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First total synthesis and determination of the absolute configuration of mueggelone

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Abstract—All the four possible stereoisomers of mueggelone, an inhibitor of fish development, were efficiently synthesized in a stereoselective manner starting from D-arabinose, and the absolute configuration was determined to be 9*R*, 12*S*, 13*S*.

1. Introduction

Mueggelone (**1**) has attracted the keen interest of scientists for its unique activity and structure since it was isolated from a bloom-foaming strain of *Aphanizomenon flos-aquae* in 1995 (Fig. 1).[1] With mueggelone at a concentration of 10 μg/mL, zebra fish larvae showed 45% mortality and the surviving larvae showed edema in the heart region and thrombosis. This compound is thought to play an ecologically important role in inhibition of the development of herbivorous fish. Mueggelone was found to have a 10-membered lactone and *trans* epoxide by spectroscopic analysis; however, no information has been obtained on the absolute configuration of the three stereocenters. Therefore, we undertook the synthesis of all the four possible stereoisomers of mueggelone (**1**, *ent*-**1**, **2**, *ent*-**2**) to determine the absolute configuration and to provide samples for further biological assay. We have already published a rapid communication,[2] and here we wish to report a full account of our work.

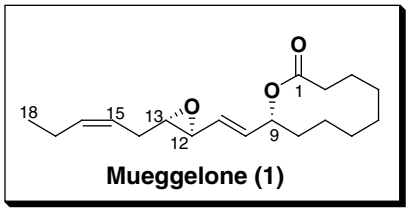

Figure 1.

2. Results and discussion

Our synthetic strategy is illustrated in Scheme 1. We decided to utilize the key intermediate **A**, which could be transformed into any of the four stereoisomers via asymmetric reduction of a ketone, macrolactonization and finally, epoxide formation. Compound **A** would be constructed by Horner–Wadsworth–Emmons (HWE) reaction of the side chain part **B** with the lactone part **C**. Aldehyde **B** and phosphonate **C** would be derived from commercially available compounds, D-arabinose and azelaic acid dimethyl ester, respectively.

The synthesis of the side chain part is outlined in Scheme 2. D-Arabinose was converted into alcohol **3** according to the known procedure.[3] Protection of the hydroxyl group followed by hydrolysis of thioacetal with mercuric salt gave aldehyde **5**, which was submitted to the Wittig reaction to afford *Z*-olefin **6**. The best ratio (*E*/*Z*=1:10) was provided by using NaHMDS as a base, and these isomers were easily separated by $AgNO_3$-impregnated silica gel column chromatography. The *Z*-olefin **6** was simply transformed into the corresponding primary alcohol **10** in 4 steps, which was then mildly oxidized[4] to give the desired aldehyde **11**.

Phosphonate **12** (prepared from azelaic acid dimethyl ester, dimethyl methylphosphonate, *n*-BuLi, THF, −78°C, 22%) was subjected to HWE reaction with the aldehyde **11** (Scheme 3). Under the condition using *n*-BuLi as a base, the *E*/*Z* ratio was 96:4; however, partial epimerization (25%) of the TBSO– group was observed. On the other hand, the procedure employing DBU–LiCl[5] resulted in very little epimerization (1–2%) with excellent *E*/*Z* selectivity (*E*/*Z* => 99 : 1). In the next step, we tried several conditions for the asymmetric reduction of enone **13**, and the best selectivity (9:1) was obtained with the CBS-

Keywords: asymmetric synthesis; reduction; lactonization; epoxides.

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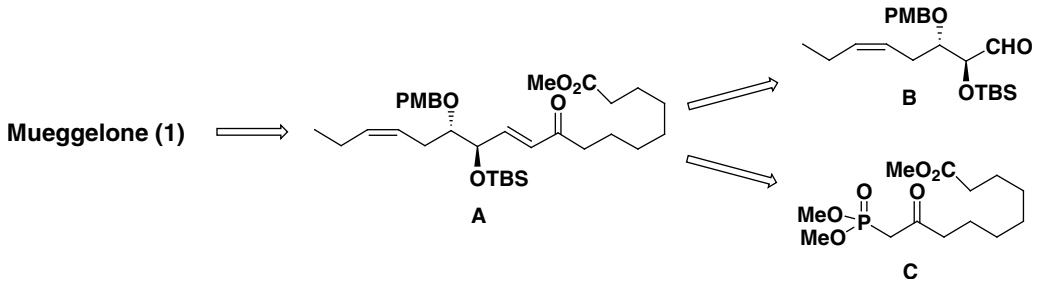
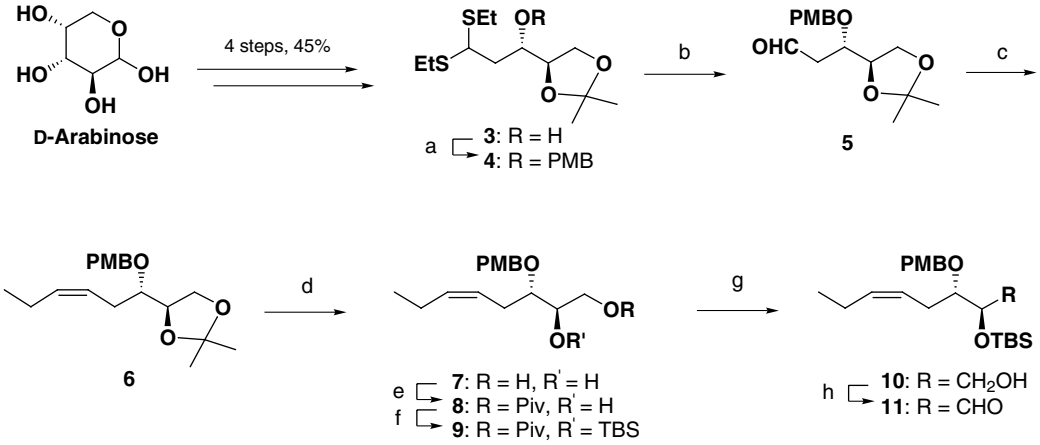
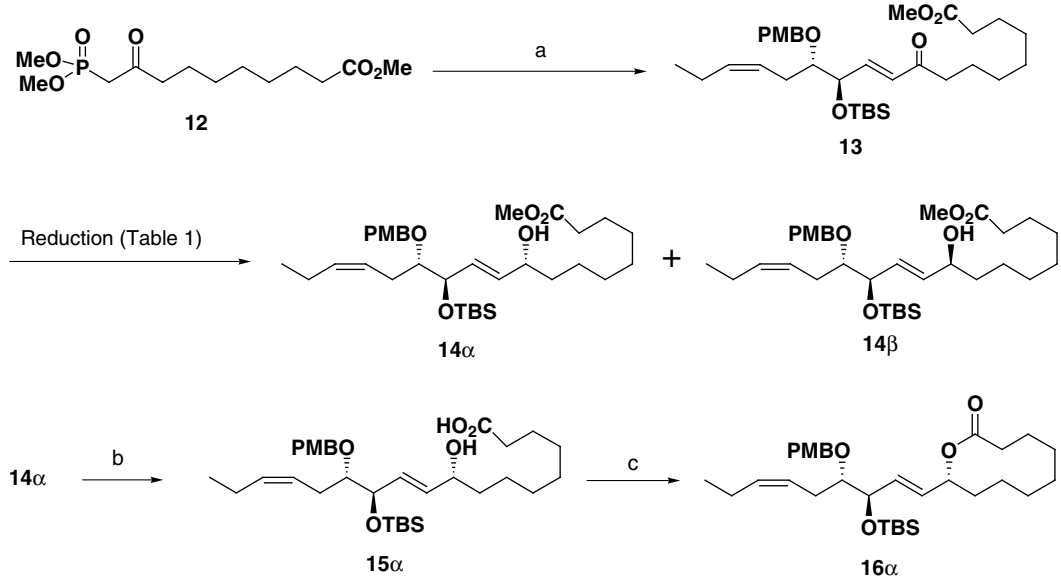


Scheme 1. Synthetic strategy toward mueggelone.



Scheme 2. (a) PMBCl, NaH, DMF, 100%; (b) $HgCl_2$, HgO, CH_3CN, H_2O, 85%; (c) *n*-propyltriphenylphosphonium bromide, NaHMDS, Et_2O, −78°C, 68%, *E*/*Z*=1:10; (d) TFA, THF, H_2O, 40°C, 96%; (e) PivCl, pyridine, 93%; (f) TBSCl, imidazole, DMF, 98%; (g) DIBAL, CH_2Cl_2, −50 to −10°C, 93%; (h) Dess–Martin periodinane, CH_2Cl_2, 96%.



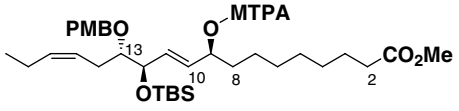
Scheme 3. (a) DBU, LiCl, **11**, CH_3CN, 93%, *E*/*Z* > 99 : 1; (b) $LiOHH_2O$, MeOH, 91%; (c) 2,4,6-trichlorobenzoyl chloride, NEt_3, THF, then DMAP, toluene, 0.6 mM, reflux, 12 h, 68%.

reagent[6] and borane–THF complex (Table 1). The resultant two isomers and other minor and undesired isomers (10*Z*-isomers, C-12 epimers) were cleanly separated by preparative HPLC and the stereochemistry of each isomer was confirmed by modified Mosher's method (Table 2).[7] Hydrolysis of **14**α with LiOH furnished pure hydroxycarboxylic acid **15**α. Lactonization of **15**α was successfully achieved by Yamaguchi's method[8] to provide **16**α in satisfactory yield, together with a small amount of a dimeric lactone (5–10%). On the other hand, Corey–Mukaiyama's method[9] was found to give only several unassignable compounds.

Table 1. Reduction of enone **13**

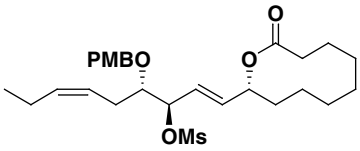
Entry	Conditions of reduction	Yield (%)	Ratio (**14**α:**14**β)
1	$NaBH_4$, $CeCl_3$, MeOH	80	1:2
2	L-Selectride, THF	–	1:2
3	(*S*)–CBS reagent, $BH_3{\cdot}SMe_2$, THF	–	3:1
4	(*R*)–CBS reagent, $BH_3{\cdot}SMe_2$, THF	58	1:2
5	(*S*)–CBS reagent, $BH_3{\cdot}THF$, THF	66	9:1
6	(*R*)–CBS reagent, $BH_3{\cdot}THF$, THF	65	1:9

Table 2. ^1H NMR (300 MHz, $CDCl_3$) data for (*S*)- and (*R*)-MTPA ester of **14**β



14β MTPA ester

	^1H chemical shift (δ)		
position	(*S*)-MTPA	(*R*)-MTPA	$\delta_S - \delta_R$
2	2.28	2.29	−0.01
8	1.63	1.64	−0.01
10	5.68	5.60	+0.08
11	5.94	5.83	+0.11
12	4.14	4.12	+0.02
13	3.32	3.30	+0.02



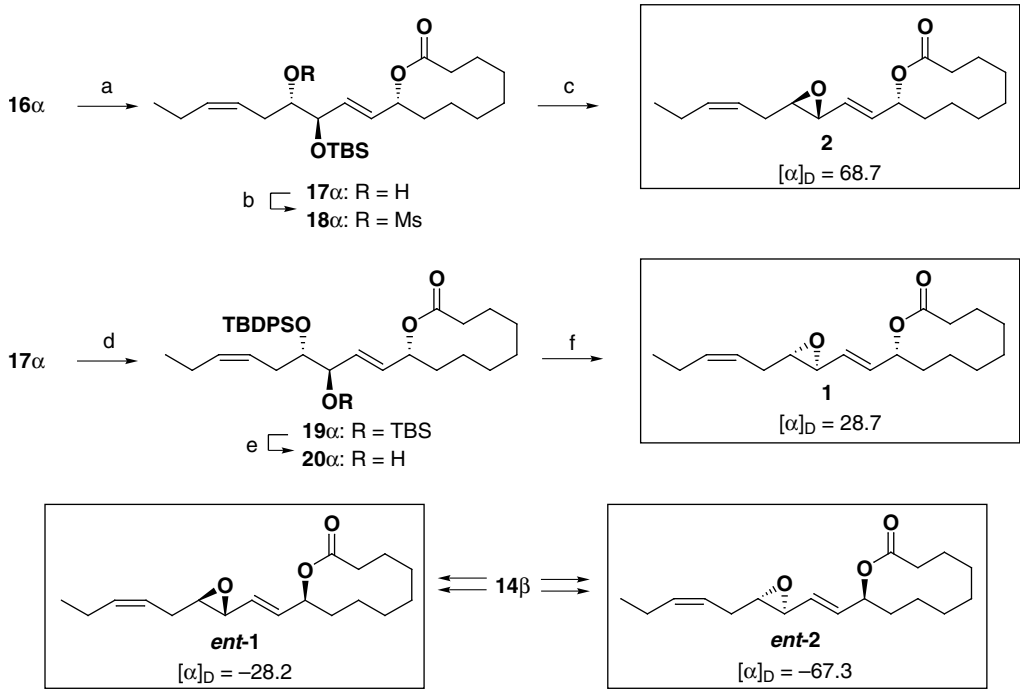
21α

Figure 2.

Table 3. ^{13}C NMR (75.5 Hz, $CDCl_3$) data for natural mueggelone, **1**/*ent*-**1** and **2**/*ent*-**2**

Carbon	natural[1]	**1**/*ent*-**1**	**2**/*ent*-**2**
1	173.5	173.4	173.4
2	35.1	35.0	35.1
3	29.9	29.8	29.9
4	27.1	27.0	27.0
5	24.2	24.1	24.2
6	23.7	23.6	23.6
7	23.4	23.3	23.4
8	20.7	20.7	20.7
9	74.9	74.8	75.1
10	132.8	132.7	132.8
11	128.6	128.5	129.1
12	57.4	57.4	57.3
13	59.9	59.9	59.9
14	29.6	29.5	29.5
15	122.3	122.2	122.2
16	135.0	134.9	134.9
17	20.7	20.7	20.7
18	14.2	14.2	14.2

In the following epoxide formation stage (Scheme 4), we anticipated that stereochemistry of the epoxide could be controlled by the direction of elimination. Initially, we decided to synthesize the (12*R*,13*R*)-isomer such as **2**. Removal of the PMB group with DDQ[10] proceeded without complication. Mesylation of alcohol **17**α followed by treatment with TBAF provided the desired epoxylactone **2** in good yield. Next, we tried to obtain the (12*S*,13*S*)-isomer by changing the position of the leaving group. So, allylic mesylate **21**α (Fig. 2) was prepared from **16**α; however, it



Scheme 4. (a) DDQ, $NaHCO_3$, CH_2Cl_2, H_2O, 99%; (b) Ms_2O, NEt_3, DMAP, CH_2Cl_2, rt, 90%; (c) TBAF, THF, 87%; (d) TBDPSCl, imidazole, DMF, 91%; (e) HF, CH_3CN, 51%; (f) MsCl, NEt_3, DMAP, CH_2Cl_2, 0°C, then TBAF, THF, 94%.

readily decomposed under the conditions of PMB deprotection. Therefore, we had to change the PMB group for another protecting group. Masking the hydroxyl group of **17**α with TBDPSCl was followed by selective removal of the TBS group with HF/acetonitrile to give the corresponding alcohol **20**α. It was mesylated and then treated with TBAF without purification to furnish **1**. Similarly, *ent*-**1** and *ent*-**2** were synthesized in the same way from **14**β.

With the four stereoisomers in hand, we analyzed the NMR spectra and specific rotations carefully. As for the ^{1}H NMR, there was little difference between **1**/*ent*-**1** and **2**/*ent*-**2** to distinguish them. However, in the ^{13}C NMR spectra (Table 3), an obvious difference was observed at the C-11 position (natural: 128.6 ppm,[1] **1**/*ent*-**1**: 128.5 ppm, **2**/*ent*-**2**: 129.1 ppm) which suggested that **1** or *ent*-**1** should be the natural isomer. In addition, the value of specific rotation (natural: +28.3, synthetic **1**: +28.7, synthetic *ent*-**1**: −28.2) showed that **1** must be the natural product, i.e., mueggelone has the absolute configuration of 9*R*, 12*S*, 13*S*.

In conclusion, we have completed the first synthesis of mueggelone (and its stereoisomers) in 3.3% overall yield from D-arabinose and determined the absolute configuration of mueggelone to be 9*R*, 12*S*, 13*S*.

3. Experimental

3.1. General

Optical rotations were recorded with a JASCO DIP-1000 polarimeter. IR spectra were measured with a JASCO FT/IR-230 spectrophotometer. ^{1}H and ^{13}C NMR were recorded on JEOL JNM AL300. Mass spectra were recorded on JEOL JMS SX102. Column chromatography was performed using Merck silica gel 60 (0.060–0.200 mm). TLC was carried out on Merck glass plates precoated with silica gel 60 F_{254} (0.25 mm). HPLC was performed using SHOWA DENKO shodex DS-4 equipped with Senshu Pak Silica-1251-N (4.6ϕ x 250 mm) or Senshu Pak silica-5251-N (20ϕ x 250 mm).

3.1.1. (1′*S*,4*R*)-4-(3′,3′-Bisethylthio-1′-*p*-methoxybenzyloxypropyl)-2,2-dimethyl-1,3-dioxolane (4). To a cooled (0°C) solution of alcohol **3** (500 mg, 1.8 mmol) in DMF (10 mL) was added NaH (80 mg of 60% in mineral oil, 2.0 mmol) and PMBCl (320 mg, 2.0 mmol) and the mixture was stirred for 2 h under argon atmosphere. The reaction mixture was poured into water and extracted with EtOAc. The organic layer was washed with water and brine, and dried with $MgSO_4$. The solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (6:1 hexanes/EtOAc) to provide **4** as a colorless oil (712 mg, 100%); n_D^{25}=1.5166; $[\alpha]_D^{26}$=−1.5 (c=0.87, $CHCl_3$); IR (film): ν_{max} 2981, 1613, 1513, 856, 822 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.23 (6H, t, J=7.5Hz, ethyl CH_3), 1.36, 1.44 (6H, two s, isopropylidene CH_3), 1.86–2.02 (2H, m, H-2′), 2.52–2.74 (4H, m, ethyl CH_2), 3.80 (3H, s, –OMe), 3.76–4.14 (5H, m, H-1′, 3′,4,5), 4.56, 4.69 (2H, two d, J=11.0 Hz, CH_2 of PMB), 6.87, 7.26 (4H, two d, J=8.6 Hz, Ar of PMB); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) 14.4, 14.4, 23.4, 24.4, 25.2, 26.5, 38.8, 47.6, 55.3, 66.0, 73.1, 76.5, 78.4, 109.2, 113.8, 129.5, 130.6, 159.3; Anal. Calcd. for $C_{20}H_{32}O_4S_2$: C, 59.96; H, 8.05. Found: C, 60.13; H, 8.06.

3.1.2. (3*S*,4′*R*)-3-(2′,2′-Dimethyl-1′,3′-dioxolan-4′-yl)-3-*p*-methoxybenzyloxypropanal (5). A solution of **4** (5.5 g, 14.2 mmol) in acetonitrile (2 mL) was added dropwise to a stirred mixture of $HgCl_2$ (8.5 g, 31.3 mmol) and yellow HgO (3.4 g, 15.7 mmol) in acetonitrile–water (4:1, 125 mL) at 0°C. The mixture was stirred for 40 min at this temperature and filtered through Celite®. The filtrate was diluted with dichloromethane–hexane (1:1, 100 mL) and washed with 5 M sodium acetate solution and brine. The organic layer was dried with $MgSO_4$ and evaporated. The residue was purified by column chromatography on silica gel (3:1–1:1 hexanes/EtOAc) to yield aldehyde **5** as a colorless oil (3.4 g, 85%); n_D^{26}=1.5028; $[\alpha]_D^{27}$=+12.3 (c=0.76, $CHCl_3$); IR (film): ν_{max} 2987, 1728, 1613, 1514, 848 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.34, 1.40 (6H, two s, isopropylidene CH_3), 2.72 (2H, m, H-2), 3.80 (3H, s, –OMe), 3.80–4.15 (4H, m, H-3′, 4, 5), 4.51, 4.57 (2H, two d, J=11.1 Hz, CH_2 of PMB), 6.87, 7.23 (4H, two d, J=8.6 Hz, Ar of PMB), 9.81 (1H, t, J=1.8 Hz, H-1); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) 25.1, 26.5, 45.8, 55.3, 66.9, 72.2, 75.0, 77.2, 109.6, 113.9, 129.6, 129.7, 159.4, 200.6; Anal. Calcd. for $C_{16}H_{22}O_5$: C, 65.29; H, 7.53. Found: C, 65.43; H, 7.51.

3.1.3. (1′*S*,3′*Z*,4*R*)-4-(1′-*p*-Methoxybenzyloxyhex-3′-enyl)-2,2-dimethyl-1,3-dioxolane (6). To a cooled (−78°C) suspension of *n*-propyltriphenylphosphonium bromide (5.1 g, 13.2 mmol) in ether (100 mL) under argon atmosphere was added NaHMDS (12.6 mL of 1 M in THF, 12.6 mmol) and the mixture was stirred for 1 h. To the resulting orange solution was added a cooled (−78°C) solution of aldehyde **5** (3.4 g, 12.6 mmol) in ether (40 mL) via a cannula at −78°C and stirred for 1 h. The reaction mixture was poured into water and extracted with ether. The combined organic layer was washed with water and brine, dried with $MgSO_4$ and concentrated under reduced pressure. Purification on silica gel (20:1 hexanes/EtOAc) gave an olefin mixture as a colorless oil (2.5 g, 68%, *E*/*Z*=1:10). *E*- and *Z*-isomers were separated by $AgNO_3$-impregnated silica gel column chromatography (9:1 hexanes/EtOAc); n_D^{25}=1.4986; $[\alpha]_D^{26}$=+37.9 (c=0.49, $CHCl_3$); IR (film): ν_{max} 2962, 1613, 1514, 855, 822 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.97 (3H, t, J=7.5 Hz, H-6′), 1.34, 1.42 (6H, two s, isopropylidene CH_3), 2.07 (2H, m, H-5′), 2.36 (2H, m, H-2′), 3.53 (1H, q, J=5.5 Hz, H-1′), 3.80 (3H, s, –OMe), 3.87 (1H, m, H-5_a), 3.99–4.10 (2H, m, H-4, 5_b), 4.51, 4.59 (2H, two d, J=11.3 Hz, CH_2 of PMB), 5.44 (1H, dt, J=10.8, 5.3 Hz, H-3′), 5.50 (1H, dt, J=10.8, 4.6 Hz, H-4′) 6.87, 7.25 (4H, two d, J=8.7 Hz, Ar of PMB); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) 14.1, 20.7, 25.4, 26.6, 28.9, 55.2, 66.5, 72.2, 77.2, 78.9, 109.0, 113.7, 124.0, 129.4, 130.6, 134.0, 159.2; Anal. Calcd. for $C_{19}H_{28}O_4$: C, 71.22; H, 8.81. Found: C, 71.21; H, 8.81.

3.1.4. (2*R*,3*S*,5*Z*)-3-*p*-Methoxybenzyloxyoct-5-ene-1,2-diol (7). To a stirred solution of **6** (50 mg, 0.16 mmol) in THF–water (4:1, 2 mL) at 0°C was added TFA (0.1 mL). The resulting solution was allowed to warm to 40°C and stirred for 30 h. The reaction was then neutralized by the

addition of saturated $NaHCO_3$ solution and extracted with EtOAc. The combined organic layer was washed with water, saturated $NaHCO_3$ solution and brine before drying with $MgSO_4$. The solvent was removed and the residue was purified by column chromatography on silica gel (3:1–1:1 hexanes/EtOAc) to yield diol **7** as a colorless oil (42 mg, 96%); n_D^{30}=1.5168; $[\alpha]_D^{29}$=+41.6 (c=1.09, $CHCl_3$); IR (film): ν_{max} 3417, 2962, 1614, 1515, 1250, 822 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.97 (3H, t, J=7.5 Hz, H-8), 2.07 (2H, m, H-7), 2.25–2.50 (2H, m, H-4), 3.58–3.80 (4H, m, H-1, 2, 3), 3.80 (3H, s, –OMe), 4.44, 4.61 (2H, two d, J=11.1 Hz, CH_2 of PMB), 5.30–5.60 (2H, m, H-5, 6), 6.88, 7.25 (4H, two d, J=8.6 Hz, Ar of PMB); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) 14.1, 20.7, 28.4, 55.3, 63.3, 72.2, 72.3, 80.8, 113.9, 123.8, 129.5, 130.1, 134.3, 159.3; FAB MS m/z (M^+) calcd 280.1675, obsd 280.1635.

3.1.5. (2*R*,3*S*,5*Z*)-2-Hydroxy-3-*p*-methoxybenzyloxyoct-5-enyl pivalate (8). To a cooled (0°C) solution of diol **7** (512 mg, 1.83 mmol) in pyridine (30 mL) was added PivCl (0.34 mL, 2.74 mmol) and the mixture was stirred for 1 h. The reaction mixture was poured into water and extracted with EtOAc. The organic layer was washed with saturated $CuSO_4$ solution, water, saturated $NaHCO_3$ solution and brine, and then dried with $MgSO_4$ and evaporated. Purification of the residue on silica gel (6:1 hexanes/EtOAc) furnished secondary alcohol **8** as a colorless oil (621 mg, 93%); n_D^{25}=1.4961; $[\alpha]_D^{26}$=+38.0 (c=0.80, $CHCl_3$); IR (film): ν_{max} 3449, 2962, 1727, 1612, 1514, 1249, 822 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.97 (3H, t, J=7.5 Hz, H-8), 1.21 (9H, s, pivaloyl CH_3), 2.08 (2H, m, H-7), 2.41 (2H, m, H-4), 3.50 (1H, q, J=5.6 Hz, H-3), 3.80 (3H, s, –OMe), 3.87 (1H, m, H-2), 4.17 (1H, dd, J=6.5, 11.6 Hz, H_a-1), 4.28 (1H, dd, J=3.5, 11.6 Hz, H_b-1), 4.44, 4.59 (2H, two d, J=11.0 Hz, CH_2 of PMB), 5.48 (2H, m, H-5, 6), 6.87, 7.25 (4H, two d, J=8.4 Hz, Ar of PMB); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) 14.1, 20.7, 27.2, 27.7, 38.8, 55.3, 65.7, 71.3, 71.9, 79.1, 113.8, 124.0, 129.5, 130.2, 134.2, 159.3, 178.9; Anal. Calcd. for $C_{21}H_{32}O_5$: C, 69.20; H, 8.85. Found: C, 69.16; H, 8.84.

3.1.6. (2*R*,3*S*,5*Z*)-2-*t*-Butyldimethylsilyloxy-3-*p*-methoxybenzyloxyoct-5-enyl pivalate (9). To a solution of alcohol **8** (140 mg, 0.38 mmol) in DMF (1.5 mL) was added imidazole (260 mg, 3.84 mmol) and TBSCl (174 mg, 1.15 mmol) and the mixture was stirred for 15 h at room temperature. The reaction mixture was poured into water and extracted with ether. The organic layer was washed with water, saturated $NaHCO_3$ solution and brine, and then dried with $MgSO_4$. After removal of the solvent, purification of the residue on silica gel (30:1 hexanes/EtOAc) provided **9** as a colorless oil (180 mg, 98%); n_D^{27}=1.4761; $[\alpha]_D^{28}$=−9.40 (c=0.45, $CHCl_3$); IR (film): ν_{max} 2960, 1731, 1614, 1515, 835, 777 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.08, 0.09 (6H, two s, –SiMe), 0.90 (9H, s, –SiBu^t), 0.96 (3H, t, J=7.5 Hz, H-8), 1.21 (9H, s, pivaloyl CH_3), 2.06 (2H, m, H-7), 2.31 (1H, m, H_a-4), 2.39 (1H, m, H_b-4), 3.50 (1H, m, H-3), 3.80 (3H, s, –OMe), 3.89 (1H, m, H-2), 4.12 (1H, dd, J=4.7, 11.7 Hz, H_a-1), 4.25 (1H, dd, J=3.6, 11.7 Hz, H_b-1), 4.52 (2H, s, CH_2 of PMB), 5.46 (2H, m, H-5, 6), 6.86, 7.24 (4H, two d, J=8.9 Hz, Ar of PMB); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) −4.6, 14.1, 18.0, 20.7, 25.8, 27.3, 28.8, 38.8, 55.3, 65.7, 72.4, 72.5, 80.3, 113.7, 125.0, 129.3, 130.7, 133.7, 159.1, 178.4; Anal. Calcd. for $C_{27}H_{46}O_5Si$: C, 67.74; H, 9.68. Found: C, 67.74; H, 9.69.

3.1.7. (2*R*,3*S*,5*Z*)-2-*t*-Butyldimethylsilyloxy-3-*p*-methoxybenzyloxyoct-5-en-1-ol (10). A stirred solution of **9** (500 mg, 1.1 mmol) in dichloromethane (10 mL) was cooled to −50°C, treated with diisobutylaluminum hydride (2.2 mL of 0.95 M in hexanes, 2.1 mmol), warmed gradually to −10°C during 1 h and quenched with saturated aqueous potassium sodium tartrate solution (10 mL). The reaction mixture was stirred for 1 h at ambient temperature before extraction with ether. The combined organic layer was washed with water and brine, dried with $MgSO_4$ and evaporated to leave a residue which was purified by column chromatography on silica gel (20:1–5:1 hexanes/EtOAc). Obtained was the desired primary alcohol **10** as a colorless oil (383 mg, 93%); n_D^{24}=1.4937; $[\alpha]_D^{25}$=−5.47 (c=1.51, $CHCl_3$); IR (film): ν_{max} 3466, 2956, 1613, 1514, 1250, 836, 777 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.09, 0.10 (6H, two s, –SiMe), 0.92 (9H, s, –SiBu^t), 0.97 (3H, t, J=7.5 Hz, H-8), 2.07 (2H, m, H-7), 2.31 (1H, m, H_a-4), 2.41 (1H, m, H_b-4), 3.51–3.79 (4H, m, H-1, 2, 3), 3.80 (3H, s, –OMe), 4.55 (2H, s, CH_2 of PMB), 5.41–5.54 (2H, m, H-5, 6), 6.87, 7.26 (4H, two d, J=8.4 Hz, Ar of PMB); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) −4.6, −4.5, 14.1, 18.0, 20.8, 25.8, 29.2, 55.2, 64.1, 72.6, 74.0, 80.8, 113.7, 124.7, 129.5, 130.5, 133.7, 159.2; Anal. Calcd. for $C_{22}H_{38}O_4Si$: C, 66.96; H, 9.71. Found: C, 66.82; H, 9.69.

3.1.8. (2*S*,3*S*,5*Z*)-2-*t*-Butyldimethylsilyloxy-3-*p*-methoxybenzyloxy-5-octenal (11). To a solution of alcohol **10** (383 mg, 0.97 mmol) in dichloromethane (6 mL) was added the Dess–Martin periodinane (620 mg, 1.46 mmol) and the mixture was stirred for 20 min. The reaction mixture was diluted with ether (10 mL), washed twice with a 1:1 mixture of saturated $NaHCO_3$ solution and 10% sodium thiosulfate solution and then washed with water and brine. The combined organic layer was dried with $MgSO_4$ and concentrated. After column chromatography on silica gel (20:1 hexanes/EtOAc), the aldehyde **11** was isolated as a colorless oil (366 mg, 96%); n_D^{27}=1.4908; $[\alpha]_D^{28}$=−15.7 (c=0.97, $CHCl_3$); IR (film): ν_{max} 2931, 1735, 1613, 1514, 1250, 839, 780 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.08, 0.09 (6H, two s, –SiMe), 0.93 (9H, s, –SiBu^t), 0.95 (3H, t, J=7.5 Hz, H-8), 2.05 (2H, m, H-7), 2.34 (1H, m, H_a-4), 2.42 (1H, m, H_b-4), 3.66 (1H, dt, J=3.2, 6.8 Hz, H-3), 3.80 (3H, s, –OMe), 4.12 (1H, dd, J=1.4, 3.2 Hz, H-2), 4.51, 4.57 (2H, two d, J=11.4 Hz, CH_2 of PMB), 5.26 (1H, m, H-5), 5.47 (1H, m, H-6), 6.87, 7.25 (4H, two d, J=9.2 Hz, Ar of PMB), 9.61 (1H, d, J=1.4 Hz, H-1); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) −4.9, −4.9, 14.0, 18.2, 20.7, 25.7, 28.4, 55.2, 71.8, 79.2, 81.2, 113.7, 123.8, 129.3, 130.2, 134.9, 159.2, 203.3; Anal. Calcd. for $C_{22}H_{36}O_4Si$: C, 67.30; H, 9.24. Found: C, 67.30; H, 9.27.

3.1.9. Trimethyl 9-oxo-10-phosphonodecanoate (12). To a cooled (−78°C) solution of dimethyl methylphosphonate (1.55 g, 12.5 mmol) in THF (30 mL) under argon was added *n*-BuLi (8.5 mL of 1.5 M in *n*-hexane, 12.8 mmol) and the mixture was stirred for 20 min. To the resultant solution was slowly added azelaic acid dimethyl ester (3.0 g, 13.9 mmol) in THF (10 mL) and stirred for 1 h at −78°C. The reaction was quenched with saturated NH_4Cl solution and extracted

with ether. The combined organic layer was washed with brine, dried with $MgSO_4$, and then evaporated. Purification of the residue on silica gel (3:1–1:10 hexanes/EtOAc) furnished phosphonate **12** as a colorless oil (940 mg, 22%); n_D^{20}=1.4505; IR (film): ν_{max} 3474, 2934, 1732, 1714, 1256, 1031, 814 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.15–1.30 (6H, m, H-4, 5, 6), 1.45–1.60 (4H, m, H-3, 7), 2.22 (2H, t, J=7.5 Hz, H-2), 2.54 (2H, t, J=7.5 Hz, H-8), 3.02 (2H, d, J=22.8 Hz, H-10), 3.59 (3H, s, $-CO_2Me$), 3.70 (6H, d, J=11.1 Hz, $-P(O)(OMe)_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) 23.1, 24.7, 28.5, 28.7, 28.8, 33.8, 41.1 (d, J=128 Hz, C-10), 43.9 (d, J=1.8 Hz, C-8), 51.3, 52.9 (d, J=6.2 Hz, $-P(O)(OMe)_2$), 174.0, 201.8 (d, J=6.2 Hz, C-9); FAB MS m/z (M^+) calcd 309.1467, obsd 309.1420.

3.1.10. Methyl (10*E*,12*R*,13*S*,15*Z*)-12-*t*-butyldimethylsilyloxy-13-*p*-methoxybenzyloxy-9-oxooctadeca-10,15-dienoate (13). To a stirred suspension of LiCl (36 mg, 0.83 mmol) in acetonitrile (4 mL) under argon at room temperature, was added phosphonate **12** (257 mg, 0.83 mmol), DBU (0.1 mL, 0.69 mmol) and finally aldehyde **11** (272 mg, 0.69 mmol). After being stirred for 90 min, the reaction mixture was poured into water and extracted with ether. The combined organic layer was washed with water and brine, dried with $MgSO_4$, and then evaporated. The residue was purified by silica gel column chromatography (20:1–6:1 hexanes/EtOAc) to provide enone **13** as a colorless oil (372 mg, 93%, E/Z=>99:1); n_D^{26}=1.4952; $[\alpha]_D^{27}$=−8.22 (c=0.44, $CHCl_3$); IR (film): ν_{max} 2932, 1739, 1680, 1514, 1250, 837, 778 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.02, 0.07 (6H, two s, –SiMe), 0.92 (9H, s, $-SiBu^t$), 0.95 (3H, t, J=7.5 Hz, H-18), 1.25–1.35 (6H, m, H-4, 5, 6), 1.50–1.70 (4H, m, H-3, 7), 2.02 (2H, m, H-17), 2.20–2.40 (2H, m, H-14), 2.29 (2H, t, J=7.5 Hz, H-2), 2.53 (2H, t, J=7.4 Hz, H-8), 3.41 (1H, m, H-13), 3.66 (3H, s, $-CO_2Me$), 3.79 (3H, s, –OMe of PMB), 4.33 (1H, m, H-12), 4.48, 4.56 (2H, two d, J=11.3 Hz, CH_2 of PMB), 5.30–5.50 (2H, m, H-15, 16), 6.28 (1H, dd, J=1.4, 16.1 Hz, H-10), 6.84 (1H, dd, J=5.3, 16.1 Hz, H-11), 6.85, 7.22 (4H, two d, J=8.6 Hz, Ar of PMB); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) −4.8, −4.5, 14.1, 18.2, 20.7, 24.1, 24.9, 25.8, 28.9, 29.0, 29.1, 34.0, 40.4, 51.4, 55.2, 72.6, 74.4, 82.5, 113.7, 124.8, 129.4, 129.8, 130.5, 133.8, 145.9, 159.1, 174.2, 200.5; Anal. Calcd. for $C_{33}H_{54}O_6Si$: C, 68.95; H, 9.47. Found: C, 68.94; H, 9.51.

3.1.11. Methyl (9*R*,10*E*,12*R*,13*S*,15*Z*)-12-*t*-butyldimethylsilyloxy-9-hydroxy-13-*p*-methoxybenzyloxyoctadeca-10,15-dienoate (14α). To a solution of enone **13** (240 mg, 0.42 mmol) in THF (5 mL) under argon was added (*S*)-CBS reagent (42 μL of 1 M in toluene, 0.042 mmol). The mixture was cooled to −20°C and BH_3·THF (410 μL of 1 M in THF, 0.42 mmol) was added. The resultant solution was stirred for 90 min with elevating temperature up to 0°C, and then quenched with 1 mL of methanol. The reaction mixture was warmed to ambient temperature and stirred for 4 h. The solvent was removed in vacuo. Purification by column chromatography on silica gel (9:1–6:1 hexanes/EtOAc) gave a mixture of isomers. These were isolated by preparative HPLC (3.9:1 hexanes/EtOAc) to furnish the desired (9*R*)-methyl ester **14**α (159 mg, 66%). n_D^{26}=1.4908; $[\alpha]_D^{27}$=−16.6 (c=0.66, $CHCl_3$); IR (film): ν_{max} 3448, 2930, 1740, 1612, 1513, 1249, 836, 776 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.02, 0.06 (6H, two s, –SiMe), 0.90 (9H, s, $-SiBu^t$), 0.94 (3H, t, J=7.5 Hz, H-18), 1.20–1.70 (12H, m, H-3, 4, 5, 6, 7, 8), 2.02 (2H, m, H-17), 2.15–2.40 (2H, m, H-14), 2.29 (2H, t, J=7.5 Hz, H-2), 3.37 (1H, m, H-13), 3.66 (3H, s, $-CO_2Me$), 3.79 (3H, s, –OMe of PMB), 4.09–4.16 (2H, m, H-9, 12), 4.49, 4.62 (2H, two d, J=11.1 Hz, CH_2 of PMB), 5.30–5.50 (2H, m, H-15, 16), 5.60–5.80 (2H, m, H-10, 11), 6.85, 7.25 (4H, two d, J=8.3 Hz, Ar of PMB); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) −4.8, −4.2, 14.1, 18.1, 20.7, 24.9, 25.3, 25.8, 29.0, 29.2, 29.3, 34.0, 37.1, 51.4, 55.2, 72.4, 72.6, 75.2, 83.1, 113.6, 125.3, 129.3, 130.8, 131.0, 133.3, 134.8, 159.0, 174.3; Anal. Calcd. for $C_{33}H_{56}O_6Si$: C, 68.71; H, 9.78. Found: C, 68.56; H, 9.79.

3.1.12. Methyl (9*S*,10*E*,12*R*,13*S*,15*Z*)-12-*t*-butyldimethylsilyloxy-9-hydroxy-13-*p*-methoxybenzyloxyoctadeca-10,15-dienoate (14β). As described for the synthesis of **14**α, **13** (370 mg, 0.64 mmol) was converted into **14**β (240 mg, 65%, colorless oil) with (*R*)-CBS reagent; n_D^{27}=1.4918; $[\alpha]_D^{27}$=−18.4 (c=0.60, $CHCl_3$); IR (film): ν_{max} 3450, 2930, 1740, 1613, 1514, 1249, 835, 776 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.03, 0.06 (6H, two s, –SiMe), 0.91 (9H, s, $-SiBu^t$), 0.94 (3H, t, J=7.5 Hz, H-18), 1.2–1.7 (12H, m, H-3, 4, 5, 6, 7, 8), 2.02 (2H, m, H-17), 2.15–2.35 (2H, m, H-14), 2.29 (2H, t, J=7.5 Hz, H-2), 3.38 (1H, m, H-13), 3.66 (3H, s, $-CO_2Me$), 3.79 (3H, s, –OMe of PMB), 4.10 (1H, q, J=6.0 Hz, H-9), 4.15 (1H, t, J=4.8 Hz, H-12), 4.49, 4.63 (2H, two d, J=11.1 Hz, CH_2 of PMB), 5.3–5.5 (2H, m, H-15, 16), 5.6–5.8 (2H, m, H-10, 11), 6.85, 7.25 (4H, two d, J=8.1 Hz, Ar of PMB); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) −4.8, −4.2, 14.1, 18.1, 20.7, 24.9, 25.4, 25.9, 29.1, 29.2, 29.2, 29.3, 34.1, 37.1, 51.4, 55.2, 72.4, 72.7, 75.2, 83.0, 113.6, 125.3, 129.4, 130.6, 131.0, 133.3, 134.7, 159.0, 174.3; Anal. Calcd. for $C_{33}H_{56}O_6Si$: C, 68.71; H, 9.78. Found: C, 68.47; H, 9.76.

3.1.13. (9*R*,10*E*,12*R*,13*S*,15*Z*)-12-*t*-Butyldimethylsilyloxy-9-hydroxy-13-*p*-methoxybenzyloxyoctadeca-10,15-dienoic acid (15α). To a solution of methyl ester **14**α (192 mg, 0.33 mmol) in methanol (10 mL) was added $LiOH·H_2O$ (500 mg) and the mixture was stirred for 12 h at room temperature. The reaction mixture was neutralized with 3N HCl and extracted with EtOAc. The organic layer was washed with brine, dried with $MgSO_4$ and evaporated. Purification of the residue on silica gel (6:1–1:1 hexanes/EtOAc) provided carboxylic acid **15**α as a colorless oil (170 mg, 91%); n_D^{30}=1.4973; $[\alpha]_D^{30}$=−16.3 (c=1.16, $CHCl_3$); IR (film): ν_{max} 2930, 1712, 1613, 1514, 1249, 836, 777 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.03, 0.06 (6H, two s, –SiMe), 0.90 (9H, s, $-SiBu^t$), 0.94 (3H, t, J=7.5 Hz, H-18), 1.2–1.7 (12H, m, H-3, 4, 5, 6, 7, 8), 2.02 (2H, m, H-17), 2.1–2.4 (2H, m, H-14), 2.32 (2H, t, J=7.5 Hz, H-2), 3.38 (1H, m, H-13), 3.79 (3H, s, –OMe), 4.0–4.2 (2H, m, H-9, 12), 4.50, 4.63 (2H, two d, J=11.3 Hz, CH_2 of PMB), 5.3–5.5 (2H, m, H-15, 16), 5.6–5.8 (2H, m, H-10, 11), 6.85, 7.25 (4H, two d, J=8.6 Hz, Ar of PMB); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) −4.8, −4.2, 14.1, 18.1, 20.7, 24.6, 25.3, 25.9, 28.9, 29.1, 29.2, 29.3, 33.9, 37.1, 55.2, 72.5, 72.7, 75.2, 83.1, 113.6, 125.2, 129.4, 130.8, 131.0, 133.4, 134.8, 159.0, 179.1; Anal. Calcd. for $C_{32}H_{54}O_6Si$: C, 68.28; H, 9.67. Found: C, 67.98; H, 9.65.

3.1.14. (9*S*,10*E*,12*R*,13*S*,15*Z*)-12-*t*-Butyldimethylsilyloxy-9-hydroxy-13-*p*-methoxybenzyloxyoctadeca-10,15-dienoic acid (15β). As described for the synthesis of **15**α, **14**β (119 mg, 0.21 mmol) was converted into **15**β (106 mg, 91%, colorless oil); n_D^{30}=1.4971; $[\alpha]_D^{32}$=−15.6 (*c*=0.84, $CHCl_3$); IR (film): ν_{max} 2931, 1713, 1613, 1514, 1249, 836, 776 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.03, 0.06 (6H, two s, –SiMe), 0.91 (9H, s, –SiBu^t), 0.94 (3H, t, *J*=7.5 Hz, H-18), 1.2–1.7 (12H, m, H-3, 4, 5, 6, 7, 8), 2.02 (2H, m, H-17), 2.1–2.4 (2H, m, H-14), 2.32 (2H, t, *J*=7.5 Hz, H-2), 3.39 (1H, m, H-13), 3.79 (3H, s, –OMe), 4.0–4.2 (2H, m, H-9, 12), 4.50, 4.64 (2H, two d, *J*=11.3 Hz, CH_2 of PMB), 5.3–5.5 (2H, m, H-15, 16), 5.6–5.8 (2H, m, H-10, 11), 6.85, 7.25 (4H, two d, *J*=8.4 Hz, Ar of PMB); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) −4.8, −4.2, 14.1, 18.1, 20.7, 24.6, 25.3, 25.9, 28.9, 29.1, 29.2, 29.3, 34.0, 37.0, 55.2, 72.4, 72.6, 75.1, 83.0, 113.6, 125.2, 129.4, 130.6, 131.0, 133.4, 134.7, 159.0, 179.2; Anal. Calcd. for $C_{32}H_{54}O_6Si$: C, 68.28; H, 9.67. Found: C, 68.16; H, 9.65.

3.1.15. (9*R*,10*E*,12*R*,13*S*,15*Z*)-12-*t*-Butyldimethylsilyloxy-13-*p*-methoxybenzyloxyoctadeca-10,15-dien-9-olide (16α). Triethylamine (205 μL, 1.47 mmol) and 2,4,6-trichlorobenzoyl chloride (192 μL, 1.23 mmol) were added to a solution of the hydroxy acid **15**α (138 mg, 0.25 mmol) in THF (3 mL). The reaction mixture was stirred for 1 h at room temperature and then diluted with dry toluene (18 mL). The resultant solution was slowly added over 12 h using a syringe pump to a refluxing and vigorously stirred solution of DMAP (720 mg, 5.88 mmol) in dry toluene (420 mL). After the addition of the substrate was complete, the reaction was stirred for an additional 2 h and then concentrated in vacuo. Column chromatography of the crude product on silica gel (30:1–5:1 hexanes/EtOAc) afforded the desired lactone **16**α (91 mg, 68%, colorless oil) together with a dimeric lactone (12.4 mg, 5%); n_D^{30}=1.5012; $[\alpha]_D^{30}$=+14.0 (*c*=0.3, $CHCl_3$); IR (film): ν_{max} 2932, 1728, 1613, 1514, 1250, 836, 758 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.03, 0.06 (6H, two s, –SiMe), 0.91 (9H, s, –SiBu^t), 0.95 (3H, t, *J*=7.5 Hz, H-18), 1.0–1.8 (10H, m, H-3$_a$, 4, 5, 6, 7, 8$_a$), 2.0–2.3 (6H, m, H-2$_a$, 3$_b$, 8$_b$, 14$_a$, 17), 2.35 (1H, m, H-14$_b$), 2.49 (1H, ddd, *J*=2.7, 6.3, 15.2 Hz, H-2$_b$), 3.34 (1H, dt, *J*=7.5, 4.8 Hz, H-13), 3.80 (3H, s, –OMe), 4.16 (1H, t, *J*=4.8 Hz, H-12), 4.47, 4.58 (2H, two d, *J*=11.1 Hz, CH_2 of PMB), 5.3–5.5 (3H, m, H-9, 15, 16), 5.7–5.9 (2H, m, H-10, 11), 6.84, 7.25 (4H, two d, *J*=8.9 Hz, Ar of PMB); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) −4.8, −4.2, 14.2, 18.2, 20.7, 20.7, 23.3, 23.4, 24.1, 25.9, 27.1, 29.1, 29.6, 35.1, 55.3, 72.6, 75.0, 75.5, 82.9, 113.6, 125.4, 129.3, 129.4, 131.0, 132.2, 133.3, 159.0, 173.3; Anal. Calcd. for $C_{32}H_{52}O_5Si$: C, 70.54; H, 9.62. Found: C, 70.48; H, 9.60.

3.1.16. (9*S*,10*E*,12*R*,13*S*,15*Z*)-12-*t*-Butyldimethylsilyloxy-13-*p*-methoxybenzyloxyoctadeca-10,15-dien-9-olide (16β). As described for the synthesis of **16**α, **15**β 42 mg, 0.075 mmol) was converted into **16**β 26 mg, 63%, colorless oil); n_D^{27}=1.5022; $[\alpha]_D^{30}$=−43.9 (*c*=0.43, $CHCl_3$); IR (film): ν_{max} 2931, 1730, 1613, 1514, 1250, 836, 777 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.04, 0.06 (6H, two s, –SiMe), 0.91 (9H, s, –SiBu^t), 0.95 (3H, t, *J*=7.5 Hz, H-18), 1.0–1.8 (10H, m, H-3$_a$, 4, 5, 6, 7, 8$_a$), 2.0–2.3 (6H, m, H-2$_a$, 3$_b$, 8$_b$, 14$_a$, 17), 2.34 (1H, m, H-14$_b$), 2.51 (1H, ddd, *J*=2.7, 6.2, 15.0 Hz, H-2$_b$), 3.35 (1H, dt, *J*=7.5, 4.9 Hz, H-13), 3.80 (3H, s, –OMe), 4.15 (1H, t, *J*=4.9 Hz, H-12), 4.48, 4.59 (2H, two d, *J*=11.0 Hz, CH_2 of PMB), 5.3–5.5 (3H, m, H-9, 15, 16), 5.7–5.9 (2H, m, H-10, 11), 6.85, 7.25 (4H, two d, *J*=8.9 Hz, Ar of PMB); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) −4.8, −4.3, 14.2, 18.2, 20.7, 20.7, 23.3, 23.4, 24.1, 25.9, 27.1, 29.1, 29.7, 35.1, 55.2, 72.6, 75.1, 75.3, 83.0, 113.6, 125.4, 129.4, 129.4, 131.0, 132.0, 133.3, 159.0, 173.4; Anal. Calcd. for $C_{32}H_{52}O_5Si$: C, 70.54; H, 9.62. Found: C, 70.60; H, 9.62.

3.1.17. (9*R*,10*E*,12*R*,13*S*,15*Z*)-12-*t*-Butyldimethylsilyloxy-13-hydroxyoctadeca-10,15-dien-9-olide (17α). To a solution of **16**α (13 mg, 0.024 mmol) in dichloromethane–water (20:1, 0.5 mL) was added sodium bicarbonate (20 mg, 0.239 mmol) and DDQ (27 mg, 0.119 mmol) at room temperature and the mixture was stirred for 1 h. The reaction mixture was poured into a 1:1 mixture of saturated $NaHCO_3$ solution and 10% sodium thiosulfate solution and extracted with ether. The organic layer was washed with water, saturated $NaHCO_3$ solution and brine, and then dried with $MgSO_4$. After removal of the solvent, purification of the residue on silica gel (40:1–10:1 hexanes/EtOAc) provided alcohol **17**α as a colorless oil (10 mg, 99%); n_D^{29}=1.4806; $[\alpha]_D^{29}$=+17.9 (*c*=0.45, $CHCl_3$); IR (film): ν_{max} 3499, 2933, 1731, 1470, 1256, 836 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.04, 0.07 (6H, two s, –SiMe), 0.90 (9H, s, –SiBu^t), 0.96 (3H, t, *J*=7.5 Hz, H-18), 1.0–1.8 (10H, m, H-3$_a$, 4, 5, 6, 7, 8$_a$), 2.0–2.3 (7H, m, H-2$_a$, 3$_b$, 8$_b$, 14, 17), 2.52 (1H, ddd, *J*=2.7, 6.3, 15.3 Hz, H-2$_b$), 3.59 (1H, dt, *J*=3.9, 6.7 Hz, H-13), 4.10 (1H, m, H-12), 5.3–5.6 (3H, m, H-9, 15, 16), 5.7–5.8 (2H, m, H-10, 11); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) −4.9, −4.2, 14.2, 18.1, 20.7, 20.7, 23.2, 23.4, 24.0, 25.8, 27.1, 29.5, 29.9, 35.0, 74.7, 75.1, 75.8, 124.5, 130.0, 130.7, 134.3, 173.3; Anal. Calcd. for $C_{24}H_{44}O_4Si$: C, 67.87; H, 10.44. Found: C, 67.84; H, 10.42.

3.1.18. (9*S*,10*E*,12*R*,13*S*,15*Z*)-12-*t*-Butyldimethylsilyloxy-13-hydroxyoctadeca-10,15-dien-9-olide (17β). As described for the synthesis of **17**α, **16**β (62 mg, 0.11 mmol) was converted into **17**β (48 mg, 99%, colorless oil); n_D^{29}=1.4805; $[\alpha]_D^{31}$=−46.7 (*c*=0.51, $CHCl_3$); IR (film): ν_{max} 3492, 2930, 1731, 1470, 1254, 837 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.05, 0.07 (6H, two s, –SiMe), 0.90 (9H, s, –SiBu^t), 0.96 (3H, t, *J*=7.5 Hz, H-18), 1.0–1.8 (10H, m, H-3$_a$, 4, 5, 6, 7, 8$_a$), 2.0–2.3 (7H, m, H-2$_a$, 3$_b$, 8$_b$, 14, 17), 2.52 (1H, ddd, *J*=2.8, 6.2, 15.4 Hz, H-2$_b$), 3.58 (1H, dt, *J*=3.6, 6.8 Hz, H-13), 4.10 (1H, m, H-12), 5.3–5.6 (3H, m, H-9, 15, 16), 5.7–5.8 (2H, m, H-10, 11); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) −4.9, −4.3, 14.2, 18.1, 20.7, 20.7, 23.3, 23.4, 24.1, 25.8, 27.1, 29.6, 29.9, 35.0, 74.7, 75.0, 75.8, 124.5, 130.0, 130.6, 134.2, 173.3; Anal. Calcd. for $C_{24}H_{44}O_4Si$: C, 67.87; H, 10.44. Found: C, 67.62; H, 10.43.

3.1.19. (9*R*,10*E*,12*R*,13*S*,15*Z*)-12-*t*-Butyldimethylsilyloxy-13-methanesulfonyloxyoctadeca-10,15-dien-9-olide (18α). To a solution of alcohol **17**α (31 mg, 0.073 mmol) in dichloromethane (0.3 mL) was added triethylamine (153 μL, 1.09 mmol) and DMAP (134 mg, 1.09 mmol). The mixture was cooled to 0°C and methanesulfonic anhydride (39 mg, 0.219 mmol) was added. The reaction was

allowed to warm up to room temperature and stirred for 3 h. The reaction mixture was poured into cold water and extracted with ether. The combined organic layer was washed with water, saturated NH_4Cl solution, saturated $NaHCO_3$ solution and brine, and then dried with $MgSO_4$ and concentrated. The residue was purified by silica gel column chromatography (20:1 hexanes/EtOAc) to provide **18**α as a colorless oil (32 mg, 90%); n_D^{28}=1.4815; $[\alpha]_D^{26}$=+23.0 (*c*=0.63, $CHCl_3$); IR (film): ν_{max} 2933, 1731, 1470, 1361, 1255, 1175, 911, 837 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.05, 0.11 (6H, two s, –SiMe), 0.91 (9H, s, –SiBu^t), 0.97 (3H, t, *J*=7.5 Hz, H-18), 1.0–1.8 (10H, m, H-3_a, 4, 5, 6, 7, 8_a), 1.95–2.13 (4H, m, H-3_b, 8_b, 17), 2.21 (1H, m, H-2_a), 2.35 (1H, m, H-14_a), 2.43–2.60 (2H, m, H-2_b, 14_b), 3.02 (3H, s, –SO_2Me), 4.42 (1H, dd *J*=2.3, 5.3 Hz, H-12), 4.58 (1H, m, H-13), 5.25–5.45 (2H, m, H-9, 15), 5.55 (1H, m, H-16), 5.65–5.85 (2H, m, H-10, 11); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) −4.9, −4.5, 14.0, 18.2, 20.6, 20.7, 23.3, 23.4, 24.0, 25.8, 27.1, 27.6, 29.6, 35.0, 38.6, 74.2, 74.9, 85.8, 122.8, 128.9, 131.4, 135.5, 173.3; FAB MS *m*/*z* (M^+) calcd 502.2784, obsd 502.2747.

3.1.20. (9*S*,10*E*,12*R*,13*S*,15*Z*)-12-*t*-Butyldimethylsilyloxy-13-methanesulfonyloxyoctadeca-10,15-dien-9-olide (18β). As described for the synthesis of **18**α, **17**β (26 mg, 0.061 mmol) was converted into **18**β (27 mg, 87%, colorless oil); n_D^{29}=1.4806; $[\alpha]_D^{28}$=−38.0 (*c*=1.34, $CHCl_3$); IR (film): ν_{max} 2959, 1731, 1470, 1360, 1256, 1175, 911, 837 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.06, 0.10 (6H, two s, –SiMe), 0.91 (9H, s, –SiBu^t), 0.97 (3H, t, *J*=7.5 Hz, H-18), 1.0–1.8 (10H, m, H-3_a, 4, 5, 6, 7, 8_a), 1.95–2.13 (4H, m, H-3_b, 8_b, 17), 2.21 (1H, m, H-2_a), 2.34 (1H, m, H-14_a), 2.44–2.60 (2H, m, H-2_b, 14_b), 3.02 (3H, s, –SO_2Me), 4.40 (1H, m, H-12), 4.58 (1H, m, H-13), 5.25–5.45 (2H, m, H-9, 15), 5.55 (1H, m, H-16), 5.65–5.85 (2H, m, H-10, 11); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) −4.9, −4.6, 14.0, 18.2, 20.7, 20.7, 23.4, 23.5, 24.1, 25.8, 27.1, 27.6, 29.7, 35.0, 38.6, 74.3, 74.9, 85.9, 122.8, 129.0, 131.4, 135.5, 173.3; FAB MS *m*/*z* (M^+) calcd 502.2784, obsd 502.2783.

3.1.21. (9*R*,10*E*,12*R*,13*R*,15*Z*)-12,13-Epoxyoctadeca-10,15-dien-9-olide (2). To a solution of **18**α (31 mg, 0.062 mmol) in THF (0.5 mL) was added TBAF (185 μL of 1 M in THF, 0.185 mmol) and the mixture was stirred for 2 h. The mixture was diluted with water and extracted with ether. The organic layer was washed with water and brine, and then dried with $MgSO_4$ and evaporated. Purification of the residue on silica gel (30:1–15:1 hexanes/EtOAc) afforded epoxylactone **2** as a colorless oil (15 mg, 87%); n_D^{27}=1.4951; $[\alpha]_D^{28}$=+68.7 (*c*=0.39, $CHCl_3$); IR (film): ν_{max} 2934, 1730, 1468, 1237, 967 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.97 (3H, t, *J*=7.5 Hz, H-18), 1.0–1.8 (10H, m, H-3_a, 4, 5, 6, 7, 8_a), 1.95–2.15 (4H, m, H-3_b, 8_b, 17), 2.20 (1H, ddd, *J*=2.6, 12.1, 15.5 Hz, H-2_a), 2.37 (2H, m, H-14), 2.51 (1H, ddd, *J*=3.0, 6.2, 15.5 Hz, H-2_b), 2.88 (1H, dt, *J*=2.0, 5.3 Hz, H-13), 3.15 (1H, dd, *J*=2.0, 7.7 Hz, H-12), 5.25–5.65 (4H, m, H-9, 11, 15, 16), 5.95 (1H, dd, *J*=6.0, 15.6 Hz, H-10); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) 14.2, 20.7, 20.7, 23.4, 23.6, 24.2, 27.0, 29.5, 29.9, 35.1, 57.3, 59.9, 75.1, 122.2, 129.1, 132.8, 134.9, 173.4; FAB MS *m*/*z* (M^++H) calcd 293.2117, obsd 293.2117.

3.1.22. (9*S*,10*E*,12*R*,13*R*,15*Z*)-12,13-Epoxyoctadeca-10,15-dien-9-olide (*ent*-1). As described for the synthesis of **2**, **18**β (26 mg, 0.052 mmol) was converted into *ent*-**1** (14 mg, 94%, colorless oil); n_D^{29}=1.4958; $[\alpha]_D^{27}$=−28.2 (*c*=0.77, $CHCl_3$); IR (film): ν_{max} 2932, 1731, 1468, 1237, 1067, 966 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.97 (3H, t, *J*=7.5 Hz, H-18), 1.0–1.8 (10H, m, H-3_a, 4, 5, 6, 7, 8_a), 1.95–2.15 (4H, m, H-3_b, 8_b, 17), 2.20 (1H, ddd, *J*=2.6, 11.9, 15.5 Hz, H-2_a), 2.36 (2H, m, H-14), 2.52 (1H, ddd, *J*=3.0, 6.2, 15.5 Hz, H-2_b), 2.87 (1H, dt, *J*=2.2, 5.3 Hz, H-13), 3.15 (1H, dd, *J*=2.2, 7.8 Hz, H-12), 5.30–5.42 (2H, m, H-9, 15), 5.46 (1H, ddd, *J*=1.4, 7.8, 15.6 Hz, H-11), 5.54 (1H, m, H-16), 5.94 (1H, dd, *J*=5.1, 15.6 Hz, H-10); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) 14.2, 20.7, 20.7, 23.3, 23.6, 24.1, 27.0, 29.5, 29.8, 35.0, 57.4, 59.9, 74.8, 122.2, 128.5, 132.7, 134.9, 173.4; Anal. Calcd. for $C_{18}H_{28}O_3$: C, 73.93; H, 9.65. Found: C, 73.75; H, 9.62.

3.1.23. (9*R*,10*E*,12*R*,13*S*,15*Z*)-12-*t*-Butyldimethylsilyloxy-13-*t*-butyldiphenylsilyloxyoctadeca-10,15-dien-9-olide (19α). To a solution of alcohol **17**α (66 mg, 0.16 mmol) and imidazole (106 mg, 1.55 mmol) in DMF (0.4 mL) under argon was added TBDPSCl (203 μL, 0.78 mmol) and the mixture was stirred for 12 h at room temperature. The reaction mixture was poured into water and extracted with ether. The organic layer was washed with water and brine, dried with $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel (30:1 hexanes/EtOAc) gave **19**α (94 mg, 91%) as a colorless oil; n_D^{29}=1.5171; $[\alpha]_D^{29}$=+38.4 (*c*=1.10, $CHCl_3$); IR (film): ν_{max} 2931, 1731, 1470, 1254, 1112, 836, 703 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) −0.03 (6H, s, –SiMe), 0.79 (3H, t, *J*=7.5 Hz, H-18), 0.85 (9H, s, –SiBu^{t}of TBS), 1.06 (9H, s, –SiBu^{t}of TBDPS), 1.2–1.9 (12H, m, H-3_a, 4, 5, 6, 7, 8_a, 17), 2.0–2.3 (5H, m, H-2_a, 3_b, 8_b, 14), 2.52 (1H, m, H-2_b), 3.75 (1H, m, H-13), 4.09 (1H, dd, *J*=2.0, 6.9 Hz, H-12), 5.14 (1H, m, H-15), 5.24 (1H, m, H-16), 5.42 (1H, m, H-9), 5.61 (1H, dd, *J*=5.7, 15.6 Hz, H-10), 5.91 (1H, dd, *J*=6.9, 15.6 Hz, H-11), 7.3–7.8 (10H, m, Ar of TBDPS); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) −4.7, −4.3, 14.0, 18.2, 19.5, 20.5, 20.6, 23.0, 23.9, 25.9, 27.0, 27.1, 27.2, 28.7, 31.7, 35.1, 75.2, 75.8, 77.7, 124.3, 127.4, 129.1, 129.4, 129.4, 131.6, 133.5, 133.9, 136.0, 136.2, 173.3; FAB MS *m*/*z* (M^+) calcd 662.4187, obsd 662.4132.

3.1.24. (9*S*,10*E*,12*R*,13*S*,15*Z*)-12-*t*-Butyldimethylsilyloxy-13-*t*-butyldiphenylsilyloxyoctadeca-10,15-dien-9-olide (19β). As described for the synthesis of **19**α, **17**β (77 mg, 0.18 mmol) was converted into **19**β (109 mg, 91%, colorless oil); n_D^{28}=1.5162; $[\alpha]_D^{27}$=−6.4 (*c*=0.75, $CHCl_3$); IR (film): ν_{max} 2931, 1731, 1470, 1254, 1112, 836, 702 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) −0.02, −0.01 (6H, two s, –SiMe), 0.81 (3H, t, *J*=7.5 Hz, H-18), 0.87 (9H, s, –SiBu^{t}of TBS), 1.07 (9H, s, –SiBu^{t}of TBDPS), 1.2–1.9 (12H, m, H-3_a, 4, 5, 6, 7, 8_a, 17), 2.0–2.3 (5H, m, H-2_a, 3_b, 8_b, 14), 2.50 (1H, m, H-2_b), 3.75 (1H, m, H-13), 4.07 (1H, dd, *J*=2.0, 6.9 Hz, H-12), 5.15 (1H, m, H-15), 5.25 (1H, m, H-16), 5.41 (1H, m, H-9), 5.62 (1H, dd, *J*=5.6, 15.8 Hz, H-10), 5.89 (1H, dd, *J*=6.9, 15.8 Hz, H-11), 7.3–7.8 (10H, m, Ar of TBDPS); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) −4.7, −4.4, 14.0, 18.2, 19.5, 20.5, 20.6, 23.2, 23.3, 24.1, 25.9, 27.0, 27.2, 29.3,

31.7, 35.1, 75.2, 75.7, 77.8, 124.3, 127.3, 129.2, 129.4, 131.6, 133.5, 133.9, 134.6, 136.0, 136.2, 173.3; FAB MS *m/z* (M^+) calcd 662.4187, obsd 662.4164.

3.1.25. (9*R*,10*E*,12*R*,13*S*,15*Z*)-13-*t*-Butyldiphenylsilyloxy-12-hydroxyoctadeca-10,15-dien-9-olide (20α). The compound **19**α (21 mg, 0.032 mmol) was dissolved in 2% HF/acetonitrile (1 mL) at 0°C and stirred for 1 h at room temperature. The reaction mixture was neutralized with saturated $NaHCO_3$ solution and extracted with ether. The combined organic layer was washed with water, saturated $NaHCO_3$ solution and brine. After drying with $MgSO_4$, the solvent was removed in vacuo. The residue was purified by silica gel column chromatography (15:1 hexanes/EtOAc) to furnish alcohol **20**α as a colorless oil (8.9 mg, 51%); n_D^{27}=1.5166; $[\alpha]_D^{28}$=+46.9 (*c*=0.81, $CHCl_3$); IR (film): ν_{max} 3449, 2930, 1726, 1111, 822, 703 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.81 (3H, t, *J*=7.5 Hz, H-18), 1.08 (9H, s, –SiBu^t), 1.2–1.8 (12H, m, H-3_a, 4, 5, 6, 7, 8_a, 17), 2.0–2.3 (5H, m, H-2_a, 3_b, 8_b, 14), 2.51 (1H, dm, *J*=15.6 Hz, H-2_b), 3.83 (1H, m, H-13), 4.09 (1H, m, H-12), 5.16 (1H, m, H-15), 5.29 (1H, m, H-16), 5.41 (1H, m, H-9), 5.70 (1H, dd, *J*=5.3, 15.9 Hz, H-10), 5.87 (1H, dd, *J*=6.0, 15.9 Hz, H-11), 7.3–7.8 (10H, m, Ar of TBDPS); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) 14.0, 19.4, 20.5, 20.6, 23.1, 23.1, 24.0, 27.0, 27.2, 29.1, 30.6, 35.1, 74.4, 75.2, 76.6, 123.9, 127.6, 127.8, 129.6, 129.8, 129.9, 130.0, 133.4, 133.6, 133.9, 135.8, 135.9, 173.3; FAB MS *m/z* (M^+) calcd 548.3322, obsd 548.3325.

3.1.26. (9*S*,10*E*,12*R*,13*S*,15*Z*)-13-*t*-Butyldiphenylsilyloxy-12-hydroxyoctadeca-10,15-dien-9-olide (20β). As described for the synthesis of **20**α, **19**β (44 mg, 0.66 mmol) was converted into **20**β (19 mg, 51%, colorless oil); n_D^{28}=1.5168; $[\alpha]_D^{28}$=+6.4 (*c*=0.83, $CHCl_3$); IR (film): ν_{max} 3478, 2931, 1730, 1111, 822, 704 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.82 (3H, t, *J*=7.5 Hz, H-18), 1.08 (9H, s, –SiBu^t), 1.2–1.8 (12H, m, H-3_a, 4, 5, 6, 7, 8_a, 17), 2.0–2.3 (5H, m, H-2_a, 3_b, 8_b, 14), 2.50 (1H, dm, *J*=15.3 Hz, H-2_b), 3.84 (1H, m, H-13), 4.08 (1H, m, H-12), 5.18 (1H, m, H-15), 5.29 (1H, m, H-16), 5.39 (1H, m, H-9), 5.72 (1H, dd, *J*=4.7, 15.7 Hz, H-10), 5.80 (1H, dd, *J*=5.1, 15.7 Hz, H-11), 7.3–7.8 (10H, m, Ar of TBDPS); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) 14.0, 19.4, 20.5, 20.6, 23.2, 23.4, 24.1, 27.0, 27.1, 29.6, 30.5, 35.0, 74.3, 75.3, 76.6, 124.0, 127.6, 127.7, 129.5, 129.8, 129.9, 129.9, 133.5, 133.6, 133.8, 135.8, 135.9, 173.3; FAB MS *m/z* (M^+) calcd 548.3322, obsd 548.3332.

3.1.27. (9*R*,10*E*,12*S*,13*S*,15*Z*)-12,13-Epoxyoctadeca-10,15-dien-9-olide (Mueggelone, 1). To a solution of alcohol **20**α (25 mg, 0.046 mmol) in dichloromethane (0.5 mL) was added triethylamine (58 μL, 0.401 mmol) and DMAP (49 mg, 0.401 mmol). The mixture was cooled to 0°C and methanesulfonyl chloride (10.6 μL, 0.137 mmol) was added. Stirring was continued for 4 h and then the reaction mixture was poured into cold water and extracted with ether. The combined organic layer was washed with water, saturated NH_4Cl solution, saturated $NaHCO_3$ solution and brine, and then dried with $MgSO_4$. After removal of the solvent, the residue was taken up into THF (0.5 mL). To this solution was added TBAF (100 μL of 1.0 M in THF, 0.1 mmol) and the mixture was stirred for 2 h at ambient temperature. The reaction mixture was diluted with water and extracted with ether. The organic layer was washed with water and brine, dried with $MgSO_4$ and evaporated. Purification of the residue on silica gel (30:1–15:1 hexanes/EtOAc) afforded the desired epoxylactone **1** as a colorless oil (13 mg, 94%); n_D^{29}=1.4948; $[\alpha]_D^{28}$=+28.7 (*c*=0.63, $CHCl_3$); IR (film): ν_{max} 2932, 1731, 1468, 1237, 1067, 966 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.97 (3H, t, *J*=7.5 Hz, H-18), 1.0–1.8 (10H, m, H-3_a, 4, 5, 6, 7, 8_a), 1.95–2.15 (4H, m, H-3_b, 8_b, 17), 2.20 (1H, ddd, *J*=2.6, 11.9, 15.5 Hz, H-2_a), 2.36 (2H, m, H-14), 2.52 (1H, ddd, *J*=3.0, 6.2, 15.5 Hz, H-2_b), 2.87 (1H, dt, *J*=2.2, 5.3 Hz, H-13), 3.15 (1H, dd, *J*=2.2, 7.8 Hz, H-12), 5.30–5.42 (2H, m, H-9, 15), 5.46 (1H, ddd, *J*=1.4, 7.8, 15.6 Hz, H-11), 5.54 (1H, m, H-16), 5.94 (1H, dd, *J*=5.1, 15.6 Hz, H-10); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) 14.2, 20.7, 20.7, 23.3, 23.6, 24.1, 27.0, 29.5, 29.8, 35.0, 57.4, 59.9, 74.8, 122.2, 128.5, 132.7, 134.9, 173.4; Anal. Calcd. for $C_{18}H_{28}O_3$: C, 73.93; H, 9.65. Found: C, 73.72; H, 9.67.

3.1.28. (9*S*,10*E*,12*S*,13*S*,15*Z*)-12,13-Epoxyoctadeca-10,15-dien-9-olide (*ent*-2). As described for the synthesis of **1**, **20**β (19 mg, 0.034 mmol) was converted into *ent*-**2** (7.5 mg, 75%, colorless oil); n_D^{28}=1.4949; $[\alpha]_D^{28}$=−67.3 (*c*=0.56, $CHCl_3$); IR (film): ν_{max} 2934, 1730, 1468, 1237, 967 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.97 (3H, t, *J*=7.5 Hz, H-18), 1.0–1.8 (10H, m, H-3_a, 4, 5, 6, 7, 8_a), 1.95–2.15 (4H, m, H-3_b, 8_b, 17), 2.20 (1H, ddd, *J*=2.6, 12.1, 15.5 Hz, H-2_a), 2.37 (2H, m, H-14), 2.51 (1H, ddd, *J*=3.0, 6.2, 15.5 Hz, H-2_b), 2.88 (1H, dt, *J*=2.0, 5.3 Hz, H-13), 3.15 (1H, dd, *J*=2.0, 7.7 Hz, H-12), 5.25–5.65 (4H, m, H-9, 11, 15, 16), 5.95 (1H, dd, *J*=6.0, 15.6 Hz, H-10); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ (ppm) 14.2, 20.7, 20.7, 23.4, 23.6, 24.2, 27.0, 29.5, 29.9, 35.1, 57.3, 59.9, 75.1, 122.2, 129.1, 132.8, 134.9, 173.4; FAB MS *m/z* (M^++H) calcd 293.2117, obsd 293.2091.

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