz, 1H), 6.36 (s, 1H), 6.28 (d, *J* = 11.2 Hz, 1H), 5.86 (d, *J* = 15.5 Hz, 1H), 5.59 (d, *J* = 8.8 Hz, 1H), 4.85 (m, 1H), 4.43 (m, 1H), 3.90 (m, 1H), 3.63 (m, 1H), 2.02 (s, 3H), 1.85 (s, 3H), 1.80-1.76 (2H), 1.59 (s, 3H), 1.47-1.37 (6H), 1.31-1.25 (4H), 1.14 (d, *J* = 4.8 Hz, 3H), 0.88 (s, 9H), 0.87 (s, 9H), 0.86 (s, 9H), 0.06 (s, 9H), 0.05 (s, 3H), 0.02 (s, 3H), -0.03 (s, 3H).



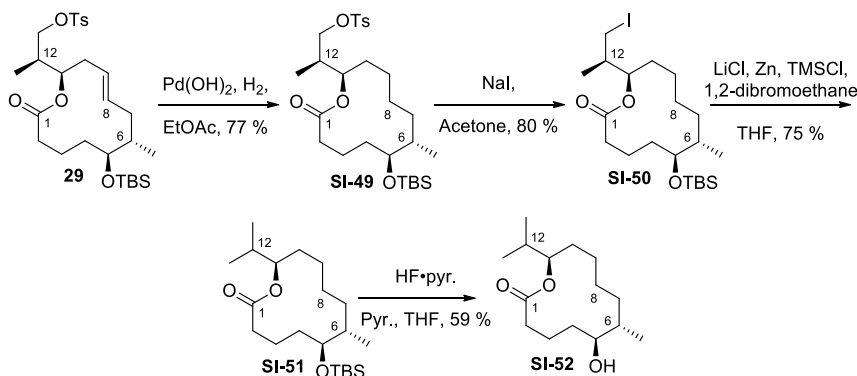
**Cyclohexyl (2*E*,4*E*,6*E*,8*E*,10*E*,12*S*,13*S*,15*S*)-12,13,15-trihydroxy-4,6,10-trimethylhexadeca-2,4,6,8,10-pentaenoate (6b)**

To a solution of **SI-48** previously obtained in THF (0.3 mL) was added TBAF (0.4 mmol, 1M in THF, 9 eq.). The solution was stirred at room temperature for 4 h. CaCO<sub>3</sub> (90 mg), Dowex 50WX8-400 (285 mg) and MeOH (0.6 mL) were added and the reaction mixture was stirred for 1 h. After being filtered and concentrated under reduced pressure, the crude product was purified by TLC preparative (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 90:10) to give **6b** (9 mg, 0.021 mmol, 58 % over two steps). A (4'*E*)/(4'*Z*) = 60:40 mixture could be detected by <sup>1</sup>H analysis.

**<sup>1</sup>H NMR (Acetone-d<sub>6</sub>, 300 MHz)** δ 7.93 (d, *J* = 15.9 Hz, 1H, *Z* isomer), 7.34 (d, *J* = 15.6 Hz, 1H, *E* isomer), 6.63 (dd, *J* = 11.1, 14.5 Hz, 1H), 6.46 (s, 1H), 6.38 (d, *J* = 14.5 Hz, 1H), 6.16 (d, *J* = 11.1 Hz, 1H), 5.92 (d, *J* = 15.6 Hz, 1H), 5.60 (d, *J* = 9.1 Hz, 1H), 4.77 (m, 1H), 4.30-4.20 (2H), 4.02-3.91 (2H), 3.69-3.58 (2H), 2.04 (s, 3H), 1.97 (s, 3H), 1.90 (s, 3H), 1.87-1.68 (6H), 1.54-1.34 (6H), 1.13 (d, *J* = 6.2 Hz, 3H).

**<sup>13</sup>C NMR (Acetone-d<sub>6</sub>, 75 MHz)** δ 167.8, 152.0, 144.0, 141.3, 138.3, 137.1, 136.3, 135.8, 133.1, 126.1, 118.6, 76.7, 73.6, 73.3, 68.7, 42.8, 33.4, 27.1, 25.4, 25.1, 22.0, 18.6, 18.1, 15.3, 14.3.

**HRMS-ESI** calculated for C<sub>25</sub>H<sub>38</sub>O<sub>5</sub>Na : *m/z* 441.2611 ([M+Na]<sup>+</sup>), found: *m/z* 441.2609 ([M+Na]<sup>+</sup>).



**(2*S*)-2-[(2*R*,7*S*,8*S*)-8-[(*tert*-butyldimethylsilyl)oxy]-7-methyl-12-oxo-1-oxacyclododecan-2-yl]propyl 4-methylbenzene-1-sulfonate (SI-49)**

To a solution of **29**<sup>1</sup> (70 mg, 0.13 mmol) in ethyl acetate (1 mL) was added Pd(OH)<sub>2</sub>. The suspension was stirred under hydrogen at room temperature overnight. The next day, the suspension was filtered through a plug of silica gel and concentrated. The crude compound was purified by preparative TLC (elution: 90:10 cyclohexane/ethyl acetate) to afford **SI-49** as a colorless oil (55 mg, 0.1 mmol, 77 %).

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)** δ 7.75 (d, *J* = 8.3 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 4.75 (td, *J* = 3.5, 10.0 Hz, 1H), 3.99 (dd, *J* = 3.5, 9.4 Hz, 1H), 3.83 (dd, *J* = 5.9, 9.4 Hz, 1H), 3.1 (m, 1H), 2.44 (s, 3H), 2.33 (m, 1H), 2.03-1.19 (15H), 0.94 (d, *J* = 6.9 Hz, 3H), 0.84 (s, 9H), 0.84 (d, *J* = 6.4 Hz, 3H), 0.03 (s, 3H), 0.01 (s, 3H).

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)** δ 172.9, 144.7, 132.7 (2C), 129.8 (2C), 127.9, 74.2, 72.8, 71.7, 35.3, 34.3, 32.9, 31.8, 29.5, 26.9, 25.9 (3C), 23.8, 21.6, 18.9, 18.1, 17.8, 17.3, 13.1, -4.3, -4.9.

**(6S,7S,12R)-6-[(*tert*-Butyldimethylsilyl)oxy]-12-[(2R)-1-iodopropan-2-yl]-7-methyl-1-oxacyclododecan-2-one (SI-50)**

To a solution of **SI-49** (55 mg; 0.1 mmol) in acetone (3 mL) was added sodium iodide (60 mg) and the solution was heated under reflux in the dark for 14 hours. The solution was cooled down to room temperature and ethyl acetate and water were added to the reaction mixture. The aqueous layer was extracted with ethyl acetate; the resulting organic extracts were rinsed with an aqueous saturated solution of sodium bisulfate, dried over anhydrous sodium sulfate, filtered and concentrated. The crude oil obtained was purified by preparative TLC (elution: 90:10 cyclohexane/ethyl acetate) to afford **SI-50** as a colorless oil (41 mg; 0.08 mmol, 80 %).

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)** δ 4.75 (td, *J* = 3.5, 9.7 Hz, 1H), 3.38 (m, 1H), 3.29 (dd, *J* = 3.1, 9.7 Hz, 1H), 3.13 (dd, *J* = 6.7, 9.7, 1H), 2.59 (ddd, *J* = 3.3, 5.1, 13.2 Hz, 1H), 2.10 (m, 1H), 1.85-1.32 (14H), 1.02 (d, *J* = 6.7 Hz, 3H), 0.90 (s, 9 H), 0.88 (d, *J* = 3.9 Hz, 3H), 0.06 (s, 3H), 0.04 (s, 3H).

**(6S,7S,12R)-6-[(*tert*-Butyldimethylsilyl)oxy]-12-isopropyl-7-methyl-1-oxacyclododecan-2-one (SI-51)**

Anhydrous LiCl (25 mg) was placed in an argon-flushed flask and dried for 30 min at 150 °C under high vacuum. Zn powder (51 mg) was added under argon and the heterogeneous mixture was dried again for 30 min at 150 °C under high vacuum. After cooling to 25 °C, the flask was evacuated and refilled with argon three times. THF (0.5 mL) was added and the Zn was activated with 1,2-dibromoethane (13 µL) and TMSCl (13 µL). After stirring for 10 minutes a solution of **SI-50** (41 mg, 0.08 mmol) in THF (0.5 mL) was added. The reaction mixture was then stirred at room temperature for 12 h before being hydrolyzed with a saturated aqueous solution of NH<sub>4</sub>Cl. The aqueous phase was extracted with ethyl acetate, and the combined organic phases were washed with brine and dried over MgSO<sub>4</sub>. After being filtered and concentrated under reduced pressure, the crude product was purified by preparative TLC (elution with heptane/ethyl acetate 90:10, to give **SI-51** (22 mg, 0.06 mmol, 75 %) as a colorless oil.

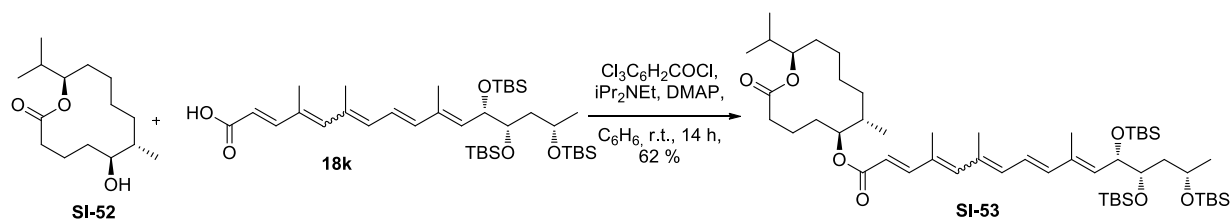
**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)** δ 4.66 (dt, *J* = 4.0, 8.7 Hz, 1H), 3.40 (m, 1H), 2.57 (ddd, *J* = 2.9, 5.5, 13.4 Hz, 1H), 2.09 (m, 1H), 1.89-1.25 (14H), 0.90 (s, 3H), 0.89 (s, 3H), 0.88 (s, 9H), 0.85 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H).

**(6S,7S,12R)-6-Hydroxy-7-methyl-12-(propan-2-yl)-1-oxacyclododecan-2-one (SI-52)**

To a solution of **SI-51** (22.0 mg, 0.06 mmol) in pyridine (1.5 mL), in a Nalgene® tube, at 0 °C was added a solution of hydrogen fluoride-pyridine (0.5 mL). The reaction was then allowed to warm up to room temperature and then heated at 40 °C for 12 hours. The cool reaction mixture was quenched by slow addition of a saturated solution of sodium bicarbonate followed by sodium carbonate powder till the bubbling stopped. The aqueous layer was extracted with ethyl acetate and the ethyl acetate extracts were washed successively with a 15% solution of copper sulfate and brine before being dried over anhydrous sodium sulfate, filtered and concentrated. The resulting crude compound was purified by

preparative TLC plate (eluting with cyclohexane/ethyl acetate 80:20) to afford alcohol **SI-52** as a colorless solid (9 mg, 0.035 mmol, 59%).

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)** δ 4.71 (ddd, *J* = 4.3, 5.4, 8.6 Hz, 1H), 3.43 (m, 1H), 2.48 (m, 1H), 2.22 (m, 1H), 1.89-1.78 (4H), 1.68-1.58 (6H), 1.43-1.27 (4H), 0.92 (d, *J* = 6.6 Hz, 3H), 0.89 (d, *J* = 6.7 Hz, 3H), 0.88 (d, *J* = 6.8 Hz, 3H).

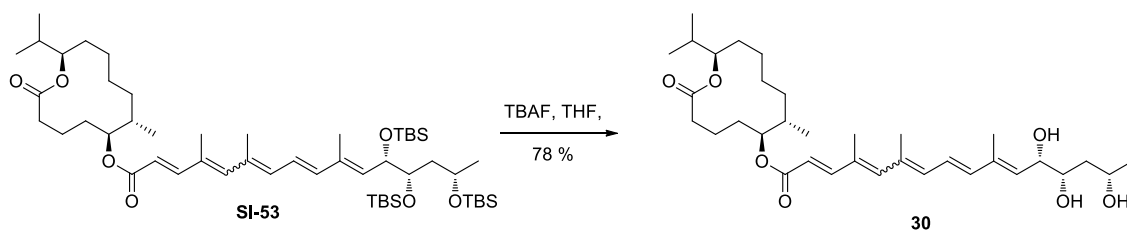


**(6*S*,7*S*,12*R*)-7-Methyl-2-oxo-12-(propan-2-yl)-1-oxacyclododecan-6-yl  
(2*E*,4*E*,6*E*,8*E*,10*E*,12*S*,13*S*,15*S*)-12,13,15-tris[(*tert*-butyldimethylsilyl)oxy]-4,6,10-trimethylhexadeca-  
2,4,6,8,10-pentaenoate (**SI-53**)**

To a solution of **18k**<sup>1</sup> (36 mg, 0.053 mmol) in benzene (0.4 mL) were added diisopropylethyl amine (36 μL, 0.20 mmol, 5.6 eq.), 2,4,6-trichlorobenzoyl chloride (17 μL, 0.11 mmol, 3 eq.), and DMAP (36 mg). The reaction mixture was stirred at room temperature for 15 min and **SI-52** (9 mg, 0.035 mmol) was added. After being stirred at room temperature for 14 h, an aqueous saturated solution of sodium hydrogenocarbonate was added to the reaction mixture. The aqueous layer was extracted three times with benzene. The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude product was purified on preparative TLC eluting with heptane/ethyl acetate 90:10 to give **SI-53** (30 mg, 0.033 mmol, 62 %) as a yellow oil. A (4'*E*)/(4'*Z*) = 80:20 mixture could be detected by <sup>1</sup>H analysis.

**<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)** δ 7.94 (d, *J* = 15.5 Hz, 1H, *Z* isomer), 7.35 (d, *J* = 15.5 Hz, 1H, *E* isomer), 6.49 (dd, *J* = 14.8, 11.4 Hz, 1H), 6.36 (d, *J* = 14.8 Hz, 1H), 6.34 (s, 1H), 6.27 (d, *J* = 11.4 Hz, 1H), 5.85 (d, *J* = 15.5 Hz, 1H), 5.57 (d, *J* = 8.7 Hz, 1H), 4.77-4.65 (2H), 4.42 (dd, *J* = 9.1, 3.6 Hz, 1H), 3.90 (m, 1H), 3.63 (m, 1H), 2.56 (m, 1H), 2.15-2.06 (2H), 2.05 (s, 3H), 2.03 (s, 3H), 1.98-1.96 (5H), 1.84 (s, 3H), 1.87-1.61 (10H), 1.13 (d, *J* = 5.9 Hz, 3H), 0.95 (s, 3H), 0.93 (s, 3H), 0.92 (s, 3H), 0.88 (s, 9H), 0.87 (s, 9H), 0.86 (s, 9H), 0.04 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H), -0.03 (s, 3H).

**HRMS-ESI** calculated for C<sub>52</sub>H<sub>96</sub>O<sub>7</sub>Si<sub>3</sub>Na : *m/z* 939.6356 ([M+Na]<sup>+</sup>), found: *m/z* 939.6340 ([M+Na]<sup>+</sup>).



**(6*S*,7*S*,12*R*)-7-Methyl-2-oxo-12-(propan-2-yl)-1-oxacyclododecan-6-yl  
(2*E*,4*E*,6*E*,8*E*,10*E*,12*S*,13*S*,15*S*)-12,13,15-trihydroxy-4,6,10-trimethylhexadeca-2,4,6,8,10-pentaenoate (30)**

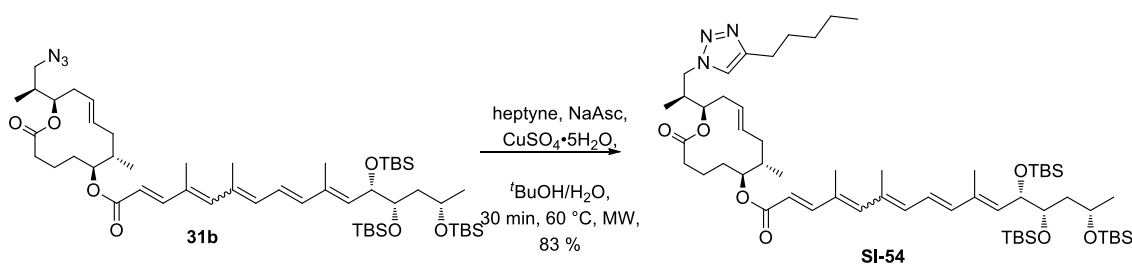
To a solution of **SI-53** (30 mg, 0.032 mmol) in THF (0.3 mL) was added TBAF (0.3 mmol, 1M in THF, 9 eq). The solution was stirred at room temperature for 4 h. CaCO<sub>3</sub> (50 mg), Dowex 50WX8-400 (150 mg) and MeOH (0.4 mL) were added and the reaction mixture was stirred for 1 h. After being filtered and concentrated under reduced pressure, the crude product was purified by TLC preparative (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 90:10) to give **30** (14 mg, 0.025 mmol, 78 %).

A (4'*E*)/(4'*Z*) = 74:26 mixture could be detected by <sup>1</sup>H analysis.

**<sup>1</sup>H NMR (Acetone-d<sub>6</sub>, 300 MHz)** δ 7.93 (d, *J* = 15.6 Hz, 1H, *Z* isomer), 7.37 (d, *J* = 15.5 Hz, 1H, *E* isomer), 6.63 (dd, *J* = 11.1, 15.0 Hz, 1H), 6.47 (s, 1H), 6.36 (d, *J* = 15.0 Hz, 1H), 6.17 (d, *J* = 11.1 Hz, 1H), 5.89 (d, *J* = 15.5 Hz, 1H), 5.59 (d, *J* = 8.8 Hz, 1H), 4.74-4.60 (2H), 4.28-4.25 (2H), 4.07-3.94 (3H), 3.66 (m, 1H), 2.59 (m, 1H), 2.12-2.08 (3H), 2.06 (s, 3H), 1.97 (s, 3H), 1.95-1.92 (2H), 1.90 (s, 3H), 1.80-1.75 (4H), 1.70-1.62 (4H), 1.54-1.49 (4H), 1.13 (d, *J* = 6.1 Hz, 3H), 0.92 (s, 3H), 0.90 (s, 3H), 0.87 (s, 3H).

**<sup>13</sup>C NMR (Acetone-d<sub>6</sub>, 75 MHz)** δ 173.9, 167.9, 152.2, 145.3, 144.1, 142.8, 141.3, 138.3, 137.2, 136.3, 135.9, 135.8, 134.2, 126.1, 118.3, 79.9, 77.7, 76.8, 73.3, 68.7, 42.8, 36.5, 33.4, 31.4, 29.1, 25.5, 25.2, 20.9, 20.7, 19.6, 18.2, 18.1, 15.3, 14.4.

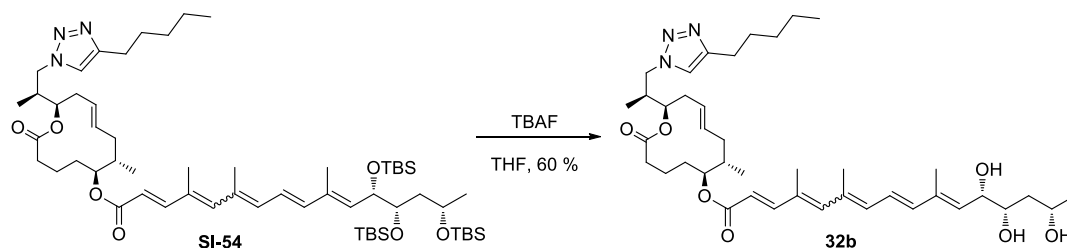
**HRMS-ESI** calculated for C<sub>34</sub>H<sub>54</sub>O<sub>7</sub>Na : *m/z* 597.3762 ([M+Na]<sup>+</sup>), found: *m/z* 597.3750 ([M+Na]<sup>+</sup>).



**(6*S*,7*S*,9*E*,12*R*)-7-Methyl-2-oxo-12-[(2*S*)-1-(4-pentyl-1*H*-1,2,3-triazol-1-yl)propan-2-yl]-1-oxacyclododec-9-en-6-yl (2*E*,4*E*,6*E*,8*E*,10*E*,12*S*,13*S*,15*S*)-12,13,15-tris[(*tert*-butyldimethylsilyl)oxy]-4,6,10-trimethylhexadeca-2,4,6,8,10-pentaenoate (SI-54)**

To a solution of **31b**<sup>1</sup> (11 mg, 0.012 mmol) in a mixture of *t*-BuOH (0.125 mL) and water (0.075 mL) were added a solution of sodium ascorbate (14 μL, 15 %) in water, a solution of CuSO<sub>4</sub>·5H<sub>2</sub>O (17 μL, 15 %) in water and heptyne (12 mg, 0.013 mmol, 1.1 eq.). The reaction mixture was heated for 30 min at 60 °C (MW irradiation), before being purified by preparative TLC (heptane/ethyl acetate 20:80) to give **SI-54** (10 mg, 0.01 mmol, 83 %). A (4'*E*)/(4'*Z*) = 52:48 mixture could be detected by <sup>1</sup>H analysis.

**<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)** δ 7.95 (d, *J* = 15.5 Hz, 1H, *Z* isomer), 7.36 (d, *J* = 15.5 Hz, 1H, *E* isomer), 7.29 (s, 1H), 6.49 (dd, *J* = 14.8, 11.2 Hz, 1H), 6.37 (d, *J* = 14.8 Hz, 1H), 6.36 (s, 1H), 6.28 (d, *J* = 11.2 Hz, 1H), 5.85 (d, *J* = 15.5 Hz, 1H), 5.52 (d, *J* = 9.0 Hz, 1H), 5.45 (m, 1H), 5.27 (m, 1H), 4.90 (m, 1H), 4.70 (m, 1H), 4.46-4.40 (2H), 4.09 (m, 1H), 3.91 (m, 1H), 3.64 (m, 1H), 2.70 (m, 1H), 2.49 (m, 1H), 2.30 (m, 1H), 2.15-2.06 (2H), 2.04 (s, 3H), 2.03 (s, 3H), 1.98-1.96 (m, 1H), 1.85 (s, 3H), 1.87-1.61 (6H), 1.13 (d, *J* = 6.0 Hz, 3H), 0.95 (s, 3H), 0.93 (s, 3H), 0.92 (s, 3H), 0.90 (s, 3H), 0.89 (s, 9H), 0.87 (s, 9H), 0.85 (s, 9H), 0.06 (s, 3H), 0.04 (s, 9H), 0.02 (s, 3H), -0.02 (s, 3H).



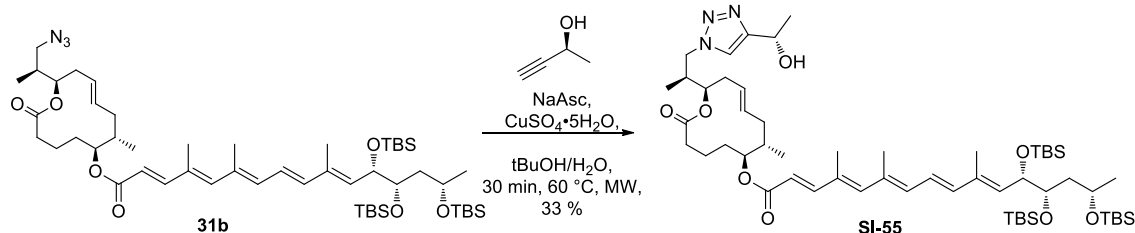
**(6*S*,7*S*,9*E*,12*R*)-12-[(2*S*)-1-(4-Pentyl-1*H*-1,2,3-triazol-1-yl)propan-2-yl]-7-methyl-2-oxo-1-oxacyclododec-9-en-6-yl (2*E*,4*E*,6*E*,8*E*,10*E*,12*S*,13*R*,15*S*)-12,13,15-trihydroxy-4,6,10-trimethylhexadeca-2,4,6,8,10-pentaenoate (32b)**

To a solution of **SI-54** (10 mg, 0.01 mmol) in THF (0.3 mL) was added TBAF (0.09 mmol, 1M in THF, 9 eq.). The solution was stirred at room temperature for 4 h. CaCO<sub>3</sub> (25 mg), Dowex 50WX8-400 (75 mg) and MeOH (0.2 mL) were added and the reaction mixture was stirred for 1 h. After being filtered and concentrated under reduced pressure, the crude product was purified by TLC preparative (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 90:10) to give **32b** (4 mg, 0.006 mmol, 60 %). A (4'*E*)/(4'*Z*) = 42:58 mixture could be detected by <sup>1</sup>H analysis.

**<sup>1</sup>H NMR (Acetone-d<sub>6</sub>, 300 MHz)** δ 7.92 (d, *J* = 15.6 Hz, 1H, *Z* isomer), 7.70 (s, 1H), 7.37 (d, *J* = 15.4 Hz, 1H, *E* isomer), 6.63 (dd, *J* = 11.1, 15.0 Hz, 1H), 6.47 (s, 1H), 6.36 (d, *J* = 15.0 Hz, 1H), 6.17 (d, *J* = 11.1 Hz, 1H), 5.89 (d, *J* = 15.5 Hz, 1H), 5.60 (d, *J* = 8.7 Hz, 1H), 5.50 (m, 1H), 5.30 (m, 1H), 4.90 (m, 1H), 4.70 (m, 1H), 4.47 (dd, *J* = 5.4, 13.7 Hz, 1H), 4.28 (m, 1H), 4.16 (dd, *J* = 8.8, 13.7 Hz, 1H), 4.04 (m, 1H), 3.67 (m, 1H), 2.67-2.60 (2H), 2.51 (m, 1H), 2.43 (m, 1H), 2.34 (m, 1H), 2.21 (m, 1H), 2.09 (s, 3H), 1.98 (s, 3H), 1.96-1.87 (2H), 1.90 (s, 3H), 1.80-1.75 (2H), 1.70-1.60 (8H), 1.54-1.51 (4H), 1.35-1.28 (4H), 1.12 (d, *J* = 6.1 Hz, 3H), 0.91 (s, 3H), 0.87 (s, 3H).

**<sup>13</sup>C NMR (Acetone-d<sub>6</sub>, 75 MHz)** δ 173.9, 167.8, 152.2, 144.1, 142.8, 141.4, 140.9, 137.0, 135.9, 135.8, 133.1, 127.4, 126.1, 123.5, 120.6, 118.4, 80.1, 76.7, 74.6, 73.3, 68.7, 53.6, 42.8, 40.5, 39.7, 37.9, 37.0, 36.0, 33.1, 27.2, 25.2, 24.1, 22.0, 21.7, 21.6, 20.8, 20.7, 18.6, 18.1, 15.3, 14.3.

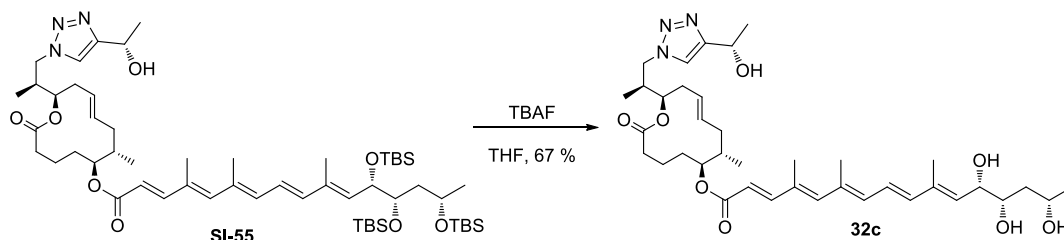
**HRMS-ESI** calculated for C<sub>41</sub>H<sub>63</sub>N<sub>3</sub>O<sub>7</sub>Na : *m/z* 732.4558 ([M+Na]<sup>+</sup>), found: *m/z* 732.4548 ([M+Na]<sup>+</sup>).



**(6*S*,7*S*,9*E*,12*R*)-12-[(2*S*)-1-{4-[(1*S*)-1-Hydroxyethyl]-1*H*-1,2,3-triazol-1-yl}propan-2-yl]-7-methyl-2-oxo-1-oxacyclododec-9-en-6-yl (2*E*,4*E*,6*E*,8*E*,10*E*,12*S*,13*S*,15*S*)-12,13,15-tris[(*tert*-butyldimethylsilyl)oxy]-4,6,10-trimethylhexadeca-2,4,6,8,10-pentaenoate (SI-55)**

To a solution of **31b**<sup>1</sup> (11 mg, 0.018 mmol) in a mixture of *t*-BuOH (0.125 mL) and water (0.075 mL) were added a solution of sodium ascorbate (14  $\mu$ L, 15 %) in water, a solution of CuSO<sub>4</sub>•5H<sub>2</sub>O (17  $\mu$ L, 15 %) in water and (*S*)-3-butyn-2-ol (20  $\mu$ L, 0.26 mmol, 1.1 eq.). The reaction mixture was heated for 30 min at 60 °C (MW irradiation), before being purified by preparative TLC (heptane/ethyl acetate 70:30) to give **SI-55** (6 mg, 0.006 mmol, 33 %). A (4'*E*)/(4'*Z*) = 61:39 mixture could be detected by <sup>1</sup>H analysis.

**HRMS-ESI** calculated for C<sub>56</sub>H<sub>99</sub>N<sub>3</sub>O<sub>8</sub>Si<sub>3</sub>Na : *m/z* 1048.6632 ([M+Na]<sup>+</sup>), found: *m/z* 1048.6621 ([M+Na]<sup>+</sup>).



**(6*S*,7*S*,9*E*,12*R*)-12-[(2*S*)-1-{4-[(1*S*)-1-hydroxyethyl]-1*H*-1,2,3-triazol-1-yl}propan-2-yl]-7-methyl-2-oxo-1-oxacyclododec-9-en-6-yl (2*E*,4*E*,6*E*,8*E*,10*E*,12*S*,13*R*,15*S*)-12,13,15-trihydroxy-4,6,10-trimethylhexadeca-2,4,6,8,10-pentaenoate (32c)**

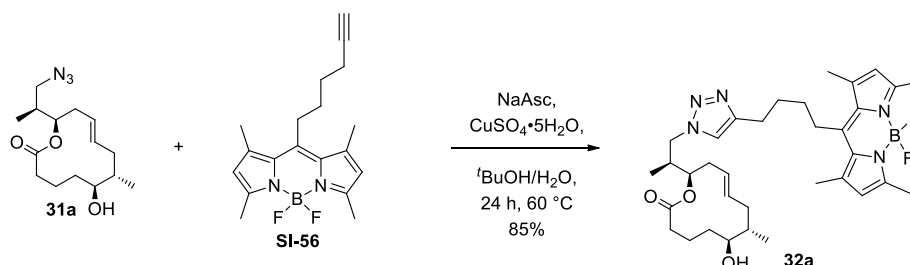
To a solution of **SI-55** (6 mg, 0.006 mmol) in THF (0.3 mL) was added TBAF (0.08 mmol, 1M in THF, 13 eq). The solution was stirred at room temperature for 4 h. CaCO<sub>3</sub> (25 mg), Dowex 50WX8-400 (75 mg) and MeOH (0.2 mL) were added and the reaction mixture was stirred for 1 h. After being filtered and concentrated under reduced pressure, the crude product was purified by TLC preparative (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 90:10) to give **32c** (3 mg, 0.004 mmol, 67 %). Due to the minute amount of **32c**, a clean <sup>13</sup>C NMR could not be obtained. However, <sup>1</sup>H NMR and HRMS analyses are unambiguous. A (4'*E*)/(4'*Z*) = 42:58 mixture could be detected by <sup>1</sup>H analysis.

**<sup>1</sup>H NMR (Acetone-d<sub>6</sub>, 300 MHz)**  $\delta$  7.92 (d, *J* = 15.6 Hz, 1H, *Z* isomer), 7.70 (s, 1H), 7.37 (d, *J* = 15.4 Hz, 1H, *E* isomer), 6.63 (dd, *J* = 11.1, 15.0 Hz, 1H), 6.47 (s, 1H), 6.36 (d, *J* = 15.0 Hz, 1H), 6.17 (d, *J* = 11.1 Hz, 1H), 5.89 (d, *J* = 15.5 Hz, 1H), 5.60 (d, *J* = 9.5 Hz, 1H), 5.50 (m, 1H), 5.30 (m, 1H), 4.99-4.88 (2H), 4.70 (m, 1H), 4.50 (dd, *J* = 5.3, 13.8 Hz, 1H), 4.30-4.18 (3H), 4.04 (m, 1H), 3.95 (m, 1H), 3.67 (m, 1H), 3.58 (m, 1H), 2.51 (m, 1H), 2.43 (m, 1H), 2.34 (m, 1H), 2.21 (m, 1H), 2.09 (s, 3H), 1.98 (s, 3H), 1.96-1.87 (2H),



1.90 (s, 3H), 1.80-1.75 (2H), 1.70-1.60 (4H), 1.54-1.51 (2H), 1.48 (d,  $J = 6.5$  Hz, 3H), 1.35-1.28 (2H), 1.12 (d,  $J = 6.1$  Hz, 3H), 0.91 (s, 3H), 0.87 (s, 3H).

**HRMS-ESI** calculated for  $C_{38}H_{57}N_3NaO_8$ :  $m/z$  706.4037 ( $[M+Na]^+$ ), found:  $m/z$  706.4030 ( $[M+Na]^+$ ).



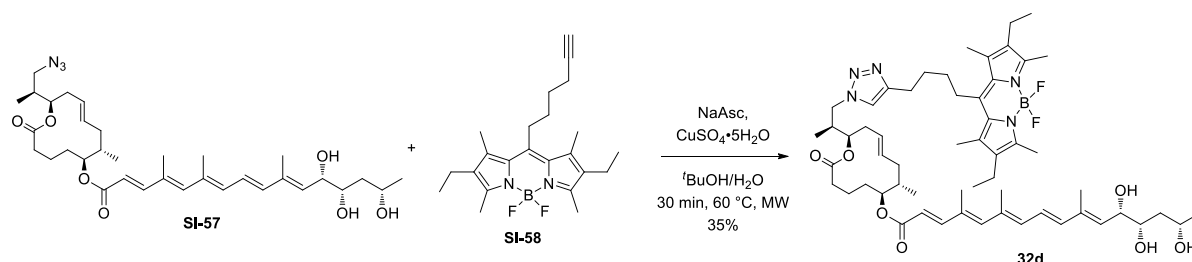
**(6*S*,7*S*,9*E*,12*R*)-12-[(2*S*)-1-[4-(4-{2,2-difluoro-4,6,10,12-tetramethyl-1 $\lambda^4$ ,3-diaza-2- $\lambda^4$ -boratricyclo[7.3.0.0<sup>3,7</sup>]dodeca-1(12),4,6,8,10-pentaen-8-yl}butyl)-1*H*-1,2,3-triazol-1-yl]propan-2-yl]-6-hydroxy-7-methyl-1-oxacyclododec-9-en-2-one (32a)**

To a solution of **31a**<sup>1</sup> (10 mg, 0.034 mmol) in a mixture of *t*-BuOH (0.130 mL) and water (0.130 mL) were added a solution of sodium ascorbate (50  $\mu$ L, 15 %) in water, a solution of  $CuSO_4 \cdot 5H_2O$  (80  $\mu$ L, 10 %) in water and **SI-56**<sup>1</sup> (11 mg, 0.034 mmol). The reaction mixture was heated for 24 h at 60 °C, before being purified by preparative TLC (heptane/ethyl acetate 25:75) to give **32a** (18 mg, 0.029 mmol, 85 %) as a red oil.

**$^1H$  NMR** ( $CDCl_3$ , 300 MHz)  $\delta$  7.31 (s, 1H), 6.03 (s, 2H), 5.45 (m, 1H), 5.20 (m, 1H), 4.95 (m, 1H), 4.42 (dd,  $J = 13.9, 5.1$  Hz, 1H), 4.07 (dd,  $J = 13.9, 8.1$  Hz, 1H), 3.44 (m, 1H), 3.00-2.94 (2H), 2.80-2.74 (2H), 2.50 (s, 6H), 2.37 (s, 6H), 2.31-2.25 (2H), 1.97-1.93 (2H), 1.93-1.75 (5H), 1.72-1.58 (6H), 1.52-1.47 (2H), 0.99 (d,  $J = 6.7$  Hz, 3H), 0.85 (d,  $J = 6.9$  Hz, 3H).

**$^{13}C$  NMR** ( $CDCl_3$ , 75 MHz)  $\delta$  174.1, 153.8 (2C), 147.3 (2C), 146.0, 140.3 (2C), 135.4, 131.4, 125.5, 121.6 (2C), 121.4, 74.3, 73.3, 52.2, 38.6, 38.0, 36.6, 35.2, 32.9, 31.4, 29.7, 28.1, 25.4, 19.2, 18.6 (2C), 16.4 (2C), 14.4 (2C), 14.1.

**HRMS-ESI** calculated for  $C_{34}H_{48}BF_2N_5O_3Na$ :  $m/z$  646,3716 ( $[M+Na]^+$ ), found:  $m/z$  646,3706 ( $[M+Na]^+$ ).



**(6*S*,7*S*,9*E*,12*R*)-12-[(2*S*)-1-[4-(4-{5,11-Diethyl-2,2-difluoro-4,6,10,12-tetramethyl-1  $\lambda^4$ ,3-diaza-2  $\lambda^4$ -boratricyclo[7.3.0.0<sup>3,7</sup>]dodeca-1(12),4,6,8,10-pentaen-8-yl}butyl)-1*H*-1,2,3-triazol-1-yl]propan-2-yl]-7-methyl-2-oxo-1-oxacyclododec-9-en-6-yl-(2*E*,4*E*,6*E*,8*E*,10*E*,12*S*,13*S*,15*S*)-12,13,15-trihydroxy-4,6,10-trimethylhexadeca-2,4,6,8,10-pentaenoate (32d)**

To a solution of **SI-57**<sup>1</sup> (11.9 mg, 0.020 mmol) in a mixture of *t*-BuOH (0.125 mL) and water (0.075 mL) were added a solution of sodium ascorbate (11  $\mu$ L, 3  $\mu$ M, 15 %) in water, a solution of CuSO<sub>4</sub>•5H<sub>2</sub>O (14  $\mu$ L, 3  $\mu$ M, 15 %) in water and **SI-58**<sup>6</sup> (8.4 mg, 0.022 mmol, 1.1 eq.). The reaction mixture was heated for 30 min at 60 °C under microwave irradiation, before being purified by preparative TLC (heptane/ethyl acetate 20:80) to give **32d** (7 mg, 0.007 mmol, 35 %) and **SI-57** (8 mg, 0.013 mmol). A (4'*E*)/(4'*Z*) = 50:50 mixture could be detected by <sup>1</sup>H analysis.

**<sup>1</sup>H NMR (Acetone-d<sub>6</sub>, 400 MHz, 4'*Z* isomer)**  $\delta$  7.92 (d, *J* = 15.6 Hz, 1H), 7.74 (s, 1H), 6.66 (dd, *J* = 15.0, 11.5 Hz), 6.45 (d, *J* = 15.5 Hz, 1H), 6.33 (s, 1H), 6.16 (d, *J* = 11.5 Hz, 1H), 5.94 (d, *J* = 15.6 Hz, 1H), 5.60 (m, 1H), 5.52 (m, 1H), 5.26 (m, 1H), 5.20 (m, 1H), 4.89 (m, 1H), 4.68 (m, 1H), 4.47 (dd, *J* = 13.8, 5.1 Hz, 1H), 4.28 (m, 1H), 4.22 (m, 1H), 4.16 (m, 1H), 4.02 (m, 1H), 3.99 (m, 1H), 3.67 (m, 1H), 3.07-3.02 (2H), 2.83-2.77 (3H), 2.52 (m, 1H), 2.45 (s, 6H), 2.43 (s, 6H), 2.35-2.30 (2H), 2.25-2.19 (3H), 2.09 (s, 3H), 2.03 (s, 3H), 1.91 (s, 3H), 1.82 (m, 1H), 1.76-1.66 (8H), 1.54-1.51 (2H), 1.12 (d, *J* = 6.1 Hz, 3H), 1.04 (t, *J* = 7.5 Hz, 6H), 0.91 (d, *J* = 6.2 Hz, 3H), 0.85 (d, *J* = 6.9 Hz, 3H).

**<sup>13</sup>C NMR (Acetone-d<sub>6</sub>, 100 MHz, 4'*Z* isomer)**  $\delta$  174.0, 167.8, 155.3 (2C), 148.7 (2C), 145.4, 144.1, 142.8, 138.3, 137.0 (3C), 136.3, 135.9, 135.8, 135.7, 134.2, 133.1, 131.0, 127.3, 126.1, 123.8, 123.4 (2C), 120.6, 80.1, 76.8, 74.6, 73.3, 68.7, 53.6, 42.8, 40.5, 39.6, 38.0, 36.9, 36.0, 33.0, 29.9, 26.9, 25.3, 22.0, 21.7, 20.8, 18.6, 18.1, 17.4 (4C), 16.0, 15.4, 15.3, 14.4, 13.2.

**<sup>1</sup>H NMR (Acetone-d<sub>6</sub>, 400 MHz, 4'*E* isomer)**  $\delta$  7.74 (s, 1H), 7.37 (d, *J* = 15.4 Hz, 1H), 6.64 (dd, *J* = 14.8, 11.2 Hz, 1H), 6.46 (s, 1H), 6.40 (d, *J* = 14.8 Hz, 1H), 6.36 (d, *J* = 11.2 Hz, 1H), 6.17 (s, 2H), 5.89 (d, *J* = 15.4 Hz, 1H), 5.60 (m, 1H), 5.53 (m, 1H), 5.28 (m, 1H), 5.20 (m, 1H), 4.89 (m, 1H), 4.68 (m, 1H), 4.47 (dd, *J* = 13.8, 5.2 Hz, 1H), 4.28 (m, 1H), 4.22 (m, 1H), 4.16 (m, 1H), 4.02 (m, 1H), 3.99 (m, 1H), 3.67 (m, 1H), 3.07-3.02 (2H), 2.83-2.77 (3H), 2.52 (m, 1H), 2.45 (s, 6H), 2.43 (s, 6H), 2.35-2.30 (2H), 2.25-2.19 (3H), 2.09 (s, 3H), 2.03 (s, 3H), 1.91 (s, 3H), 1.82 (m, 1H), 1.76-1.66 (8H), 1.54-1.51 (2H), 1.12 (d, *J* = 6.1 Hz, 3H), 1.04 (t, *J* = 7.5 Hz, 6H), 0.91 (d, *J* = 6.2 Hz, 3H), 0.85 (d, *J* = 6.9 Hz, 3H).

**<sup>13</sup>C NMR (Acetone-d<sub>6</sub>, 75 MHz, 4'*E* isomer)**  $\delta$  174.0, 167.8, 155.3 (2C), 152.2, 148.7 (2C), 141.4, 140.9, 138.3, 137.2, 137.0 (3C), 136.3, 135.9, 135.8, 134.2, 133.1, 131.0, 127.3, 126.1, 123.8, 123.4 (2C), 118.3, 80.1, 76.8, 74.6, 73.3, 68.7, 53.6, 42.8, 40.5, 39.6, 38.0, 36.9, 36.0, 33.0, 29.9, 26.9, 25.3, 22.0, 21.6, 20.8, 18.6, 18.1, 17.4 (4C), 16.0, 15.4, 15.3, 14.4, 13.2.

**<sup>11</sup>B NMR (Acetone-d<sub>6</sub>, 128 MHz)**  $\delta$  3.83-3.32 (t, *J* = 33.0 Hz).

**<sup>19</sup>F NMR (Acetone-d<sub>6</sub>, 373 MHz)**  $\delta$  -140.75, -141.03 (2 q, *J* = 32.7 Hz).

**HRMS-ESI** calculated for C<sub>57</sub>H<sub>82</sub>BF<sub>2</sub>N<sub>5</sub>O<sub>7</sub>Na: *m/z* 1020.6160 ([M+Na]<sup>+</sup>), found: *m/z* 1020,6177 ([M+Na]<sup>+</sup>).

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