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Total Synthesis of Marine Oxylipin Bacillariolides I–III

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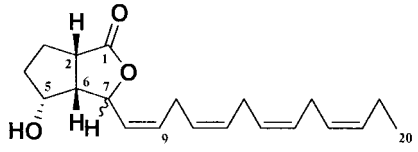
Abstract—Marine oxylipin bacillariolides I–III were synthesized from (*R*)-malic acid, using diastereoselective one-pot formation of the chiral cyclopentane derivative from the anion of allyl phenyl sulfone and chiral epoxymesylate as the key reaction.

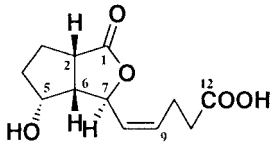
Marine carbocyclic oxylipins are of considerable interest for their unique structural features, peculiar biosynthetic pathways and diverse biological activities.[1] Bacillariolides I (**1**) and II (**2**), isolated from the marine diatom, *Pseudo-nitzschia multiseries*,[2] a causative diatom of so-called amnesic shellfish poisoning (ASP),[3] are cyclopentane-containing structurally unique oxylipins.[4] Bacillariolide III (**3**), isolated from the culture broth of the same marine diatom, is an extracellular metabolic oxylipin derived from bacillariolide I.[5] The relative configurations of bacillariolides I–III were determined by spectroscopic analysis and the absolute configuration of bacillariolide I was established by X-ray crystallography of its (−)-camphanic acid derivative.[6] The absolute configurations of bacillariolides II and III were estimated based on an apparent biosynthetic relationship of bacillariolides II and III with bacillariolide I. Bacillariolide I possesses significant inhibitory activity toward phospholipase A_2.[7] The unique structural features and biological activity of bacillariolides prompted the authors to undertake their total synthesis. The previous communication reported the total synthesis of bacillariolide II using one-pot formation of the chiral cyclopentane derivative as the key step.[8] In this paper, the authors wish to report the detail of synthesis of bacillariolide II along with synthesis of bacillariolides I and III (Fig. 1).

The authors reported one-pot synthesis of cycloalkane derivatives using allyl phenyl sulfone and epoxymesylate (Fig. 2).[9] The synthesis involves the following sequences: (1) an anion of allyl phenyl sulfone reacts with epoxide **i** to give epoxy sulfone **ii**; (2) a deprotonation of **ii** by an anion of allyl phenyl sulfone in situ generates an anion **iii**; and (3) cyclization of **iii** gives cycloalkane derivative **iv**. Previously, the synthesis of cyclopropane-containing marine oxylipin constanolactone E using the one-pot synthesis of cyclopropane **iv** (n=0) was reported.[10] This one-pot reaction using chiral epoxide **i** (n=2) is applied to the synthesis of cyclopentane-containing bacillariolides I–III.

The authors considered that the synthesis should be carried out via a common synthetic intermediate for all of bacillariolides I–III (Fig. 3). The one-pot synthesis of cyclopentane is used for the synthesis of the C-1∼8 segment **e**.[11] In this synthesis, an anion of allyl phenyl sulfone is reacted with chiral epoxide **a**, prepared from (*R*)-malic acid, to give epoxysulfone **b**, which is deprotonated in situ by base to generate an anion **c**, then cyclized to give chiral cyclopentane **d**. Cyclopentane **d** is converted to aldehyde **e** possessing the chiral centers at C-2, C-5, C-6 and C-7 for bacillariolide II by oxidative cleavage of vinyl group and removal of phenylsulfonyl group. By the coupling reaction



7α-H : bacillariolide I (1)
7β-H : bacillariolide II (2)



bacillariolide III (3)

Figure 1.

Keywords: marine metabolites; eicosanoids; sulfones; cyclopentanes.

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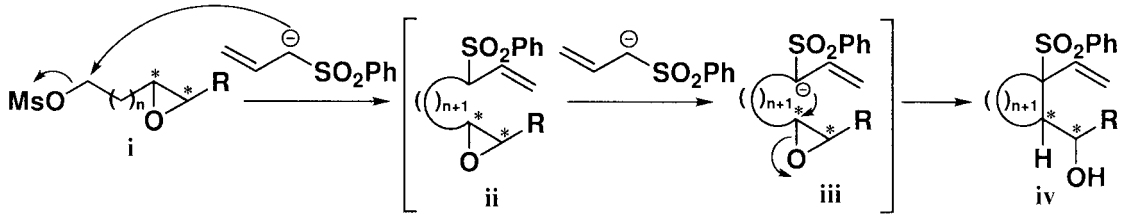


Figure 2.

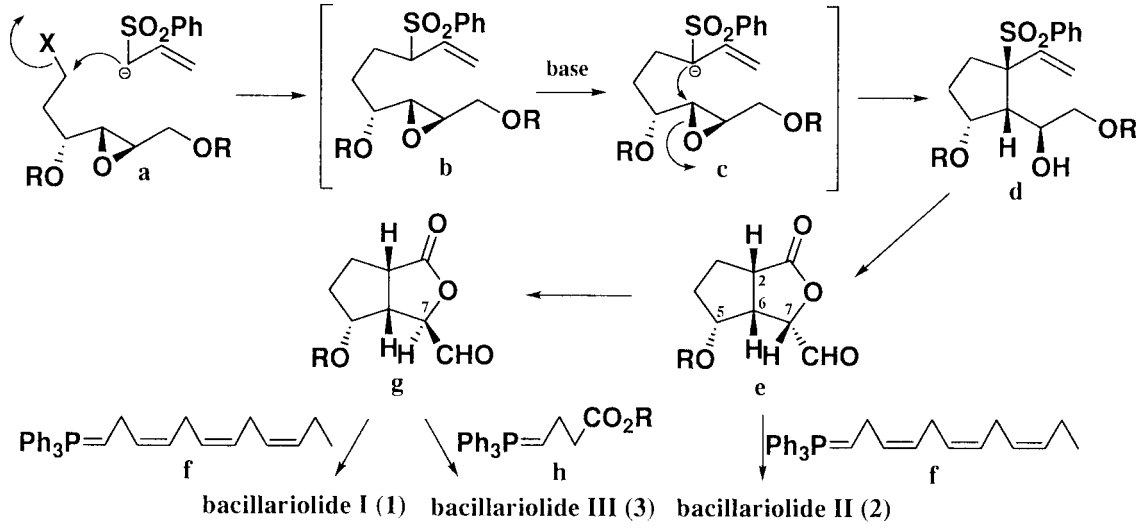


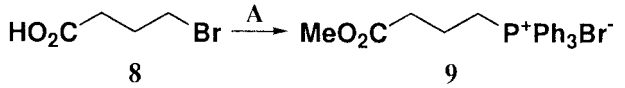
Figure 3.

of aldehyde **e** with Wittig reagent **f**, corresponding to C-9~20 segment, bacillariolide II (**2**) is obtained. Epimerization of the C-7 position in aldehyde **e** gives aldehyde **g** having requisite chiral centers at C-2, C-5, C-6 and C-7 for bacillariolide I and III. The coupling reaction of aldehyde **g** with Wittig reagent **f** or **h** leads to bacillariolide I (**1**) or III (**3**), respectively.

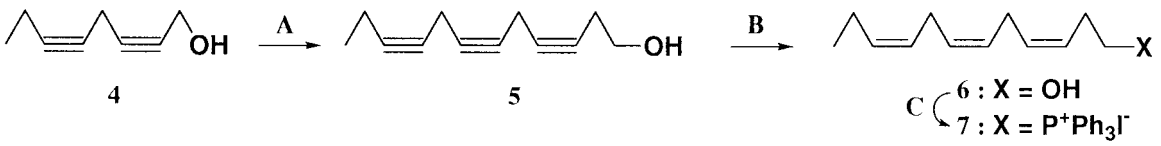
Phosphonium iodide **7** corresponding to C-9~20 segment **f** for bacillariolides I and II was prepared from 2,5-octadiyn-1-ol (**4**) (Scheme 1). Bromination of 2,5-octadiyn-1-ol (**4**)[12] was carried out by treating with carbon tetrabromide and triphenylphosphine to give 1-bromo-2,5-octadiyne. The coupling reaction of 1-bromo-2,5-octadiyne with 3-butyn-1-ol in the presence of CuI, K_2CO_3 and NaI in DMF[13] gave 3,6,9-dodecatriyn-1-ol (**5**). The stereoselective partial hydrogenation of triynol **5** was efficiently carried out in the presence of Pd–$BaSO_4$ and quinoline to afford (*Z*,*Z*,*Z*)-trienol **6**. (*Z*,*Z*,*Z*)-Trienol **6** was converted to phosphonium iodide **7** via iodide in three steps: (1) tosylation of hydroxyl group; (2) treatment with NaI in acetone to give iodide; and (3) treatment with triphenylphosphine in benzene.

Phosphonium bromide **9** corresponding to C-9~12 segment **h** for bacillariolide III was prepared from 4-bromobutyric acid (**8**) (Scheme 2). 4-Bromobutyric acid (**8**) was treated with acetyl chloride in MeOH to provide methyl ester and subsequent treatment with triphenylphosphine in CH_3CN to give phosphonium bromide **9**.

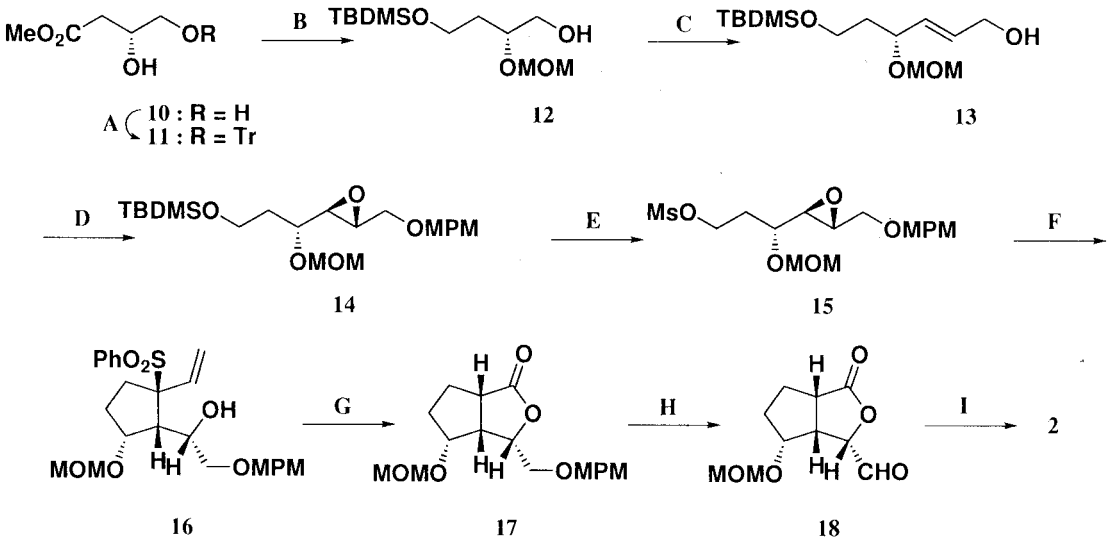
Stereoselective synthesis of bacillariolide II using one-pot formation of the chiral cyclopentane derivative as the key step was carried out (Scheme 3). The primary hydroxyl group of methyl (*R*)-3,4-dihydroxybutanoate (**10**),[14] prepared from (*R*)-malic acid, was selectively protected as triphenylmethyl (trityl) ether to give trityl ether **11**.[15] Trityl ether **11** was converted to alcohol **12** in four steps: (1) protection of the secondary hydroxyl group as MOM



Scheme 2. Reagents and conditions: A. (i) Ac-Cl, MeOH, rt, (ii) Ph_3P, CH_3CN, reflux, 65% (2 steps).



Scheme 1. Reagents and conditions: A. (i) CBr_4, Ph_3P, CH_2ClCH_2Cl, 0°C, (ii) 3-butyn-1-ol, K_2CO_3, CuI, NaI, DMF, rt, 80% (2 steps); B. H_2, Pd–$BaSO_4$, quinoline, MeOH, rt, 76%; C. (i) Ts-Cl, Py, $CHCl_3$, rt, quant., (ii) NaI, acetone, rt, 71%, (iii) Ph_3P, benzene, reflux, 75%.



Scheme 3. Reagents and conditions: A. Tr-Cl, Et_3N, DMAP, DMF, 65°C, 87%; B. (i) MOM-Cl, $^iPr_2NEt$, $CHCl_3$, 50°C, (ii) $LiAlH_4$, Et_2O, 0°C, (iii) TBDMS-Cl, imidazole, DMF, rt, (iv) Na, liq. NH_3–EtOH–THF, −34°C, 94% (4 steps); C. (i) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, −78°C; (ii) $(^iPrO)_2P(O)CH_2CO_2Et$, ^{t}BuOK, THF, −42°C, (iii) DIBAL-H, toluene, −78°C, 89% (3 steps); D. (i) TBHP, D-(−)-DET, $(^iPrO)_4Ti$, 4ÅMS, CH_2Cl_2, −20°C, 89%, (ii) MPM−Br, NaH, THF–DMF, 0°C, 95%; E. (i) Bu_4NF, THF, rt, (ii) Ms-Cl, DMAP, CH_2Cl_2, 0°C∼rt, quant. (2 steps); F. allyl phenyl sulfone, BuLi, THF, −78°C∼rt, 99%; G. (i) OsO_4, $NaIO_4$, 1,4-dioxane-H_2O, rt, (ii) Jones ox., acetone, 0°C, 82% (2 steps), (iii) Na–Hg, Na_2HPO_4, MeOH, rt, 91%; H. (i) CAN, CH_3CN–H_2O, rt, 88%, (ii) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, −78°C, quant.; I. (i) **7**, BuLi, THF–HMPA, −78°C, 66%, (ii) AcOH–conc. HCl (50:1), 40°C, 97%.

ether; (2) reduction of the ester with $LiAlH_4$; (3) protection of the primary hydroxyl group as TBDMS ether; and (4) removal of the trityl group. The primary hydroxyl group of **12** was oxidized by Swern procedure followed by Horner–Emmons reaction to give (*E*)-α,β-unsaturated ester as the sole product, which was then reduced with DIBAL-H to give allylic alcohol **13**. The stereoselective epoxidation of allylic alcohol **13** according to Sharpless procedure[16] was carried out followed by protection of hydroxyl group as MPM ether to give **14**. TBDMS ether **14** was converted to epoxymesylate **15** by removal of the TBDMS group and mesylation of the primary hydroxyl group. Reaction of the lithio derivative of allyl phenyl sulfone (2.4 equiv.) with epoxymesylate **15** (1.0 equiv.) in THF at −78°C to room temperature over 12 h, gave cyclopentane **16** as the sole product in 99% yield. Relative configuration at C-2 position in **16** was determined by NOESY correlations between H-1 (δ_H 6.42) and H-7 (δ_H 4.05) and H-6 (δ_H 3.15) and phenyl protons (δ_H 7.81) (Fig. 4).

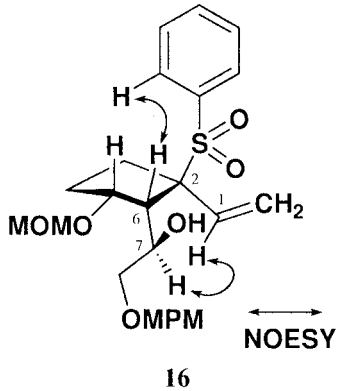
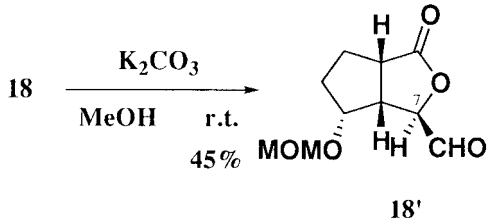


Figure 4.

The terminal olefin in **16** was oxidized by OsO_4–$NaIO_4$ to give hemiacetal, then oxidized with Jones reagent to give lactone and the phenylsulfonyl group was removed by treatment with Na–Hg to give lactone **17** bearing the requisite chiral centers at C-2, C-5, C-6 and C-7 corresponding to C-1∼8 segment **e**. Removal of MPM group in **17** by treatment of CAN afforded an alcohol, then oxidized according to Swern procedure to give aldehyde **18**. Coupling reaction of aldehyde **18** with Wittig reagent, prepared from phosphonium iodide **7** and BuLi, in the presence of HMPA afforded (8*Z*,11*Z*,14*Z*,17*Z*)-tetraene as the sole product. Finally, removal of the MOM group completed the synthesis of bacillariolide II (**2**), $[\alpha]_D$= −58.5° (*c*=0.33, MeOH). The spectral data of **2** and natural bacillariolide II, $[\alpha]_D$=−59.2° (*c*=0.33, MeOH),[4] as well as the sign of optical rotation were identical.

Stereoselective synthesis of bacillariolides I and III by isomerization at C-7 position was carried out as shown in Scheme 4. Aldehyde **18** was treated with K_2CO_3 in MeOH to give aldehyde **18′**, which was isomerized at C-7 position, at only 45% yield.

The lactone portion was protected as methyl acetal. Lactone **17** was reduced with DIBAL-H to give hemiacetal, which was treated with PPTS in MeOH to afford methyl acetal **19**



Scheme 4.

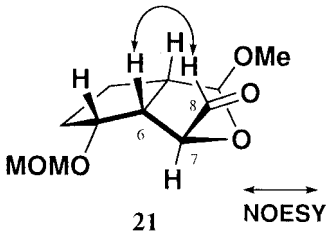


Figure 5.

as the sole product. Removal of the MPM group in **19** by treatment with DDQ afforded an alcohol, subsequently oxidized by the Swern procedure to give aldehyde **20**. Aldehyde **20** was treated with K_2CO_3 in MeOH at room temperature and isomerization of C-7 proceeded to afford aldehyde **21**, possessing requisite chiral centers at C-2, C-5, C-6 and C-7 corresponding to C-1~8 segment **g**. Relative configuration at C-7 position in **21** was confirmed by NOESY correlation between H-6 (δ_H 3.12) and aldehyde proton H-8 (δ_H 9.70) (Fig. 5).

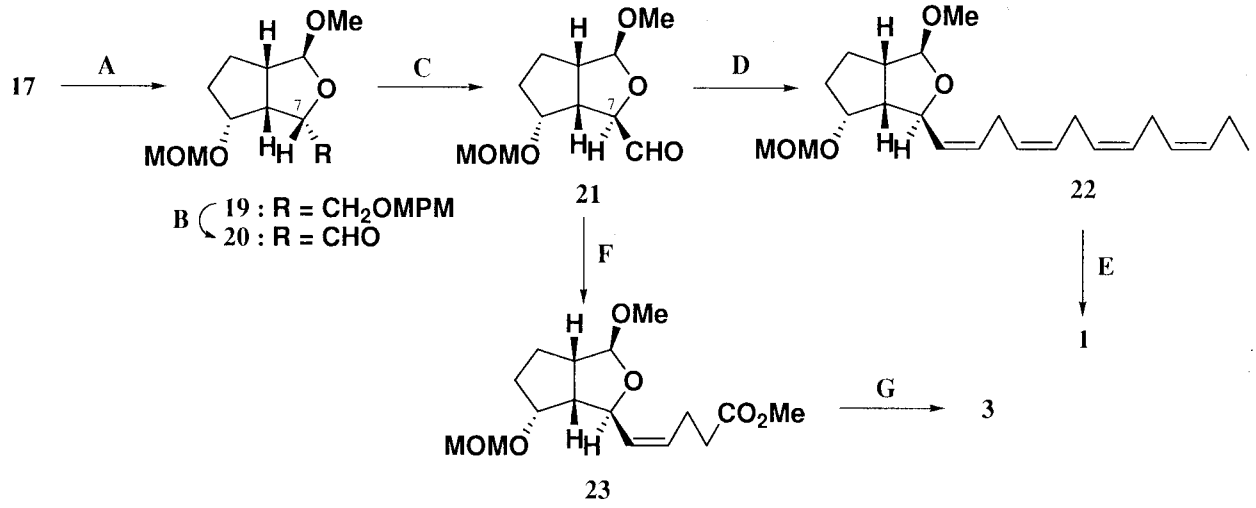
Coupling reaction of aldehyde **21** with Wittig reagent, prepared using phosphonium iodide **7** afforded all-*Z*-tetraene **22** as the sole product. Hydrolysis of methyl acetal by treatment with AcOH–H_2O (4:1), oxidation of hemiacetal with Jones reagent to give lactone and removal of MOM group with AcOH–conc.HCl (50:1) afforded bacillariolide I (**1**), $[\alpha]_D$=−23.6° (*c*=0.55, MeOH). The spectral data of **1** and natural bacillariolide I, $[\alpha]_D$=−25.9° (*c*=0.21, MeOH),[4] as well as the sign of optical rotation were identical. Coupling reaction of aldehyde **21** with Wittig reagent, prepared from phosphonium bromide **9**, corresponding to C-9~12 segment **h**, and LiHMDS afforded *Z*-olefin **23** as the sole product. Hydrolysis of methyl acetal **23** with AcOH−H_2O (4:1) gave hemiacetal and oxidation of hemiacetal with Jones reagent produced lactone. Finally, hydrolysis of methyl ester and MOM ether by treatment with 1N HCl, followed by purification with silica gel afforded bacillariolide III (**3**), $[\alpha]_D$=−54.2° (*c*=0.31, MeOH). NMR spectrum and optical rotation of synthesized bacillariolide III were not identical with reported spectral data.[5] Natural bacillariolide III, for which analytical data were obtained, was finally purified with ODS. Synthesized bacillariolide III was also purified with ODS. The NMR spectral data of synthesized bacillariolide III, purified with ODS, was identical with those of natural bacillariolide III. For further confirmation, synthesized bacillariolide III was converted to the bacillariolide III sodium salt by filtration through Chelex 100 Na^+ form. Spectral data of the sodium salt of bacillariolide III was identical with those of the sodium salt of natural bacillariolide III.[17] The total synthesis of bacillariolide III was thus considered to have been achieved. Discrepancy in the value of optical rotation of synthesized and natural bacillariolide III was shown to arise from difference in purity (Scheme 5).

This paper presents the first total synthesis of bacillariolides I–III and absolute configurations of bacillariolides II and III were confirmed as **2** and **3**, respectively.

Experimental

General experimental procedures

Melting points were measured on Yazawa BY-2 micro melting point apparatus and uncorrected. Optical rotations were measured with a JASCO DIP-360 automatic polarimeter. IR spectra were recorded with a Perkin–Elmer FT-IR 1710 spectrometer or JASCO FT-IR/620 spectrometer, UV spectra with a JASCO V-550 spectrophotometer and ^1H and ^{13}C NMR spectra with a Varian Gemini-300, a Bruker DPX-400 or a Bruker DRX-500. Chemical shifts are given on a δ (ppm) scale with tetramethylsilane (TMS) or sodium 3-(trimethylsilyl)propionate (TSP) as the internal standard (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad). EIMS was obtained with a Thermo Quest TSQ 700 spectrometer. FABMS spectra, high resolution EIMS (HREIMS) spectra and high resolution FABMS



Scheme 5. Reagents and conditions: A. (i) DIBAL-H, toluene, −78°C; (ii) PPTS, MeOH, rt, 99% (2 steps); B. (i) DDQ, CH_2Cl_2–H_2O, rt, 92%, (ii) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, −78°C, 96%; C. K_2CO_3, MeOH, rt, 82%; D. **7**, BuLi, THF–HMPA, −78°C, 99%; E. (i) AcOH–H_2O (4:1), rt, 87%, (ii) Jones ox., acetone, 0°C, 89%, (iii) AcOH–conc.HCl (50:1), rt, 90%; F.**9**, LiHMDS, THF–HMPA, −78~0°C, 95%, G. (i) AcOH–H_2O (4:1), rt, 67%, (ii) Jones ox., acetone, 0°C, quant., (iii) 1N HCl, 60°C, 70%.

(HRFABMS) spectra were obtained with a VG Auto Spec E spectrometer. Column chromatography was carried out on Merck silica gel 60 (70–230 mesh), Merck silica gel 60 (230–400 mesh) or ODS Wakogel® LP-40 C-18. Preparative TLC was conducted on a Merck silica gel 60 F_{254} plate.

3,6,9-Dodecatriyn-1-ol (5). To a solution of 2,5-octandiyn-1-ol (**4**) (11.5 g, 94.1 mmol) in 1,2-dichloroethane (280 mL) were added a solution of tetrabromomethane (34.3 g, 104 mmol) and triphenylphosphine (32.1 g, 122 mmol) in 1,2-dichloroethane (34.0 mL). The mixture was stirred at rt for 1 h, diluted with hexane and filtered through silica gel. The filtrate was concentrated under reduced pressure to give crude bromide for use in the reaction below without purification. A portion of a crude bromide was purified for spectral analysis by silica gel column chromatography (eluted with hexane). Colorless oil; IR (neat) 2977, 2234, 612 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ ppm: 1.12 (3H, t, J=7.5 Hz), 2.17 (2H, ddt, J=15.0, 7.5, 2.3 Hz), 3.21 (2H, m), 3.92 (2H, t, J=2.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 9.8, 12.1, 13.6, 14.7, 72.0, 75.1, 81.8, 82.3; EIMS (m/z): 184 (M^+, 40), 77 (100).

To a suspension of K_2CO_3 (20.9 g, 151 mmol), NaI (22.7 g, 151 mmol) and CuI (14.4 g, 75.7 mmol) in DMF was added a solution of 2-butyn-1-ol (6.40 mL, 83.3 mmol) and the above crude bromide in DMF (16.4 mL) and stirred at rt for 6 h. The reaction mixture was diluted with Et_2O and filtered through celite. The filtrate was washed with saturated aqueous NH_4Cl, H_2O and saturated aqueous NaCl, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluted with hexane–EtOAc=3:1) to give 3,6,9-dodecatriyn-1-ol (**5**) (11.7 g, 80%, 2 steps) as a colorless oil. IR (neat) 3368, 2938, 2216 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ ppm: 1.12 (3H, t, J=7.5 Hz), 2.17 (2H, ddt, J=15.0, 7.5, 2.3 Hz), 2.44 (2H, tt, J=6.2, 2.3 Hz), 3.14 (4H, m), 3.70 (2H, t, J=6.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 9.4, 9.5, 12.1, 13.6, 22.7, 60.8, 72.8, 74.2, 74.9, 75.6, 77.1, 81.9.

(3*Z*,6*Z*,9*Z*)-Dodecatrien-1-ol (6). A solution of 3,6,9-dodecatriyn-1-ol (**5**) (4.01 g, 23.0 mmol) in MeOH (13.0 mL) containing quinoline (0.4 mL) was hydrogenated at rt over 5% Pd–$BaSO_4$ (1.3 g). The mixture was stirred at rt under a balloon pressure of hydrogen for 3 h. The catalyst was filtered through celite and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluted with hexane–EtOAc=2:1) to give (3*Z*,6*Z*,9*Z*)-dodecatrien-1-ol (**6**) (3.14 g, 76%) as a colorless oil. IR (neat) 3339, 2964, 1653 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ ppm: 0.98 (3H, t, J=7.6 Hz), 2.08 (2H, qd, J=7.6, 6.9 Hz), 2.37 (2H, dt, J=7.2, 6.6 Hz), 2.83 (4H, m), 3.65 (2H, m), 5.26–5.45 (5H, m), 5.54 (1H, dtt, J=10.7, 7.2, 1.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 14.0, 20.3, 25.2, 25.4, 30.5, 61.7, 125.5, 126.7, 127.5, 128.3, 130.2, 131.7; EIMS (m/z): 180 (M^+, 10), 79 (100); HREIMS: Calcd for $C_{12}H_{20}O$ (M^+) 180.1514; Found: 180.1507.

(3*Z*,6*Z*,9*Z*)-1-Dodecatrienyltriphenylphosphonium iodide (7). To a solution of alcohol **6** (1.92 g, 10.6 mmol) in $CHCl_3$ (11.0 mL) were added pyridine (3.42 mL, 42.4 mmol) and *p*-toluenesulfonyl chloride (2.84 g, 14.9 mmol) and the mixture was stirred at rt for 3 h. The reaction mixture was diluted with Et_2O–$CHCl_3$ (4:1), washed with H_2O and saturated aqueous NaCl, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluted with hexane–EtOAc=4:1) to give tosylate (3.63 g, quantitative yield) as a colorless oil. IR (neat) 2964, 1599 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ ppm:0.97 (3H, t, J=7.5 Hz), 2.06 (2H, m), 2.42 (2H, td, J=6.9, 1.5 Hz), 2.45 (3H, s), 2.76 (4H, br dd, J=11.6, 6.3 Hz), 4.02 (2H, t, J=6.9 Hz), 5.21–5.52 (6H, m), 7.34 (2H, m), 7.79 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm:14.2, 20.5, 21.5, 25.4, 25.5, 27.0, 69.5, 123.1, 126.7, 127.2, 127.8, 128.8, 129.7, 131.6, 132.0, 133.0, 144.6; EIMS (m/z):334 (M^+, 0.5), 91 (100); HREIMS: Calcd for $C_{19}H_{26}O_3S$ (M^+): 334.1602; Found: 334.1584.

To a solution of the above tosylate (2.72 g, 8.13 mmol) in acetone (16.0 mL) was added NaI (3.66 g, 24.4 mmol) followed by stirring at rt for 24 h. The reaction mixture was diluted with Et_2O, washed with H_2O, saturated aqueous $Na_2S_2O_3$ and saturated aqueous NaCl, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluted with hexane) to give iodide (1.67 g, 71%) as a colorless oil. IR (neat) 2963 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ ppm: 0.98 (3H, t, J=7.5 Hz), 2.08 (2H, qdd, J=7.5, 7.0, 0.8 Hz), 2.67 (2H, td, J=7.3, 1.0 Hz), 2.81 (4H, br t, J=6.3 Hz), 3.15 (2H, t, J=7.3 Hz), 5.26–5.45 (5H, m), 5.52 (1H, dtt, J=10.7, 7.3, 1.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 5.1, 14.2, 20.4, 25.4, 25.6, 31.3, 126.7, 127.2, 128.0, 128.5, 130.2, 131.8; EIMS (m/z): 290 (M^+, 5), 79 (100); HREIMS: Calcd for $C_{12}H_{19}I$ (M^+): 290.0531; Found: 290.0564, Anal. Calcd for $C_{12}H_{19}I$: C, 49.67; H, 6.60. Found: C, 49.58; H, 6.71.

To a solution of the above iodide (1.48 g, 5.09 mmol) in benzene (5.00 mL) was added Ph_3P (1.47 g, 5.09 mmol) and refluxed for 24 h. The reaction mixture was concentrated under reduced pressure to give phosphonium iodide **7** (2.11 g, 75%) as a pale yellow oil. IR (neat) 2962, 1587 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ ppm: 0.94 (3H, t, J=7.6 Hz), 2.01 (2H, qdd, J=7.6, 7.0, 0.8 Hz), 2.46 (2H, m), 2.68 (4H, m), 3.49 (2H, m), 5.16–5.55 (6H, m), 7.80–7.95 (15H, m); ^{13}C NMR (75 MHz, CD_3OD) δ ppm: 14.7, 21.3, 21.4, 21.4, 22.9 (d, J_{P-C}=49.2 Hz), 26.4 (d, J_{P-C}=9.6 Hz), 119.6 (d, J_{P-C}=85.5 Hz), 127.6 (d, J_{P-C}=16.0 Hz), 128.0 (d, J_{P-C}=19.3 Hz), 129.6 (d, J_{P-C}=7.0 Hz), 129.8 (d, J_{P-C}=9.2 Hz), 131.5 (d, J_{P-C}=12.4 Hz), 132.9, 134.5, 134.8 (d, J_{P-C}=10.3 Hz), 136.2 (d, J_{P-C}=3.0 Hz); FABMS (m/z): 425 (M^+-I, 100); HRFABMS: Calcd for $C_{30}H_{34}P$ (M^+-I): 425.2398; Found: 425.2400.

3-Methoxycarbonylpropyltriphenylphosphonium bromide (9). To a solution of 4-bromobutyric acid (1.15 g, 6.89 mmol) in MeOH (7.00 mL) was added acetyl chloride (0.12 mL) at 0°C and the mixture was stirred at rt for 24 h. The reaction mixture was concentrated under reduced pressure to give crude methyl ester for use in the reaction below without purification. Colorless oil; IR (neat) 2953, 1737 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ ppm: 2.18 (2H, tt, J=7.1, 6.4 Hz), 2.51 (2H, t, J=7.1 Hz), 3.47 (2H,

t, J=6.4 Hz), 3.69 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 27.5, 32.0, 32.6, 51.5, 172.7; EIMS (*m*/*z*): 180 (M^+, 1), 149 (M^+-OMe, 11), 43 (100).

To a solution of the above crude ester in acetonitrile (7.00 mL) was added Ph_3P (1.80 g, 6.89 mmol), followed by refluxing for 24 h. The reaction mixture was concentrated under reduced pressure to give crude phosphonium bromide and recrystallized from acetonitrile–Et_2O to give phosphonium bromide **9** as white crystals. mp 166–168°C; IR (KBr) 2886, 1719, 1587 cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD) δ ppm: 1.93 (2H, m), 2.62 (2H, td, J=6.7, 1.1 Hz), 3.46 (2H, m), 3.70 (3H, s), 7.73–7.94 (15H, m); ^{13}C NMR (75 MHz, CD_3OD) δ ppm: 19.2, 22.1 (d, J_{P-C}= 52.4 Hz), 34.2 (d, J_{P-C}=18.8 Hz), 52.3, 119.7 (d, J_{P-C}= 86.0 Hz), 131.6 (d, J_{P-C}=12.5 Hz), 134.9 (d, J_{P-C}= 9.8 Hz), 136.4 (d, J_{P-C}=3.2 Hz), 174.4; FABMS (*m*/*z*): 363 (M^+-Br, 100).

Methyl (*R*)-3-hydroxy-4-(triphenylmethyl)oxybutyrate (11). To a solution of diol **10** (9.90 g, 73.8 mmol) in DMF (74.0 mL) were added Et_3N (20.6 mL, 148 mmol), DMAP (904 mg, 7.40 mmol) and chlorotriphenylmethane (26.7 g, 95.9 mmol) followed by stirring at 65°C for 4 h. The reaction mixture was diluted with Et_2O, washed with H_2O and saturated aqueous NaCl, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluted with hexane–EtOAc=5:1) to give alcohol **11** (24.2 g, 67%) as colorless crystals. $[\alpha]_D$=+3.6° (c=1.00, $CHCl_3$); mp 75.5–76.5°C; IR (KBr) 3527, 2928, 1733 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.53 (1H, dd, J=16.2, 7.7 Hz), 2.57 (1H, dd, J=16.2, 4.8 Hz), 3.17 (2H, d, J=5.4 Hz), 3.68 (3H, s), 4.23 (1H, ddd, J=7.7, 5.4, 4.8 Hz), 7.22–7.45 (15H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 38.3, 51.7, 66.5, 67.5, 86.7, 127.0, 127.8, 128.6, 143.6, 172.6; EIMS (*m*/*z*): 376 (M^+, 4.0), 328 (M^+–MeOH, 18), 243 (100); Anal. Calcd for $C_{24}H_{24}O_4$: C, 76.57; H, 6.43. Found: C, 76.76; H, 6.43.

(*R*)-4-(*tert*-Butyldimethylsilyl)oxy-2-(methoxymethyl)-oxybutan-1-ol (12). To a solution of alcohol **11** (114 g, 303 mmol) in $CHCl_3$ (303 mL) were added *N*,*N*-diisopropylethylamine (79.2 mL, 455 mmol) and chloromethyl methyl ether (27.6 mL, 364 mmol). The mixture was stirred at 50°C for 24 h, diluted with Et_2O, washed with H_2O and saturated aqueous NaCl, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to give crude ether for use in the reaction below without purification. A portion of a crude ether was purified for spectral analysis by silica gel column chromatography (eluted with hexane–EtOAc=5:1). Colorless oil; $[\alpha]_D$=+20.9° (c=1.00, $CHCl_3$); IR (neat) 2950, 1740 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.61 (1H, dd, J=15.6, 7.6 Hz), 2.63 (1H, dd, J=15.6, 5.2 Hz), 3.16 (1H, dd, J=9.7, 5.3 Hz), 3.24 (1H, dd, J=5.3, 4.4 Hz), 3.27 (3H, s), 3.66 (3H, s), 4.18 (1H, m), 4.65 (1H, d, J=6.9 Hz), 4.66 (1H, d, J=6.9 Hz), 7.20–7.47 (15H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 37.9, 51.4, 55.4, 65.1, 73.4, 86.6, 96.1, 126.9, 127.7, 128.5, 143.7, 171.6; EIMS (*m*/*z*): 420 (M^+, 0.5), 388 (M^+–MeOH, 0.3), 243 (100); Anal. Calcd for $C_{26}H_{28}O_5$: C, 74.26; H, 6.71. Found: C, 74.24; H, 6.74.

To a solution of the above ester in Et_2O (1.52 L) was added $LiAlH_4$ (10.4 g, 273 mmol) at 0°C, followed by stirring for 10 min. The reaction mixture was diluted with Et_2O, saturated aqueous NaCl was added and the mixture was stirred at rt for 3 h. The organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to give crude alcohol for use in the reaction below without purification. A portion of a crude alcohol was purified for spectral analysis by silica gel column chromatography (eluted with hexane–EtOAc=2:1). Colorless oil; $[\alpha]_D$=+41.0° (c=1.00, $CHCl_3$); IR (neat) 3444, 2932 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 1.77 (2H, m), 3.13 (1H, dd, J=9.9, 4.4 Hz), 3.22 (1H, dd, J=9.9, 6.0 Hz), 3.39 (3H, s), 3.70 (1H, m), 3.75 (1H, m), 3.93 (1H, m), 4.69 (1H, d, J=6.6 Hz), 4.85 (1H, d, J=6.6 Hz), 7.21–7.46 (15H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 34.6, 55.7, 59.3, 66.3, 75.1, 86.7, 96.6, 127.0, 127.8, 128.6, 143.8; EIMS (*m*/*z*): 392 (M^+, 0.1), 243 (100).

To a solution of the above alcohol in DMF (253 mL) were added imidazole (26.8 g, 394 mmol) and *tert*-butyldimethylsilyl chloride (TBDMS-Cl) (50.2 g, 333 mmol). After stirring at rt for 3 h, the reaction mixture was diluted with Et_2O, washed with H_2O and saturated aqueous NaCl, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to give crude silyl ether for use in the reaction below without purification. A portion of a crude silyl ether was purified for spectral analysis by silica gel column chromatography (eluted with hexane–EtOAc= 20:1). Colorless oil; $[\alpha]_D$=+18.0° (c=1.00, $CHCl_3$); IR (neat) 2928 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 0.01 (6H, s), 0.86 (9H, s), 1.76 (1H, d, J=6.4 Hz), 1.80 (1H, d, J=6.4 Hz), 3.15 (2H, d, J=4.9 Hz), 3.34 (3H, s), 3.65 (2H, m), 3.89 (1H, m), 4.68 (1H, d, J=6.7 Hz), 4.76 (1H, d, J=6.7 Hz), 7.20–7.47 (15H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: −5.4, 18.2, 25.9, 35.6, 55.4, 59.4, 66.1, 73.7, 86.5, 96.1, 126.9, 127.7, 128.7, 144.0; EIMS (*m*/*z*): 360 (M^+−TBDMS–OMe, 0.01), 243 (Tr^+, 30), 45 (100); Anal. Calcd for $C_{31}H_{42}O_4Si$: C, 73.48; H, 8.35. Found: C, 73.54; H, 8.40.

To a cold solution of the above trityl ether in THF (640 mL) and EtOH (80 mL) was introduced liquid NH_3 and sodium (ca. 8 g) was added at −78°C. The mixture was warmed to −34°C, stirred for 30 min, NH_4Cl was added then and removed with NH_3. The reaction mixture was diluted with Et_2O, washed with H_2O and saturated aqueous NaCl, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluted with hexane–EtOAc=4:1) to give alcohol **12** (75.0 g, 94%, 4 steps) as a colorless oil. $[\alpha]_D$= −21.4° (c=1.00, $CHCl_3$); IR (neat) 3436, 2931 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 0.05 (6H, s), 0.89 (9H, s), 1.71 (2H, m), 3.32 (1H, dd, J=8.6, 4.5 Hz), 3.42 (3H, s), 3.56 (1H, ddd, J=11.9, 6.6, 4.5 Hz), 3.62 (1H, ddd, J=11.9, 8.6, 3.3 Hz), 3.71 (2H, m), 3.77 (1H, m), 4.69 (1H, d, J=6.8 Hz), 4.72 (1H, d, J=6.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: −5.8, 17.8, 25.6, 34.5, 55.0, 58.8, 65.1, 77.8, 96.4; EIMS (*m*/*z*): 233 (M^+−MeOH, 0.6), 45 (100); Anal. Calcd for $C_{12}H_{28}O_4Si$: C, 54.51; H, 10.67. Found: C, 54.48; H, 10.56.

(*E*)-(*R*)-6-(*tert*-Butyldimethylsilyl)oxy-4-(methoxymethyl)-oxy-2-hexen-1-ol (13). To a cold (−78°C) solution of

oxalyl chloride (17.7 mL, 197 mmol) in CH_2Cl_2 (400 mL) was added DMSO (17.5 mL, 246 mmol) in CH_2Cl_2 (32.0 mL). The mixture was stirred at −78°C for 15 min, treated with a solution of alcohol **12** (13.0 g, 49.2 mmol) in CH_2Cl_2 (60.0 mL) and stirred for 15 min and then with Et_3N (41.1 mL, 295 mmol). The mixture was stirred for 15 min, warmed to rt and stirred for 20 min. The reaction mixture was diluted with Et_2O–benzene (5:1), washed with H_2O, saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to give crude aldehyde for use in the reaction below without purification. A portion of a crude aldehyde was purified for spectral analysis by silica gel column chromatography (eluted with hexane–EtOAc=3:1). Colorless oil; $[\alpha]_D$=+9.1° (c=1.20, $CHCl_3$); IR (neat) 2929, 1736 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ ppm: 0.04 (6H, s), 0.89 (9H, s), 1.92 (2H, m), 3.42 (3H, s), 3.74 (2H, m), 4.11 (1H, d, J=6.8 Hz), 4.72 (1H, d, J=6.8 Hz), 4.73 (1H, d, J=6.8 Hz), 9.67 (1H, d, J=1.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: −5.6, −5.5, 18.1, 25.6, 33.7, 55.8, 57.9, 79.4, 79.4, 96.7, 202.5; EIMS (m/z): 233 (M^+−CHO, 3), 45 (100).

To a solution of ethyl diisopropylphosphonoacetate (37.2 g, 148 mmol) in THF (200 mL) was added ^{t}BuOK (13.8 g, 123 mmol) at 0°C. The mixture was warmed to rt, stirred for 45 min, cooled to −78°C and to which a solution of the above crude aldehyde in THF (46.0 mL) was added followed by warming to −42°C and stirring for 30 min. The reaction mixture was diluted with Et_2O, washed with saturated aqueous NH_4Cl, H_2O and saturated aqueous NaCl, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to give crude ester for use in the reaction below without purification. A portion of a crude ester was purified for spectral analysis by silica gel column chromatography (eluted with hexane–EtOAc=7:1). Colorless oil; $[\alpha]_D$=+43.3° (c=1.00, $CHCl_3$); UV (EtOH):λ_{max} 208 nm (ϵ 10800); IR (neat) 2931, 1724 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ ppm: 0.05 (6H, s), 0.89 (9H, s), 1.29 (3H, t, J=7.1 Hz), 1.78 (2H, m), 3.38 (3H, s), 3.70 (2H, m), 4.17 (1H, d, J=7.2 Hz), 4.21 (1H, d, J=7.2 Hz), 4.40 (1H, dd, J=12.7, 6.3 Hz), 4.61 (1H, d, J=6.8 Hz), 4.63 (1H, d, J=6.8 Hz), 5.99 (1H, dd, J=15.7, 1.3 Hz), 6.85 (1H, d, J=15.7, 6.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: −5.7, 13.9, 17.8, 25.5, 37.9, 55.1, 58.5, 59.9, 72.0, 94.5, 121.3, 147.7, 165.6; EIMS (m/z): 275 ($M^+-{}^t$Bu, 2), 45 (100); Anal. Calcd for $C_{16}H_{32}O_5Si$: C, 57.80; H, 9.70. Found: C, 57.70; H, 9.61.

To a cold (−78°C) solution of the above crude ester in toluene (246 mL) was added DIBAL-H (124 mL, 118 mmol, 0.95 M in hexane). The mixture was stirred for 30 min, treated with MeOH (20 mL), diluted with Et_2O, treated with saturated aqueous NaCl and stirred at rt for 5 h. The organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluted with hexane–EtOAc=2:1) to give allylic alcohol **13** (12.7 g, 89%, 3 steps) as a colorless oil. $[\alpha]_D$=+58.3° (c=1.00, $CHCl_3$); IR (neat) 3422, 2930 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ ppm: 0.04 (6H, s), 0.89 (9H, s), 1.71 (1H, m), 1.83 (1H, tt, J=13.6, 6.0 Hz), 3.36 (3H, s), 3.67 (1H, td, J=10.2, 6.0 Hz), 3.71 (1H, ddd, J=10.2, 7.0, 6.0 Hz), 4.16 (2H, td, J=6.2, 1.4 Hz), 4.23 (1H, dd, J=13.6, 7.8 Hz), 4.54 (1H, d, J=6.6 Hz), 4.69 (1H, d, J=6.6 Hz), 5.60 (1H, ddt, J=15.6, 7.8, 1.4 Hz), 5.82 (1H, dtd, J=15.6, 5.3, 0.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: −5.5, 18.0, 25.7, 38.6, 55.1, 59.0, 62.1, 73.1, 93.5, 130.4, 132.3; EIMS (m/z): 245 (M^+−MOM, 2), 89 (100).

(2*R*,3*R*,4*R*)-6-(*tert*-Butyldimethylsilyl)oxy-2,3-epoxy-4-(methoxymethyl)oxy-1-{[4′-methoxyphenyl)methyl]oxy}-hexane (14). A mixture of powdered 4 Å molecular sieves (300 mg) and CH_2Cl_2 (7.80 mL) was cooled to −20°C and then to which were added of $Ti(O^iPr)_4$ (0.117 mL, 0.40 mmol) and D-(−)-diethyl tartrate (DET) (103 mg, 0.50 mmol). After stirring for 30 min, *tert*-butyl hydroperoxide (TBHP) (1.20 mL, 3.60 mmol, 3.0 M in CH_2Cl_2) was added, followed by stirring for 30 min and the addition of allylic alcohol **13** (585 mg, 1.95 mmol) in CH_2Cl_2 (1.20 mL). Stirring was continued at −20°C for 5 h. The reaction mixture was warmed to 0°C, water (2.0 mL) was added and the mixture was stirred for 1 h. Aqueous solution of NaOH (30%) saturated with NaCl (0.50 mL) was added and the mixture was stirred vigorously. After 1 h stirring, the mixture was filtered through celite. The filtrate was diluted with Et_2O, washed with 1N NaOH, H_2O and saturated aqueous NaCl, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluted with hexane–EtOAc=2:1) to give epoxy alcohol (552 mg, 89%) as a colorless oil. $[\alpha]_D$=+9.6° (c=1.00, $CHCl_3$); IR (neat) 3451, 2930, 1256 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ ppm: 0.05 (6H, s), 0.88 (9H, s), 1.76 (1H, ddt, J=14.0, 8.4, 5.3 Hz), 1.88 (1H, ddd, J=14.0, 7.4, 4.2 Hz), 2.96 (1H, dd, J=5.9, 2.2 Hz), 3.15 (1H, dt, J=3.8, 2.2 Hz), 3.38 (3H, s), 3.58 (1H, ddd, J=8.4, 5.9, 4.2 Hz), 3.71 (1H, dt, J=12.4, 3.8 Hz), 3.75 (2H, dt, J=7.4, 5.3 Hz), 3.80 (1H, ddd, J=12.4, 4.7, 3.8 Hz), 4.66 (1H, d, J=6.9 Hz), 4.69 (1H, d, J=6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: −5.5, −5.5, 18.1, 25.9, 35.7, 55.4, 57.1, 57.2, 58.7, 61.5, 73.7, 96.4; EIMS (m/z): 249 ($M^+-{}^t$Bu, 4), 157 (100); Anal. Calcd for $C_{14}H_{30}O_5Si$: C, 54.87; H, 9.87. Found: C, 54.90; H, 9.74.

To a cold (0°C) solution of the above epoxy alcohol (5.20 g, 17.0 mmol) in THF (68.0 mL) and DMF (17.0 mL) were added 4-methoxybenzyl bromide (3.85 mL, 18.7 mmol) and NaH (884 mg, 22.1 mmol, 60%). The mixture was stirred at 0°C for 1 h, diluted with Et_2O, washed with saturated aqueous $NaHCO_3$, H_2O and saturated aqueous NaCl, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluted with hexane–EtOAc=10:1) to give MPM ether **14** (6.92 g, 95%) as a colorless oil. $[\alpha]_D$=+22.8° (c=1.00, $CHCl_3$); IR (neat) 2953, 1250 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ ppm: 0.04 (6H, s), 0.88 (9H, s), 1.75 (1H, ddt, J=14.1, 8.5, 5.3 Hz), 1.85 (1H, m), 2.88 (1H, dd, J=5.5, 2.2 Hz), 3.18 (1H, dt, J=5.8, 2.2 Hz), 3.34 (3H, s), 3.42 (1H, dd, J=11.5, 5.7 Hz), 3.61 (1H, m), 3.72 (1H, m), 3.76 (2H, dd, J=7.2, 2.1 Hz), 3.80 (3H, s), 4.49 (1H, d, J=11.5 Hz), 4.52 (1H, d, J=11.5 Hz), 4.62 (1H, d, J=6.7 Hz), 4.68 (1H, d, J=6.7 Hz), 6.88 (2H, m), 7.26 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: −5.5, −5.5, 18.1, 25.8, 35.7, 55.0, 55.3, 55.7, 56.7, 58.7, 69.4, 72.7, 73.2, 96.3, 113.6, 129.2, 129.8, 159.1; EIMS (m/z): 395

(M^+-OMe, 5), 369 ($M^+-{}^tBu$, 5), 121 (100); Anal. Calcd for $C_{22}H_{38}O_6Si$: C, 61.94; H, 8.98. Found: C, 61.84; H, 8.93.

(2*R*,3*R*,4*R*)-2,3-Epoxy-4-(methoxymethyl)oxy-1-{[(4′-methoxyphenyl)methyl]oxy}hexyl-6-methanesulfonate (15). To a solution of TBDMS ether **14** (4.45 g, 9.96 mmol) in THF (10.0 mL) was added tetrabutylammonium fluoride (TBAF) (12.0 mL, 12.0 mmol, 1.0 M in THF). After stirring at rt for 1 h, the reaction mixture was diluted with Et_2O, washed with H_2O and saturated aqueous NaCl, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to give crude alcohol for use in the reaction below without purification. A portion of a crude alcohol was purified for spectral analysis by silica gel column chromatography (eluted with hexane–EtOAc=1:1). Colorless oil; IR (neat) 3446, 2937, 1250 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ ppm: 1.85 (1H, ddt, *J*=14.4, 8.1, 5.5 Hz), 1.91 (1H, m), 2.90 (1H, dd, *J*=5.5, 2.2 Hz), 3.21 (1H, m), 3.37 (3H, s), 3.47 (1H, dd, *J*=11.5, 5.5 Hz), 3.68 (2H, dt, *J*=8.1, 4.9 Hz), 3.73 (2H, dd, *J*=11.5, 3.0 Hz), 3.80 (3H, s), 4.49 (1H, d, *J*=11.6 Hz), 4.50 (1H, d, *J*=11.6 Hz), 4.50 (1H, d, *J*=6.8 Hz), 4.62 (1H, d, *J*=6.8 Hz), 6.88 (2H, m), 7.26 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 35.0, 55.1, 55.5, 55.7, 56.4, 58.9, 69.2, 72.8, 74.3, 96.2, 113.6, 129.2, 129.7, 159.1.

To a cold (0°C) solution of the above crude alcohol in CH_2Cl_2 (50.0 mL) was added 4-*N*,*N*-dimethylaminopyridine (DMAP) (1.90 g, 15.9 mmol). After stirring for 10 min, methanesulfonyl chloride (1.00 mL, 12.9 mmol) was added and stirred for 15 min. The reaction mixture was diluted with Et_2O, washed with H_2O and saturated aqueous NaCl, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluted with hexane–EtOAc=1:1) to give mesylate **15** (3.89 g, quantitative yield) as a colorless oil. $[\alpha]_D=+24.7°$ (*c*=1.00, $CHCl_3$); IR (neat) 2937, 1248 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ ppm: 2.00 (1H, ddt, *J*=14.5, 8.5, 5.5 Hz), 2.11 (1H, m), 2.87 (1H, dd, *J*=6.0, 2.2 Hz), 3.00 (3H, s), 3.17 (1H, m), 3.35 (3H, s), 3.45 (1H, dd, *J*=11.5, 5.5 Hz), 3.54 (1H, ddd, *J*=8.5, 6.0, 4.1 Hz), 3.73 (1H, dd, *J*=11.5, 2.8 Hz), 3.80 (3H, s), 4.38 (2H, m), 4.49 (1H, d, *J*=11.8 Hz), 4.50 (1H, d, *J*=11.8 Hz), 4.61 (1H, d, *J*=6.9 Hz), 4.79 (1H, d, *J*=6.9 Hz), 6.88 (2H, m), 7.26 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 32.1, 37.1, 55.1, 55.5, 56.0, 56.0, 65.9, 68.9, 72.7, 72.8, 96.2, 113.6, 129.2, 129.6, 159.1; EIMS (*m*/*z*): 390 (M^+, 2), 121 (100); HREIMS: Calcd for $C_{17}H_{26}O_8S$ (M^+) 390.1348: Found: 390.1344.

(1*S*,1′*S*,2*S*,3*R*)-2-{1′-Hydroxy-2′-[4″-(methoxyphenyl)-methyl]oxy}ethyl-3-(methoxymethyl)oxy-1-phenylsulfonyl-1-vinylcyclopentane (16). To a cold (−78°C) solution of allyl phenyl sulfone (9.40 g, 61.5 mmol) in THF (206 mL) was added BuLi (40.2 mL, 59.0 mmol, 1.47 M in hexane). The mixture was stirred at −78°C for 30 min, treated with a solution of epoxy mesylate **15** (9.60 g, 24.6 mmol) in THF (20.0 mL), stirred for 30 min, warmed to rt over 3 h and then stirred at rt for 3 h. The reaction mixture was diluted with Et_2O, washed with saturated aqueous NH_4Cl, H_2O and saturated aqueous NaCl, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluted with hexane–EtOAc=2:1) to give cyclopentane **16** (11.6 g, 99%) as a colorless oil. $[\alpha]_D=-74.4°$ (*c*=1.00, $CHCl_3$); IR (neat) 2935, 1295, 1142 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ ppm: 1.84 (1H, m), 1.93 (1H, m), 2.25 (1H, ddd, *J*=14.1, 11.8, 6.8 Hz), 2.36 (1H, ddd, *J*=14.1, 7.4, 2.2 Hz), 3.15 (1H, dd, *J*=4.6, 3.6 Hz), 3.28 (3H, s), 3.60 (2H, d, *J*=6.0 Hz), 3.81 (3H, s), 4.05 (1H, m), 4.47 (1H, d, *J*=11.5 Hz), 4.50 (1H, d, *J*=6.9 Hz), 4.56 (1H, d, *J*=6.9 Hz), 4.57 (1H, d, *J*=11.5 Hz), 4.59 (1H, m), 5.11 (1H, d, *J*=17.3 Hz), 5.37 (1H, d, *J*=10.7 Hz), 6.42 (1H, dd, *J*=17.3, 10.7 Hz), 6.90 (2H, m), 7.31 (2H, m), 7.45 (2H, m), 7.61 (1H, m), 7.81 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 30.0, 30.3, 48.5, 55.1, 56.0, 69.3, 72.6, 72.9, 74.9, 82.2, 95.1, 113.6, 119.9, 128.2, 129.4, 130.1, 130.7, 133.5, 134.4, 135.2, 159.0; EIMS (*m*/*z*): 476 (M^+, 3), 444 (M^+-OMe, 10), 121 (100); HREIMS: Calcd for $C_{25}H_{32}O_7S$ (M^+) 476.1869: Found: 476.1886.

(1*S*,4*S*,5*S*,6*R*)-6-(Methoxymethyl)oxy-4-{[(4′-methoxyphenyl)methyl]oxy}methyl-3-oxabicyclo[3.3.0]octan-2-one (17). To a solution of cyclopentane **16** (2.80 g, 5.58 mmol) in 1,4-dioxane (29 mL) and H_2O (29 mL) were added OsO_4 (14 mg, 55.8 μmol) and $NaIO_4$ (5.03 g, 23.6 mmol) over 2 h. After stirring for 24 h, the reaction mixture was diluted with EtOAc, washed with H_2O and saturated aqueous NaCl, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to give a crude anomeric mixture of hemiacetals (about 10:1) for use in the reaction below without purification. A portion of a crude hemiacetal was purified for spectral analysis by silica gel column chromatography (eluted with hexane–EtOAc=3:2). Colorless oil; IR (neat) 3436, 2939, 1303, 1145 cm^{-1}; EIMS (*m*/*z*): 478 (M^+, 2.5), 121 (100); **major isomer:** ^1H NMR (300 MHz, $CDCl_3$) δ ppm: 1.78 (1H, dtd, *J*=13.2, 9.9, 3.3 Hz), 2.08 (1H, m), 2.89 (2H, m), 3.29 (1H, m), 3.31 (3H, s), 3.71 (1H, dd, *J*=9.6, 6.0 Hz), 3.76 (1H, dd, *J*=9.6, 6.6 Hz), 3.80 (3H, s), 4.25 (1H, m), 4.26 (1H, m), 4.37 (1H, d, *J*=6.4 Hz), 4.40 (1H, d, *J*=6.8 Hz), 4.53 (1H, d, *J*=6.8 Hz), 4.57 (1H, d, *J*=6.8 Hz), 5.61 (1H, d, *J*=11.6 Hz), 6.87 (2H, m), 7.23 (2H, m), 7.57 (2H, m), 7.68 (1H, m), 7.94 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 25.5, 34.2, 52.7, 55.3, 56.5, 69.4, 72.9, 77.8, 81.1, 83.6, 96.1, 98.2, 113.8, 129.3, 129.4, 129.5, 129.9, 134.2, 136.5, 159.3.

To a cold (0°C) solution of the above hemiacetal in acetone (50.0 mL) was added Jones reagent (3.0 mL), followed by stirring for 10 min and treatment with 2-propanol (3.0 mL). After stirring for 15 min, the reaction mixture was diluted with Et_2O, washed with H_2O, saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluted with hexane–EtOAc=2:1) to give lactone (2.40 g, 82%, 2 steps) as a colorless oil. $[\alpha]_D=-15.6°$ (*c*=1.00, $CHCl_3$); IR (neat) 2942, 1768, 1309, 1147 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ ppm: 2.15 (1H, m), 2.30 (1H, m), 3.24 (3H, s), 3.59 (1H, dd, *J*=6.8, 4.3 Hz), 3.81 (3H, s), 3.86 (1H, dd, *J*=10.6, 5.0 Hz), 4.00 (1H, dd, *J*=10.6, 5.0 Hz), 4.35 (1H, m), 4.47 (1H, d, *J*=7.0 Hz), 4.48 (1H, d, *J*=11.8 Hz), 4.51 (1H, d, *J*=7.0 Hz), 4.57 (1H, d, *J*=11.8 Hz), 5.07 (1H, dt, *J*=6.8, 5.0 Hz), 6.90 (2H, m), 7.26 (2H, m), 7.59 (2H, m), 7.72 (1H,

m), 7.92 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 29.7, 32.3, 51.1, 54.8, 55.9, 67.9, 72.5, 77.7, 79.5, 79.9, 94.9, 113.4, 128.7, 129.1, 129.4, 129.9, 134.4, 134.9, 128.9, 171.4; EIMS (*m/z*): 476 (M^+, 6), 431 (M^+-MOM, 70), 121 (100); Anal. Calcd for $C_{24}H_{28}O_8S$: C, 60.49; H, 5.92. Found: C, 60.34; H, 6.05.

To a solution of the above lactone (2.50 g, 5.25 mmol) in MeOH (105 mL) were added NaH_2PO_4 (5.00 g) and 5% Na–Hg (6.90 g). After stirring at rt for 30–min, the reaction mixture was diluted with EtOAc and filtered through silica gel. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluted with hexane–EtOAc=1:1) to give lactone **17** (1.60 g, 91%) as a colorless oil. $[\alpha]_D=-33.8°$ (*c*=1.00, $CHCl_3$); IR (neat) 2937, 1768 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 1.50 (1H, m), 2.09 (2H, m), 2.18 (1H, br t, *J*=4.1 Hz), 2.76 (1H, ddd, *J*=9.8, 6.1, 3.9 Hz), 3.12 (1H, m), 3.29 (3H, s), 3.80 (3H, s), 3.86 (1H, dd, *J*=10.6, 4.5 Hz), 4.03 (1H, dd, *J*=10.6, 6.7 Hz), 4.14 (1H, m), 4.47 (1H, d, *J*=11.5 Hz), 4.49 (1H, d, *J*=6.9 Hz), 4.57 (1H, d, *J*=6.9 Hz), 4.58 (1H, d, *J*=11.5 Hz), 4.76 (1H, td, *J*=6.7, 4.5 Hz), 6.88 (2H, m), 7.27 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 29.7, 32.3, 51.1, 54.8, 55.9, 67.9, 72.5, 77.7, 79.5, 79.9, 94.9, 113.4, 128.7, 129.1, 129.4, 129.9, 134.4, 134.9, 128.9, 171.4; EIMS (*m/z*): 336 (M^+, 2), 291 (M^+-MOM, 90), 121 (100); Anal. Calcd for $C_{18}H_{24}O_6$: C, 64.27; H, 7.19. Found: C, 64.02; H, 7.18.

(1*S*,4*S*,5*S*,6*R*)-4-Formyl-6-(methoxymethyl)oxy-3-oxabicyclo[3.3.0]octan-2-one (18). To a solution of MPM ether **17** (764 mg, 2.27 mmol) in acetonitrile–H_2O (9:1) (23.0 mL) was added CAN (1.87 g, 3.41 mmol) followed by stirring at rt for 1 h. The reaction mixture was diluted with $CHCl_3$, washed with H_2O and saturated aqueous NaCl, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluted with hexane–acetone=1:1) to give alcohol (430 mg, 88%) as white crystals. mp 115–117°C; $[\alpha]_D=-1.1°$ (*c*=1.00, $CHCl_3$); IR (KBr) 3446, 2955, 1762 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 1.60 (1H, m), 2.10 (3H, m), 2.81 (1H, ddd, *J*=9.6, 6.4, 4.6 Hz), 3.17 (1H, m), 3.36 (3H, s), 3.92 (1H, ddd, *J*=12.1, 8.0, 4.1 Hz), 4.20 (1H, m), 4.27 (1H, ddd, *J*=12.1, 7.5, 4.4 Hz), 4.60 (1H, d, *J*=6.8 Hz), 4.64 (1H, d, *J*=6.8 Hz), 4.71 (1H, td, *J*=7.5, 4.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 23.8, 32.1, 44.3, 47.2, 56.0, 61.5, 78.6, 78.7, 81.3, 94.9, 180.0; EIMS (*m/z*): 217 (M^++1, 0.2), 185 (M^+-MeOH, 9), 45 (100); Anal. Calcd for $C_{10}H_{16}O_5$:C, 55.55; H, 7.46. Found: C, 55.33; H, 7.75.

To a cold (−78°C) solution of oxalyl chloride (129 μL, 1.48 mmol) in CH_2Cl_2 (2.0 mL) was added DMSO (131 μL, 1.85 mmol) in CH_2Cl_2 (300 μL). The mixture was stirred at −78°C for 15 min, treated with a solution of the above alcohol (80.0 mg, 370 μmol) in CH_2Cl_2 (1.40 mL) and stirred for 15 min and then with Et_3N (309 μL, 2.22 mmol). The mixture was stirred for 15 min and warmed to rt and stirred for 20 min. The reaction mixture was diluted with Et_2O–benzene (5:1), washed with H_2O, saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluted with hexane–EtOAc=1:1) to give aldehyde **18** (79.0 mg, quantitative yield) as a colorless oil. $[\alpha]_D=-118.3°$ (*c*=0.46, $CHCl_3$); IR (neat) 2948, 1768, 1730 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 1.60 (1H, m), 2.05–2.27 (3H, m), 3.23 (1H, m), 3.31 (3H, s), 3.36 (1H, m), 4.12 (1H, td, *J*=3.9, 0.9 Hz), 4.47 (1H, d, *J*=7.0 Hz), 4.58 (1H, d, *J*=7.0 Hz), 4.75 (1H, d, *J*=7.3 Hz), 9.86 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 24.9, 31.2, 43.3, 50.7, 56.3, 77.9, 80.2, 95.2, 178.8, 200.3; EIMS (*m/z*): 185 (M^+-CHO, 8), 169 (M^+-MOM, 12), 45 (100); HREIMS: Calcd for $C_{10}H_{15}O_5$ (M^++1) 215.0919: Found: 215.0911.

Bacillariolide II (2). To a cold (0°C) suspension of phosphonium iodide **7** (17.7 mg, 321 μmol) in THF (0.80 mL) was added BuLi (146 μL, 214 μmol, 1.47 M in hexane). The mixture was stirred at 0°C for 20 min to give Wittig reagent. To a cold (−78°C) solution of aldehyde **18** (23.0 mg, 107 μmol) and HMPA (186 μL, 1.07 mmol) in THF (4.60 mL) was added the above prepared Wittig reagent and stirred at −78°C for 10 min. The reaction mixture was diluted with Et_2O, washed with H_2O and saturated aqueous NaCl, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by preparative silica gel TLC (developed with hexane–EtOAc=3:1, R_f 0.3) to give 5-*O*-methoxymethylbacillariolide II (25.6 mg, 66%) as a colorless oil. $[\alpha]_D=-61.5°$ (*c*=0.33, $CHCl_3$); IR (neat) 2957, 1767 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 0.98 (3H, t, *J*=7.5 Hz), 1.51 (1H, m), 2.08 (2H, qdd, *J*=7.5, 7.5, 0.7 Hz), 2.15 (3H, m), 2.75–2.92 (7H, m), 3.13 (1H, m), 3.36 (3H, s), 4.10 (1H, br t, *J*=3.3 Hz), 4.58 (1H, d, *J*=7.0 Hz), 4.65 (1H, d, *J*=7.0 Hz), 5.27–5.48 (7H, m), 5.62 (1H, dtd, *J*=11.0, 7.5, 1.5 Hz), 5.91 (1H, ddt, *J*=11.0, 7.7, 1.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 14.2, 20.6, 24.6, 25.5, 25.6, 26.2, 32.3, 44.2, 51.1, 56.3, 75.5, 78.9, 95.4, 126.6, 126.8, 127.0, 127.4, 128.8, 129.1, 131.5, 132.1, 179.8; EIMS (*m/z*): 360 (M^+, 0.04), 315 (M^+-MOM, 2), 45 (100); HREIMS: Calcd for $C_{20}H_{27}O_3$ (M^+-MOM) 315.1960; Found: 315.1972.

A mixture of AcOH and conc.HCl (50:1) (810 μL) was added to 5-*O*-methoxymethylbacillariolide II (29.2 mg, 81.0 μmol) and stirred at 40°C for 6 h. The reaction mixture was diluted with Et_2O, washed with saturated aqueous $NaHCO_3$, H_2O and saturated aqueous NaCl, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by preparative silica gel TLC (developed with hexane–EtOAc=2:1, R_f 0.3) to give bacillariolide II (**2**) (24.8 mg, 97%) as a colorless oil. $[\alpha]_D=-58.5°$ (*c*=0.33, MeOH); IR ($CHCl_3$) 3528, 2964, 1763 cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD) δ ppm: 0.97 (3H, t, *J*=7.5 Hz), 1.65 (1H, m), 1.82 (1H, m), 2.0–2.2 (4H, m), 2.77 (1H, ddd, *J*=9.3, 6.0, 3.5 Hz), 2.83 (2H, t, *J*=5.8 Hz), 2.88 (2H, t, *J*=5.7 Hz), 2.95 (2H, m), 3.19 (1H, dt, *J*=5.1, 9.5 Hz), 4.21 (1H, t, *J*=3.0 Hz), 5.25–5.35 (6H, m), 5.50 (1H, m), 5.64 (1H, ddt, *J*=11.0, 1.4, 7.6 Hz), 6.05 (1H, ddt, *J*=11.0, 8.3, 1.6 Hz); ^{13}C NMR (75 MHz, CD_3OD) δ ppm: 14.7, 21.5, 25.5, 26.4, 26.5, 27.0, 36.9, 45.3, 52.6, 73.4, 77.7, 127.5, 128.1, 128.4, 128.8, 129.6, 129.9, 132.9, 133.1, 183.6; EIMS (*m/z*): 316 (M^+,0.01), 67 (100); HREIMS: Calcd for $C_{20}H_{28}O_3$ (M^+) 316.2038; Found: 316.2034.

(1*S*,2*S*,4*S*,5*S*,6*R*)-2-Methoxy-6-(methoxymethyl)oxy-4-{[(4″-methoxyphenyl)methyl]oxy}methyl-3-oxabicyclo-[3.3.0]octane (19). To a cold (−78°C) solution of lactone **17** (1.60 g, 4.76 mmol) in toluene (48.0 mL) was added DIBAL-H (5.51 mL, 5.24 mmol, 0.95 M in hexane). The mixture was stirred for 1 h, treated with MeOH (1.0 mL), diluted with Et_2O, treated with saturated aqueous NaCl and stirred at rt for 6 h. The organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to give a crude anomeric mixture of hemiacetals (about 7:1) for use in the reaction below without purification. A portion of a crude hemiacetals was purified for spectral analysis by silica gel column chromatography (eluted with hexane–EtOAc=1:1). Colorless oil; IR (neat) 3418, 2948, 1142 cm^{-1}; EIMS (*m/z*): 338 (M^+, 0.2), 320 (M^+-H_2O, 1), 121 (100); Anal. Calcd for $C_{18}H_{26}O_6$: C, 63.89; H, 7.74. Found: C, 63.76; H, 7.93; **major isomer:** ^1H NMR (300 MHz, $CDCl_3$) δ ppm: 1.58–1.90 (4H, m), 2.60–2.80 (2H, m), 3.30 (3H, s), 3.79 (3H, s), 3.85 (1H, dd, *J*=10.6, 3.1 Hz), 3.93 (1H, dd, *J*=10.6, 8.4 Hz), 4.00 (1H, td, *J*=6.3, 4.2 Hz), 4.47 (1H, d, *J*=11.5 Hz), 4.55 (1H, d, *J*=6.7 Hz), 4.57 (1H, d, *J*=6.7 Hz), 4.58 (1H, d, *J*=11.5 Hz), 4.59 (1H, m), 5.29 (1H, s), 6.87 (2H, m), 7.27 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 26.3, 32.1, 47.7, 49.8, 50.5, 55.1, 55.5, 69.7, 72.7, 79.2, 80.4, 95.5, 98.8, 104.5, 113.5, 113.6, 113.7, 129.3, 129.4, 130.0, 158.9.

A solution of PPTS in MeOH (0.1%, 23.8 mL) was added to the above hemiacetals and stirred at rt for 3 h. The reaction mixture was diluted with Et_2O, washed with H_2O and saturated aqueous NaCl, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluted with hexane–EtOAc=3:1) to give methyl acetal **19** (1.66 g, 99%, 2 steps) as a colorless oil. $[\alpha]_D$=+34.3° (*c*=1.00, $CHCl_3$); IR (neat) 2948 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 1.60 (2H, m), 1.85 (2H, m), 2.61 (1H, ttd, *J*=8.9, 5.0, 0.9 Hz), 2.71 (1H, dt, *J*=8.9, 6.4 Hz), 3.31 (3H, s), 3.34 (3H, s), 3.80 (3H, s), 3.91 (1H, dd, *J*=10.9, 3.7 Hz), 3.95 (1H, dd, *J*=10.9, 7.2 Hz), 4.02 (1H, td, *J*=6.0, 4.5 Hz), 4.38 (1H, dt, *J*=7.2, 3.7 Hz), 4.45 (1H, d, *J*=11.6 Hz), 4.55 (1H, d, *J*=6.8 Hz), 4.59 (1H, d, *J*=6.8 Hz), 4.62 (1H, d, *J*=11.6 Hz), 4.78 (1H, s), 6.87 (2H, m), 7.28 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 26.4, 32.3, 47.9, 49.1, 54.3, 54.9, 55.5, 69.6, 72.5, 79.2, 80.3, 95.4, 110.8, 113.4, 129.1, 130.4, 158.8; EIMS (*m/z*): 352 (M^+, 0.2), 320 (M^+−MeOH, 2), 121 (100); Anal. Calcd for $C_{19}H_{28}O_6$: C, 64.75; H, 8.01. Found: C, 64.69; H, 8.07.

(1*S*,2*S*,4*S*,5*S*,6*R*)-4-Formyl-2-methoxy-6-(methoxymethyl)-oxy-3-oxabicyclo[3.3.0]octane (20). To a solution of MPM ether **19** (43.0 mg, 122 μmol) in CH_2Cl_2–H_2O (20:1) (1.20 mL) was added DDQ (33.0 mg, 146 μmol) and stirred at rt for 1 h. The reaction mixture was diluted with $CHCl_3$, washed with H_2O and saturated aqueous NaCl, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by preparative silica gel TLC (developed with hexane–EtOAc=1:3, R_f 0.4) to give alcohol (26.0 mg, 92%) as a colorless oil. $[\alpha]_D$=−75.5° (*c*=1.00, $CHCl_3$); IR (neat) 3479, 2947 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 1.64–1.83 (4H, m), 2.63 (1H, m), 2.82 (1H, dd, *J*=15.0, 7.4 Hz), 3.13 (1H, t, *J*=7.1 Hz), 3.30 (3H, s), 3.38 (3H, s), 3.99 (2H, m), 4.07 (1H, m), 4.23 (1H, dd, *J*=13.2, 6.3 Hz), 4.67 (1H, d, *J*=6.6 Hz), 4.68 (1H, d, *J*=6.6 Hz), 4.74 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 25.9, 30.6, 45.7, 48.0, 53.9, 55.5, 61.4, 80.3, 81.2, 95.8, 110.4; EIMS (*m/z*): 201 (M^+−OMe, 8), 45 (100); Anal. Calcd for $C_{11}H_{20}O_5$: C, 56.88; H, 8.68. Found: C, 56.77; H, 8.61.

To a cold (−78°C) solution of oxalyl chloride (158 μL, 1.81 mmol) in CH_2Cl_2 (3.0 mL) was added DMSO (160 μL, 2.26 mmol) in CH_2Cl_2 (500 μL). The mixture was stirred at −78°C for 15 min, treated with a solution of the above alcohol (105 mg, 452 μmol) in CH_2Cl_2 (1.00 mL) and stirred for 15 min and then with Et_3N (378 μL, 2.71 mmol). The mixture was stirred for 15 min and warmed to rt and stirred for 20 min. The reaction mixture was diluted with Et_2O–benzene (5:1), washed with H_2O, saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluted with hexane–EtOAc=4:1) to give aldehyde **20** (79.0 mg, 96%) as a colorless oil. $[\alpha]_D$=+3.2° (*c*=0.87, $CHCl_3$); IR (neat) 2954, 1729 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 1.64 (2H, m), 1.87 (2H, m), 2.67 (1H, dd, *J*=15.5, 8.8 Hz), 3.27 (1H, m), 3.31 (3H, s), 3.34 (3H, s), 4.06 (1H, m), 4.40 (1H, d, *J*=7.4 Hz), 4.48 (1H, d, *J*=6.8 Hz), 4.56 (1H, d, *J*=6.8 Hz), 4.89(1H, s), 9.86 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm:27.1, 32.6, 49.9, 52.1, 54.7, 55.9, 79.0, 82.4, 95.8, 110.5, 200.6; EIMS (*m/z*): 201 (M^+−CHO, 2), 45 (100); HREIMS: Calcd for $C_9H_{13}O_4$ (M^+−CHO−Me) 185.0813; Found: 185.0808.

(1*S*,2*S*,4*R*,5*S*,6*R*)-4-Formyl-2-methoxy-6-(methoxymethyl)-oxy-3-oxabicyclo[3.3.0]octane (21). A solution of K_2CO_3 in MeOH (0.5%, 13.1 mL) was added to aldehyde **20** (302 mg, 1.31 mmol) and the mixture was stirred at rt for 6 h. The reaction mixture was diluted with Et_2O–$CHCl_3$ (5:1), washed with H_2O and saturated aqueous NaCl, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluted with hexane–EtOAc=3:1) to give aldehyde **21** (246 mg, 82%) as a colorless oil. $[\alpha]_D$=+198.5° (*c*=0.52, $CHCl_3$); IR (neat) 2953, 1732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 1.58 (2H, m), 1.73 (1H, m), 1.81 (1H, m), 2.56 (1H, td, *J*=7.5, 2.7 Hz), 3.12 (1H, td, *J*=7.5, 2.8 Hz), 3.35 (3H, s), 3.38 (3H, s), 4.14 (1H, m), 4.63 (1H, d, *J*=2.8 Hz), 4.64 (1H, d, *J*=6.6 Hz), 4.67 (1H, d, *J*=6.6 Hz), 4.85 (1H, s), 9.70 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 25.7, 30.4, 46.3, 47.9, 55.2, 55.6, 78.4, 83.9, 95.6, 112.9, 204.4; EIMS (*m/z*): 231 (M^++1, 1), 45 (100); HREIMS: Calcd for $C_{10}H_{17}O_4$ (M^+−CHO) 201.1127; Found: 201.1122.

(1′*Z*,4′*Z*,7′*Z*,10′*Z*)-(1*S*,2*S*,4*R*,5*S*,6*R*)-2-Methoxy-6-(methoxymethyl)oxy-4-trideca-1′,4′,7′,10′-tetraenyl-3-oxabicyclo[3.3.0]octane (22). To a cold (0°C) suspension of phosphonium iodide **7** (177 mg, 3.21 mmol) in THF (13.5 mL) was added BuLi (1.33 mL, 2.14 mmol, 1.61 M in hexane). The mixture was stirred at 0°C for 20 min to give Wittig reagent. To a cold (−78°C) solution of aldehyde **21** (246 mg, 1.07 mmol) and HMPA (1.86 mL, 10.7 mmol) in THF (40.0 mL) was added the prepared above Wittig reagent and the mixture was stirred at −78°C for 10 min. The reaction mixture was diluted with Et_2O, washed with

H_2O and saturated aqueous NaCl, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluted with hexane–EtOAc=10:1) to give olefin **22** (400 mg, 99%) as a colorless oil. $[\alpha]_D$=+40.5° (*c*=1.00, $CHCl_3$); IR (neat) 2961 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 0.96 (3H, t, *J*=7.6 Hz), 1.53–1.89 (4H, m), 2.08 (2H, qd, *J*=7.6, 7.0 Hz), 2.64–3.05 (8H, m), 3.30 (3H, s), 3.34 (3H, s), 4.13 (1H, dt, *J*=9.6, 6.2 Hz), 4.60 (2H, s), 4.73 (1H, s), 5.15 (1H, dd, *J*=9.5, 3.1 Hz), 5.28–5.43 (7H, m), 5.56 (1H, ddt, *J*=10.8, 9.5, 1.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 14.2, 20.4, 25.3, 25.3, 25.4, 25.5, 29.6, 48.6, 51.0, 54.0, 55.2, 76.0, 78.9, 95.4, 112.1, 126.7, 127.7, 127.8, 128.3, 128.4, 128.8, 131.8, 133.3; EIMS (*m/z*): 376 (M^+, 0.1), 45 (100); HREIMS: Calcd for $C_{22}H_{32}O_3$ (M^+−MeOH) 344.2351; Found: 344.2369.

Bacillariolide I (1). A mixture of AcOH and H_2O (4:1) (5.00 mL) was added to methyl acetal **22** (35.8 mg, 95.1 μmol) and the mixture was stirred at rt for 12 h. The reaction mixture was concentrated under reduced pressure. The residue was purified by preparative silica gel TLC (developed with hexane–EtOAc=4:1, R_f 0.2) to give an anomeric mixture of hemiacetals (30.0 mg, 87%) as a colorless oil. IR (neat) 3408, 2962 cm^{-1}; EIMS (*m/z*): 299 (M^+−MOM, 6), 45 (100); HREIMS: Calcd for $C_{22}H_{32}O_3$ (M^+−H_2O) 344.2351; Found 344.2363; **major isomer:** ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 0.97 (3H, t, *J*=7.6 Hz), 1.58–1.94 (4H, m), 2.07 (2H, qd, *J*=7.6, 6.9 Hz), 2.51–3.05 (9H, m), 3.34 (3H, s), 4.16 (1H, dt, *J*=9.5, 6.4 Hz), 4.60 (2H, t, *J*=6.9 Hz), 5.15 (1H, dd, *J*=9.4, 4.4 Hz), 5.27–5.49 (8H, m), 5.66 (1H, ddt, *J*=10.8, 9.4, 1.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 14.2, 20.4, 25.1, 25.3, 25.4, 25.5, 25.9, 49.5, 51.1, 55.2, 76.1, 78.8, 95.3, 105.6, 126.9, 127.7, 127.8, 128.3, 128.5, 129.2, 131.9, 133.2.

To a cold (0°C) solution of the above hemiacetals (162 mg, 447 μmol) in acetone (4.47 mL) was added Jones reagent (300 μL), followed by stirring for 10 min and treatment with 2-propanol (1.0 mL). After stirring for 10 min, the reaction mixture was diluted with Et_2O, washed with H_2O and saturated aqueous NaCl, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluted with hexane–EtOAc=4:1) to give 5-*O*-methoxymethylbacillariolide I (144 mg, 89%) as a colorless oil. $[\alpha]_D$=−23.5° (*c*=1.36, $CHCl_3$); IR (neat) 2925, 1771 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 0.97 (3H, t, *J*=7.5 Hz), 1.69 (1H, m), 1.93 (2H, m), 2.08 (3H, m), 2.75 (1H, ddd, *J*=9.8, 7.2, 3.0 Hz), 2.81 (2H, t, *J*=6.7 Hz), 2.84 (2H, t, *J*=6.5 Hz), 2.96 (2H, m), 3.09 (1H, br td, *J*=9.8, 2.3 Hz), 3.35 (3H, s), 4.20 (1H, m), 4.61 (1H, d, *J*=6.7 Hz), 4.65 (1H, d, *J*=6.7 Hz), 5.27–5.63 (9H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 14.1, 20.4, 25.4, 25.5, 25.8, 26.3, 30.5, 42.9, 48.5, 55.4, 74.4, 78.8, 95.5, 126.7, 126.7, 127.4, 128.6, 128.7, 129.0, 132.0, 132.3, 180.0; EIMS (*m/z*): 360 (M^+, 0.3), 45 (100); HREIMS: Calcd for $C_{20}H_{27}O_3$ (M^+): 315.1960; Found: 315.1950.

A mixture of AcOH and conc. HCl (50:1) (3.00 mL) was added to 5-*O*-methoxymethylbacillariolide I (11.6 mg, 32.3 μmol) and stirred at rt for 1 h. The reaction mixture was diluted with Et_2O, washed with saturated aqueous $NaHCO_3$, H_2O and saturated aqueous NaCl, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by preparative silica gel TLC (developed with hexane–EtOAc=1:1, R_f 0.4) to give bacillariolide I (**1**) (9.2 mg, 90%) as a colorless oil. $[\alpha]_D$=−23.6° (*c*=0.55, MeOH); IR ($CHCl_3$) 3474, 2968, 1760 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ ppm: 0.97 (3H, t, *J*=7.5 Hz), 1.62 (1H, m), 1.84 (1H, m), 1.99 (2H, dd, *J*=14.3, 6.9 Hz), 2.09 (2H, dq, *J*=7.5, 7.5 Hz), 2.65 (1H, ddd, *J*=9.6, 6.5, 2.6 Hz), 2.83 (2H, t, *J*=6.0 Hz), 2.88 (2H, t, *J*=5.4 Hz), 3.00 (2H, m), 3.18 (1H, dt, *J*=9.6, 6.5 Hz), 4.30 (1H, dt, *J*=6.5, 5.0 Hz), 5.26–5.46 (6H, m), 5.49–5.61 (3H, m); ^{13}C NMR (100 MHz, CD_3OD) δ ppm: 14.7, 21.5, 26.4, 26.5, 26.9, 27.2, 34.6, 44.7, 51.8, 74.5, 76.5,128.1, 128.2, 128.8, 129.6, 130.1, 130.1, 132.8, 133.0, 183.4; EIMS (*m/z*): 316 (M^+, 2.5), 91 (100); HREIMS: Calcd for $C_{20}H_{28}O_3$ (M^+): 316.2038; Found: 316.2020.

(1′*Z*)-(1*S*,4*R*,5*S*,6*R*)-2-Methoxy-6-(methoxymethyl)oxy-4-[(5′-methoxycarbonyl)pent-1′-enyl]-3-oxabicyclo[3.3.0]-octane (23). To a suspension of phosphonium bromide **9** (214 mg, 484 μmol) in THF (1.40 mL) was added LiHMDS (518 μL, 518 μmol, 1.0 M in THF) at 0°C. The mixture was stirred at 0°C for 20 min, added with HMPA (291 μL, 1.67 mmol) and cooled to −78°C. A solution of aldehyde **21** (38.5 mg, 167 μmol) in THF (0.30 mL) was added to the mixture, warmed to 0°C and stirred at 0°C for 30 min. The reaction mixture was diluted with Et_2O, washed with H_2O and saturated aqueous NaCl, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluted with hexane–EtOAc=5:1) to give olefin **23** (50.0 mg, 95%) as a colorless oil. $[\alpha]_D$=+68.7° (*c*=0.87, $CHCl_3$); IR (neat) 2952, 1739 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 1.53–1.77 (3H, m), 1.86 (1H, m), 2.38 (2H, m), 2.44 (1H, m), 2.52 (1H, m), 3.29 (3H, s), 3.34 (3H, s), 3.67 (3H, s), 4.13 (1H, dt, *J*=9.3, 6.1 Hz), 4.60 (1H, d, *J*=6.7 Hz), 4.61 (1H, d, *J*=6.7 Hz), 4.72 (1H, s), 5.11 (1H, dd, *J*=9.4, 2.8 Hz), 5.38 (1H, dt, *J*=10.8, 6.7 Hz), 5.57 (1H, ddt, *J*=10.8, 9.4, 1.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 22.5, 25.3, 29.6, 33.8, 48.5, 51.1, 51.4, 54.0, 55.2, 75.9, 79.0, 95.4, 112.1, 128.4, 134.4, 173.3; EIMS (*m/z*): 314 (M^+, 0.4), 299 (M^+−Me, 1), 45 (100); HREIMS: Calcd for $C_{15}H_{23}O_6$ (M^+−Me): 299.1495; Found: 299.1519.

Bacillariolide III (3). A mixture of AcOH and H_2O (4:1) (3.00 mL) was added to methyl acetal **23** (50.0 mg, 159 μmol) and stirred at rt for 12 h. The reaction mixture was concentrated under reduced pressure. The residue was purified by preparative silica gel TLC (developed with hexane–EtOAc=3:1, R_f 0.3) to give an anomeric mixture of hemiacetals (32.0 mg, 67%) as a colorless oil. IR (neat) 3445, 2954, 1733 cm^{-1}; EIMS (*m/z*): 283 (M^+−OH, 1), 45 (100); HREIMS: Calcd for $C_{13}H_{18}O_4$ (M^+−MOM−OH) 238.1205; Found 238.1163; **major isomer:** ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 1.55–1.93 (4H, m), 2.36–2.78 (6H, m), 3.34 (3H, s), 3.67 (3H, s), 4.13 (1H, m), 4.60 (2H, s), 5.10 (1H, dd, *J*=9.4, 4.8 Hz), 5.25 (1H, d, *J*=2.7 Hz), 5.48 (1H, m), 5.68 (1H, ddt, *J*=10.9, 9.4, 1.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 22.5, 25.0, 29.6, 33.8, 49.4, 51.2, 51.4, 55.2, 75.9, 78.9, 95.4, 105.5, 128.6, 134.3, 173.2.

To a cold (0°C) solution of the above hemiacetals (32.0 mg, 107 μmol) in acetone (2.00 mL) was added Jones reagent (70.0 μL), stirred for 10 min and treated with 2-propanol (0.5 mL). After stirring for 10 min, the reaction mixture was diluted with Et_2O, washed with H_2O and saturated aqueous NaCl, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluted with hexane–EtOAc=3:1) to give 5-*O*-methoxymethylbacillariolide III methyl ester (32.0 mg, quantitative yield) as a colorless oil. $[\alpha]_D=-9.8°$ (c=0.82, $CHCl_3$); IR (neat) 2952, 1766, 1737 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 1.68 (1H, m), 1.94 (2H, m), 2.08 (1H, m), 2.39–2.48 (3H, m), 2.53 (1H, m), 2.73 (1H, ddd, J=9.6, 7.1, 3.3 Hz), 3.08 (1H, td, J=9.6, 2.7 Hz), 3.36 (3H, s), 3.67 (3H, s), 4.20 (1H, ddd, J=8.5, 7.1, 5.1 Hz), 4.63 (1H, d, J=6.8 Hz), 4.65 (1H, d, J=6.8 Hz), 5.45 (1H, dd, J=9.0, 3.4 Hz), 5.49 (1H, m), 5.58 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 22.9, 26.3, 30.6, 33.4, 42.9, 48.6, 51.5, 55.5, 74.4, 78.9, 95.5, 129.8, 131.9, 172.9, 180.0; EIMS (*m/z*): 299 (M^++1, 2), 45 (100); HREIMS: Calcd for $C_{13}H_{17}O_5$ (M^+−MOM) 253.1076; Found: 253.1064.

Method A (purification with preparative silica gel TLC). A solution of 5-*O*-methoxymethylbacillariolide III methyl ester (22.5 mg, 75.4 μmol) in 1N HCl (754 μL) was stirred at 60°C for 6 h. The reaction mixture was extracted with $CHCl_3$. The organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by preparative silica gel TLC (developed with hexane–THF–AcOH=10:10:0.1, R_f 0.4) to give bacillariolide III (**3**) (14.6 mg, 70%) as a colorless oil. $[\alpha]_D=-54.2°$ (c=0.31, MeOH); IR ($CHCl_3$) 3029, 2977, 1758, 1719 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ ppm: 1.63 (1H, m), 1.82 (1H, m), 1.99 (2H, m), 2.41 (2H, m), 2.48 (2H, m), 2.64 (1H, ddd, J=9.6, 6.4, 1.7 Hz), 3.18 (1H, dt, J=9.6, 6.6 Hz), 4.32 (1H, ddd, J=11.4, 5.1, 1.7 Hz), 5.54–5.67 (3H, m); ^{13}C NMR (100 MHz, CD_3OD) δ ppm: 24.1, 27.1, 34.6, 34.6, 44.6, 52.0, 74.5, 76.4, 131.1, 133.0, 176.6, 183.4; EIMS (*m/z*): 241 (M^+, 1), 45 (100); HREIMS: Calcd for $C_{12}H_{14}O_4$ (M^+-H_2O): 222.0892; Found: 222.0906.

Method B (purification with ODS column chromatography). A solution of 5-*O*-methoxymethylbacillariolide III methyl ester (40.3 mg, 135 μmol) in 1N HCl (1.35 mL) was stirred at 60°C for 6 h. The reaction mixture was extracted with $CHCl_3$. The organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by ODS column chromatography (eluted with H_2O–acetonitrile–AcOH=90:10:0.5) to give bacillariolide III (**3**) complex (25.1 mg) as a colorless oil. $[\alpha]_D=-47.9°$ (c=0.28, MeOH); ^1H NMR (400 MHz, CD_3OD) δ ppm: 1.62 (1H, m), 1.83 (1H, m), 1.99 (2H, br dd, J=13.9, 6.5 Hz), 2.35 (2H, t, J=7.1 Hz), 2.47 (2H, m), 2.64 (1H, ddd, J=9.5, 6.5, 1.8 Hz), 3.18 (1H, dt, J=9.5, 6.4 Hz), 4.32 (1H, dd, J=11.5, 6.4 Hz), 5.54 (2H, m), 5.63 (1H, dt, J=9.3, 7.4 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ ppm: 24.8, 27.1, 34.6, 36.2, 44.6, 51.9, 74.5, 76.5, 130.7, 133.6, 183.2, 183.4.

Bacillariolide III sodium salt. An aqueous solution of bacillariolide III (**3**) (15.1 mg, 62.8 μmol) was passed through Chelex 100 Na^+ form. The aqueous solution was concentrated under reduced pressure to give the bacillariolide III sodium salt (15.6 mg, 95%) as a white amorphous solid. $[\alpha]_D=-43.6°$ (c=0.16, H_2O); IR (KBr) 3541, 1769, 1577, 1413 cm^{-1}; ^1H NMR (400 MHz, D_2O) δ ppm:1.69 (1H, m), 1.94 (2H, m), 2.10 (1H, m), 2.30 (1H, dt, J=14.3, 7.9 Hz), 2.31 (1H, dt, J=14.3, 6.4 Hz), 2.46 (2H, m), 2.82 (1H, ddd, J=9.6, 6.3, 2.6 Hz), 3.37 (1H, td, J=9.6, 3.2 Hz), 4.43 (1H, td, J=6.3, 4.7 Hz), 5.58–5.64 (2H, m), 5.74 (1H, m); ^{13}C NMR (100 MHz, D_2O) δ ppm:26.4, 27.8, 34.7, 39.3, 45.7, 52.5, 75.6, 79.0, 130.1, 136.3, 184.6, 187.1; EIMS (*m/z*): 222 (M^+−NaOH, 63), 127 (100); FABMS (*m/z*): 263 (M^+, 50), 135 (100); HREIMS: Calcd for $C_{12}H_{14}O_4$ (M^+−NaOH): 222.0892; Found: 222.0893.

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