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TOTAL SYNTHESIS OF THE PROPOSED STRUCTURES OF EUSHEARILIDE

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Abstract – Total synthesis of (3*R*,16*Z*,20*E*,23*S*)- and (3*R*,16*Z*,20*E*,23*R*)-eushearilide was accomplished in 15 steps, respectively. Using either enantiomer of one of the four building blocks to assemble the phosphonium salt for the latter Wittig reaction, two diastereomers of eushearilide were prepared. Shiina macrolactonization (2-methyl-6-nitrobenzoic anhydride) was a key step in production of the 24-membered lactone in high yield.

INTRODUCTION

Eushearilide (**1**), which was isolated from *Eupenicillium shearii* by Hosoe in 2006, shows broad-spectrum antifungal activity against various fungi and yeasts including the human pathogens *Aspergillus fumigatus*, *Trichophyton* sp. and *Candida* sp.[1] Its planar structure was elucidated by a combination of ^{1}H, ^{13}C and ^{31}P NMR, IR and MS spectroscopy. It is a novel 24-membered macrolide with two asymmetric carbons and two non-conjugated double bonds, and a choline attached to a phosphate diester at the C3 hydroxyl group (Figure 1). This structure is quite different from that of well-known antifungal drugs such as amphotericin B, terbinafine hydrochloride, and isoconazole. Eushearilide is expected to be a promising antifungal drug. Because the absolute configuration at C3 and C23 in **1** has not been clarified, we attempted to synthesize two diastereomers with different chirality at C23, and determine the correct structure and stereochemistry of the natural product by an extensive spectroscopic study.

Dedicated to Dr. Victor Snieckus, Professor of Queen's University, on the occasion of his 77th birthday.

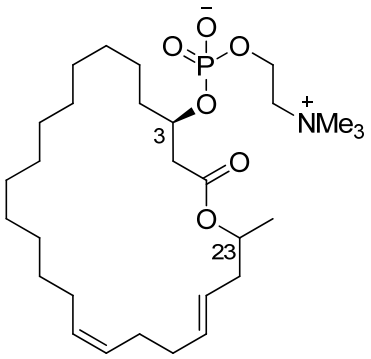

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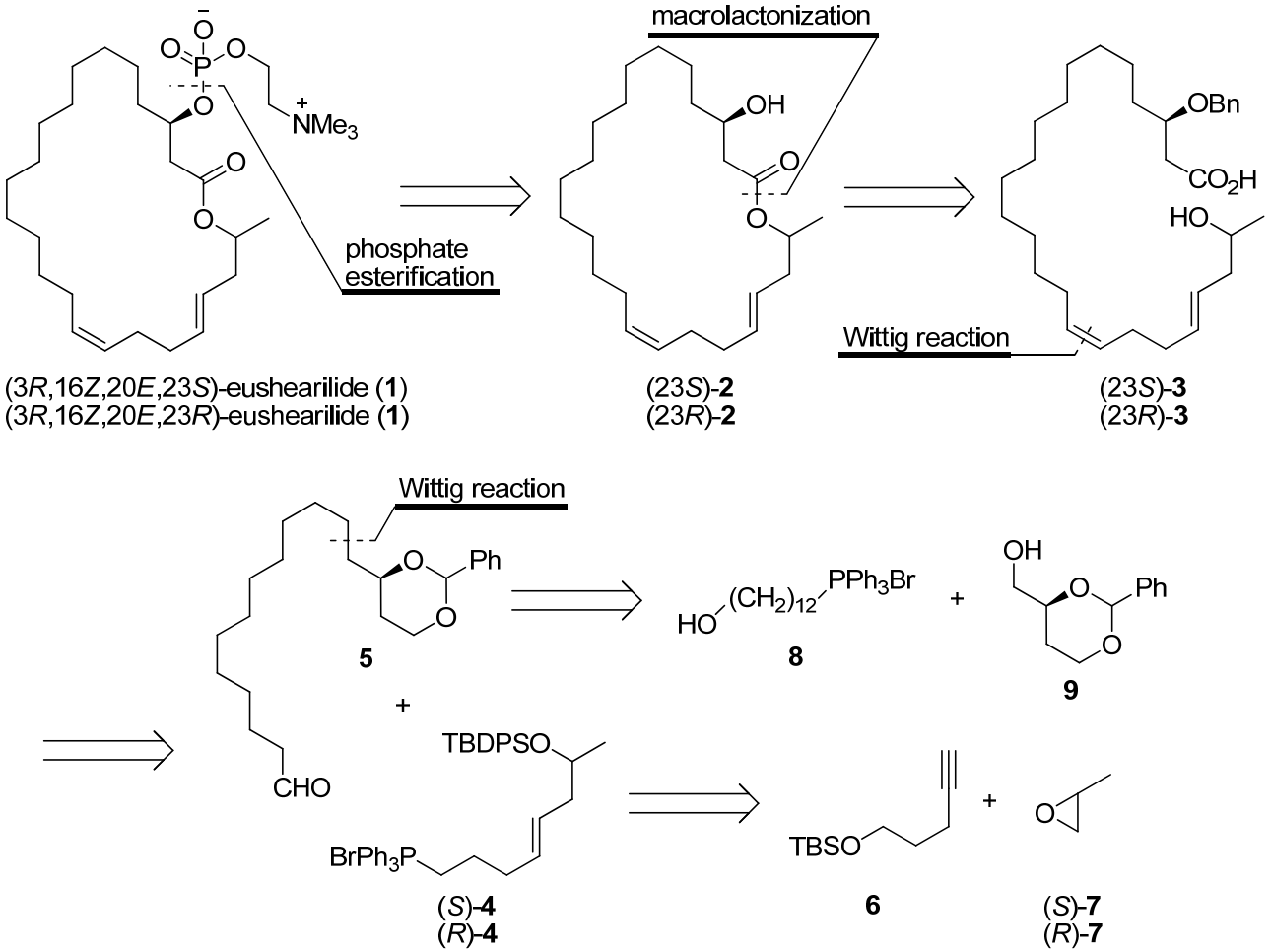
Figure 1. The proposed structure of eushearilide (**1**)

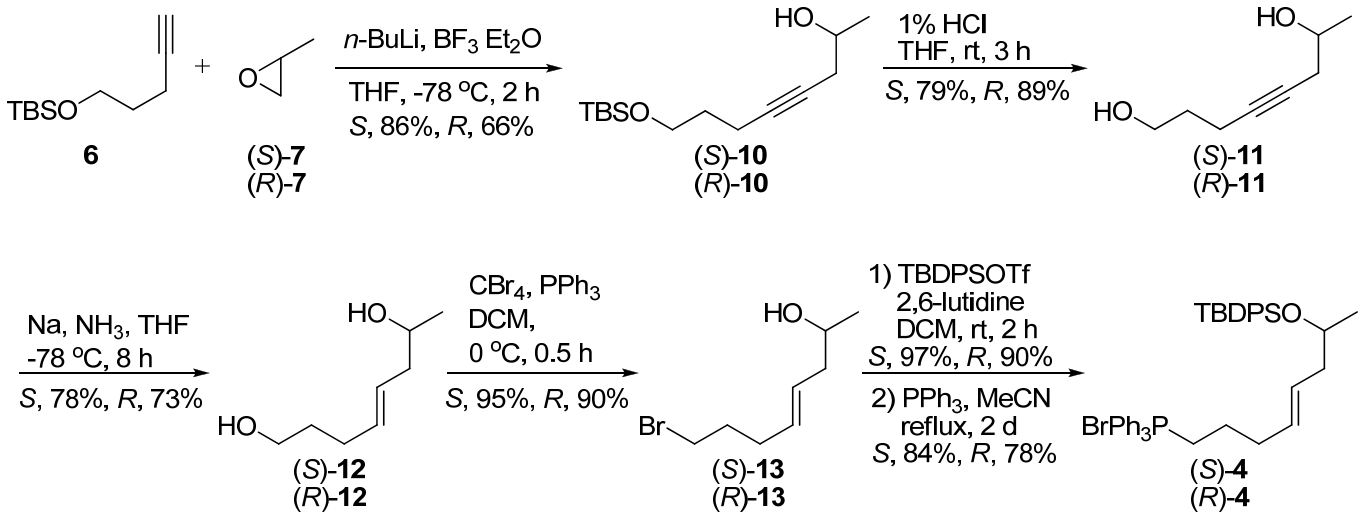
RESULTS AND DISCUSSION

Our initial retrosynthetic analysis for (3*R*,16*Z*,20*E*,23*S*)- and (3*R*,16*Z*,20*E*,23*R*)-**1** is shown in Scheme 1. We attempted to optimize access to a key intermediate of **1** by a convergent synthesis. Esterification of 3-hydroxy-lactone **2** was expected to produce the choline phosphate ester chain in **1**. Macrolactonization of seco acid **3** by an efficient condensation reagent would be the key step to produce the desired macrolide core **2**. The (16*Z*)-substrate **3** for macrolactonization would be prepared by a Wittig reaction of aldehyde **5** with phosphonium salt **4**. In this manner, coupling of two components for total synthesis of eushearilide using the Wittig reaction was envisaged. Phosphonium salt **4** was envisaged to result from alkylation of lithiated acetylene **6** to propylene oxide **7**. Aldehyde **5** would be obtained by Wittig reaction of long chain hydroxyphosphonium salt **8** and aldehyde prepared by oxidation of alcohol **9**. Finally, the chiral center in alcohol **9** was to be established from L-malic acid. The other eushearilide isomer with a 3*R*,16*Z*,20*E* configuration, that is, (3*R*,16*Z*,20*E*,23*R*)-**1** was to be obtained in a completely analogous fashion, employing the enantiomer of building blocks (*R*)-**7**.

Synthesis of the phosphonium salts (*S*)-**4** and (*R*)-**4** was investigated for their use as precursors in the Wittig reaction (Scheme 2). Regioselective addition of the known acetylene **6**[2] with enantiopure propylene oxide (**7**) (*S*>99 % ee, and *R*>99 % ee), which was prepared from racemic propylene oxide by hydrolytic kinetic resolution using Jacobsen's reagent with excellent enantioselectivity,[3] produced the expected secondary alcohol **10** as a single enantiomer.[4] Subsequent desilylation of **10** under acidic conditions, followed by Birch reduction of the resulting diol **11** afforded (*E*)-olefin **12** as a single diastereomer.[5] Regioselective bromination of diol **12** with CBr_4 and PPh_3 proceeded smoothly producing the desired bromide **13** in high yield. As the last step, protection of alcohol **13** with TBDPSOTf[6] followed by treatment with PPh_3 produced the phosphonium salt (*S*)- and (*R*)-**4**, respectively.[7]

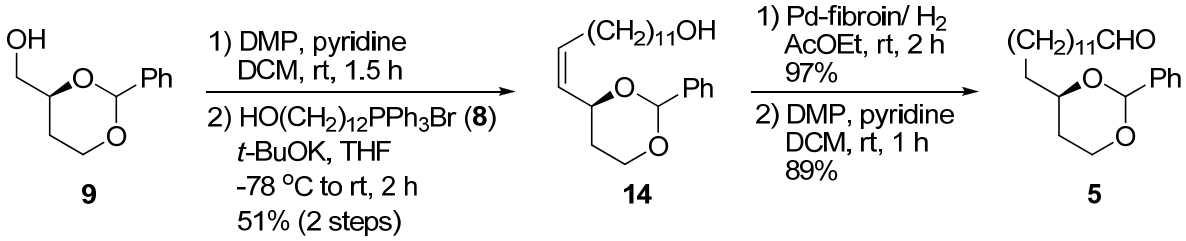


Scheme 1. Retrosynthesis of eushearilide (**1**)



Scheme 2. Synthesis of phosphonium salts (*S*)- and (*R*)-**4**

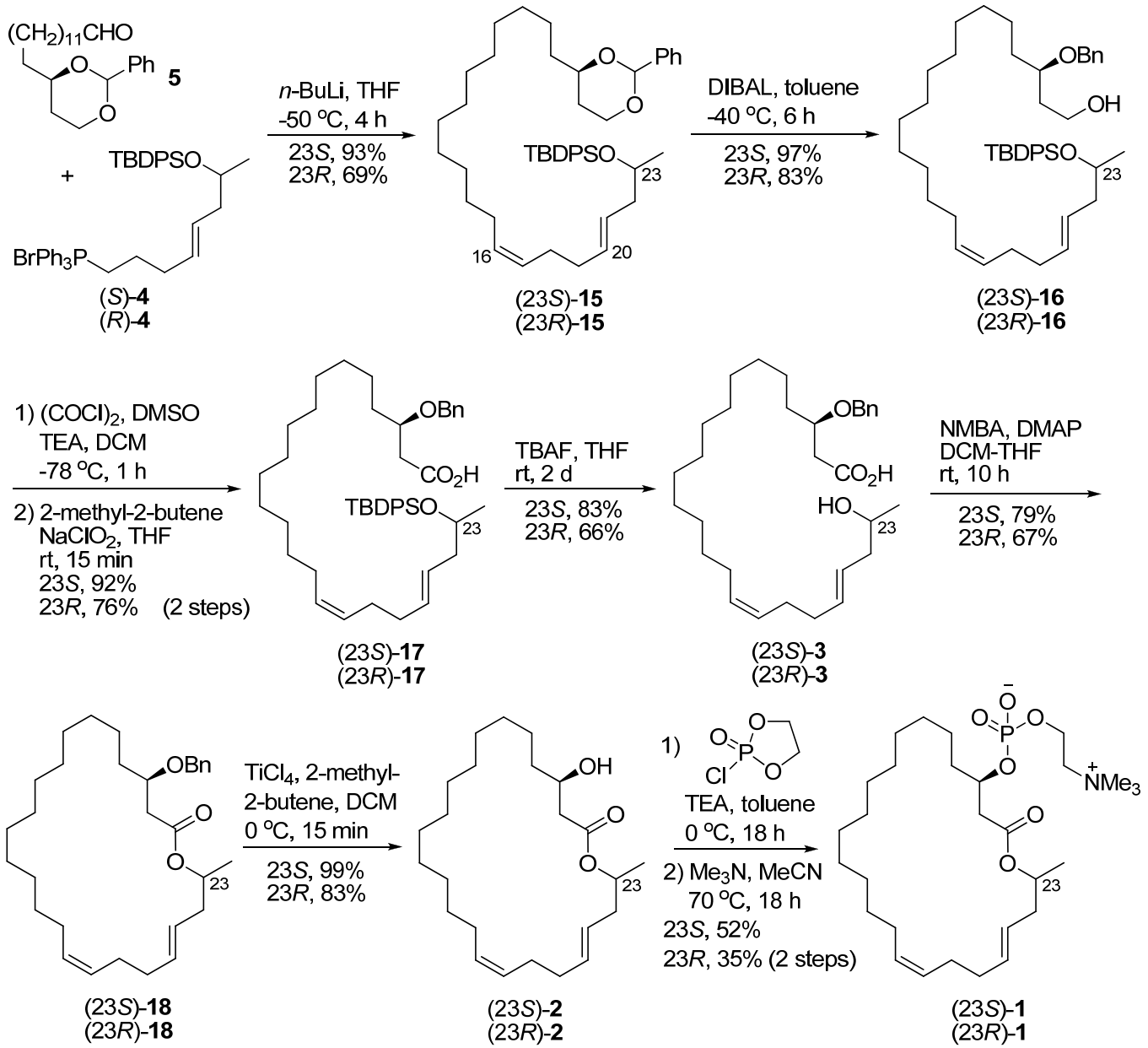
Scheme 3 outlines the synthesis of aldehyde **5**. L-Malic acid is an inexpensive, commercially available compound that is an appropriate starting material for synthesis of **1**. In the synthesis, chiral center on alcohol **9** derived from malic acid will remain at the C-3 position of the natural product. The known alcohol **9** was prepared from L-malic acid in high yield in two steps.[8] Dess–Martin periodinane (DMP) oxidation of the primary alcohol **9** was followed by the standard Wittig reaction with known hydroxyphosphonium bromide, which was prepared from commercially available dodecane-1,12-diol in two steps.[9] These steps produced the expected alcohol **14** in low yield because of an unstable aldehyde intermediate. The reaction yield was increased to 51 % by optimizing the reaction conditions and handling. Treatment of **14** with Pd-fibroin in a H_2 atmosphere (1 atm) and subsequent DMP oxidation produced the desired aldehyde **5**.



Scheme 3. Synthesis of aldehyde **5**

After successful synthesis of the enantiomeric phosphonium salts (*S*)-**4** and (*R*)-**4**, synthesis of the two diastereomers of **1** was attempted. Synthesis of (3*R*,16*Z*,20*E*,23*S*)- and (3*R*,16*Z*,20*E*,23*R*)-**1** is depicted in Scheme 4. First, successive Wittig reaction of aldehyde **5** with phosphonium bromide **4** led to the formation of the long chain (16*Z*)-diene **15** as a single diastereomer. Regioselective reduction of benzylidene acetal **15** with DIBAL proceeded successfully to form the 3-benzyloxy-alcohol **16**.[10] Conversion of **16** by Swern and Pinnick oxidations gave carboxylic acid **17** in excellent yield.[11] Deprotection of the TBDPS group with TBAF provided seco acid **3**. The conventional Yamaguchi reagent (2,4,6-trichlorobenzoyl chloride)[12] and Shiina reagent (2-methyl-6-nitrobenzoic anhydride)[13] were compared for the macrolactonization. In highly dilute conditions, each condensation of (23*S*)-**3** gave the requisite macrolide (23*S*)-**18** as the sole product in 68% (Yamaguchi) or 79% (Shiina) yield. Compared to the Shiina reaction, the Yamaguchi reaction required a higher temperature (reflux in toluene vs. room temperature). Treatment of benzyl ether **18** with $TiCl_4$ provided β-hydroxy-lactone **2**.[14] Finally, alcohol **2** was successfully converted to (3*R*,16*Z*,20*E*,23*S*)- and (3*R*,16*Z*,20*E*,23*R*)-**1** in two steps by phosphate esterification with ethylene chlorophosphate under basic conditions, followed by cleavage of the dioxyphospholane ring with trimethylamine.[15] Although the spectroscopic properties of the synthetic diastereomers of **1** were similar, they were not completely identical to those of the proposed natural product **1**. In particular, ^{13}C NMR spectrum showed the chemical

shifts of C14–18 at both synthetic compound **1** moved slightly upfield as compared with that of natural product (Table 1). It has been known as the common phenomenon attributed to p orbital compression. Therefore, we speculate that the geometry at C16 and C20 of the natural product is *trans* (*E*) and *trans* (*E*). In conclusion, this is the first report of a total synthesis of the two diastereomers (3*R*,16*Z*,20*E*,23*S*)- and (3*R*,16*Z*,20*E*,23*R*)-**1** via coupling of four components to form the macrolide core. The Shiina reaction was highly efficient for macrolactonization of the 24-membered macrolide. Synthesis of derivatives of **1** is important for structural research for development of antifungal drugs.



Scheme 4. Completion of total synthesis of (3*R*,16*Z*,20*E*,23*S*)- and (3*R*,16*Z*,20*E*,23*R*)-eushearilide (**1**)

Table 1. Chemical shift in ^{13}C NMR spectrum for natural product, (23*S*)-**1** and (23*R*)-**1**

	natural product	(23*S*)-**1**	(23*R*)-**1**
C-14	29.5	27.5	27.5
C-15	32.8	29.6	29.7
C-16	131.8	131.3	131.3
C-17	131.2	130.2	130.3
C-18	33.6	29.7	29.8

EXPERIMENTAL

All melting points were measured with a Yanagimoto Micro melting point apparatus without collection. IR spectra were recorded on a JASCO FT/IR-200 spectrophotometer. ^1H and ^{13}C NMR spectra were obtained on a Bruker AVIII-400 instrument, and chemical sifts are reported in ppm on the δ-scale from internal Me_4Si. MS spectra were measured with a JEOL JMS D-600 and JMS T-100LP spectrometer by using the chemical ionization (CI) with isobutene, the electron impact (EI) methods, and ElectroSpray Ionization (ESI) methods. Elemental analyses were performed on a Perkin-Elmer 240-B instrument. Optical rotation were taken with a JASCO-DIP-370 polarimeter at rt. Shibata Glass Tube Oven GTO-350RD was used as distillation apparatus. Column chromatography was performed on Silica gel 60 (100−210 μm, Kanto Chemical Co., Inc.), Chromatorex NH (100−200 mesh, Fuji Silysia Chemical LTD), and Sephadex LH−20 (GE Healthcare Bio−Sciences AB). HPLC analysis was performed on a Shimazu LC-20AD. Chiralpac OD column was purchased from Daicel Chemical Industry. The reaction solvents were prepared as the following. HMPA was distilled over sodium metal. Acetonitrile and DMSO were distilled over calcium hydride. Hexane was distilled over sodium hydride. Anhydrous THF, DCM, and toluene were purchased from Wako Pure Chemical Industries and Kanto Chemical.

(*S*)-8-(*tert*-Butyldimethylsilyloxy)oct-4-yn-2-ol ((*S*)-10). To a solution of **6** (30 mmol, 6.0 g) in THF (70 mL) was added *n*-BuLi (1.6 M in THF, 33 mmol, 20 mL) dropwise under N_2 atmosphere at –78 °C and stirred for 1 h at –78 °C. After BF_3•Et_2O (3 mL) was added, the reaction mixture was stirred for 10 min. The solution of (*S*)-propylene oxide (**7**) (33 mmol, 1.9 g) in THF (15 mL) was added dropwise at –78 °C, and stirred for additional 2 h at –78 °C. The reaction mixture was quenched with saturated aqueous NH_4Cl, and extracted with AcOEt. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtrated, and evaporated under reduced pressure. The crude product was purified by column chromatography with silica gel (hexane / AcOEt = 4: 1) to afford (*S*)-**10** (6.7 g, 86%). $[\alpha]_D^{27}$ +7.51 (*c* 1.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ: 3.93–3.87 (1H, m), 3.69 (2H, t, *J* = 6.1 Hz), 2.40–2.24 (4H, m), 1.99 (1H, d, *J* = 4.0 Hz), 1.73–1.67 (2H, m), 1.24 (3H, d, *J* = 6.2 Hz), 0.90 (9H, s), 0.06 (6H, s). ^{13}C NMR

(100 MHz, $CDCl_3$) δ: 82.7, 76.2, 66.5, 61.6, 32.0, 29.4, 25.9, 22.2, 18.3, 15.1. IR (film) cm^{-1}: 3460, 2960, 2930, 2900, 2860. MS (ESI+) *m/z*: 279 ($M+Na^+$, base peak). HRMS (ESI+) *m/z*: Found 279.1776 (Calcd for $C_{14}H_{28}NaO_2Si$ ($M+Na^+$) 279.1756). (*R*)-**10**, $[\alpha]_D^{23}$ –7.71 (*c* 1.53, $CHCl_3$).

(*S*)-Oct-4-yne-1,7-diol (*S*)-11. To a solution of (*S*)-**10** (33 mmol, 8.5 g) in THF (120 mL) was added 1% HCl (120 mL) at rt and stirred for 3 h. The reaction mixture was alkalized with saturated aqueous sodium hydrogen carbonate and extracted with AcOEt. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtrated, and evaporated under reduced pressure. The crude product was purified by column chromatography with silica gel ($CHCl_3$ / MeOH = 15: 1) to afford (*S*)-**11** (3.7 g, 79%). $[\alpha]_D^{29}$ +16.0 (*c* 1.01, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ: 3.91 (1H, sext, *J* = 5.7 Hz), 3.74 (2H, t, *J* = 6.0 Hz), 2.59 (1H, br), 2.46 (1H, br), 2.39–2.24 (4H, m), 1.74 (2H, quin, *J* = 6.2 Hz), 1.24 (3H, d, *J* = 6.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 82.3, 77.0, 66.5, 61.9, 31.4, 29.3, 22.3, 15.5. IR (film) cm^{-1}: 3350, 2970, 2930, 2880. MS (ESI+) *m/z*: 165 ($M+Na^+$, base peak). HRMS (ESI+) *m/z*: Found 165.0900 (Calcd for $C_8H_{14}NaO_2$ ($M+Na^+$) 165.0892). (*R*)-**11**, $[\alpha]_D^{25}$ –16.0 (*c* 1.00, $CHCl_3$).

(*S*,*E*)-Oct-4-ene-1,7-diol (*S*,*E*)-12. To a solution of (*S*)-**11** (26 mmol, 3.7 g) in THF (40 mL) was added liquid NH_3 (150 mL) and Na metal at –78 °C under N_2 atmosphere and stirred for 8 h at –78 °C. After NH_4Cl was added slowly, the reaction mixture was stirred for additional 14 h at rt and extracted with Et_2O. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtrated, and evaporated under reduced pressure. The crude product was purified by column chromatography with silica gel ($CHCl_3$ / MeOH = 15: 1) to afford (*S*,*E*)-**12** (3.0 g, 78%). $[\alpha]_D^{28}$ +10.9 (*c* 1.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ: 5.61–5.43 (2H, m), 3.84–3.76 (1H, m), 3.66 (2H, t, *J* = 6.4 Hz), 2.24–2.06 (4H, m), 1.72 (2H, br), 1.66 (2H, quin, *J* = 6.8 Hz), 1.19 (3H, d, *J* = 6.2 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 133.5, 126.5, 67.2, 62.1, 42.3, 32.0, 29.2, 22.6. IR (film) cm^{-1}: 3340, 2965, 2930, 2880, 1650. MS (CI) *m/z*: 145 ($M+H^+$), 69 (base peak). HRMS (CI) *m/z*: Found 145.1231 (Calcd for $C_8H_{17}O_2$ ($M+H^+$) 145.1228). (*R*,*E*)-**12**, $[\alpha]_D^{27}$ –10.7 (*c* 1.00, $CHCl_3$).

(*S*,*E*)-8-Bromooct-4-en-2-ol (*S*,*E*)-13. To a solution of (*S*,*E*)-**12** (2.7 mmol, 400 mg) in DCM (20 mL) was added a solution of CBr_4 (3.6 mmol, 1.2 g) in DCM (5 mL) and PPh_3 (3.7 mmol, 1.0 g) in DCM (5 mL) under N_2 atmosphere at 0 °C. The reaction mixture was stirred for 30 min at 0 °C, filtered through silica gel, and evaporated under reduced pressure. The crude product was purified by column chromatography with silica gel (hexane / AcOEt = 4: 1) to afford (*S*,*E*)-**13** (540 mg, 95%). $[\alpha]_D^{25}$ +7.51 (*c* 1.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ: 5.55–5.45 (2H, m), 3.85–3.77 (1H, m), 3.41 (2H, t, *J* = 6.7 Hz), 2.24–2.08 (4H, m), 1.93 (2H, quin, *J* = 6.9 Hz), 1.68 (1H, br), 1.19 (3H, d, *J* = 6.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 131.7, 127.6, 67.1, 42.3, 33.1, 32.0, 30.8, 22.6. IR (film) cm^{-1}: 3420, 2960, 2930, 2840, 1640. MS (ESI+) *m/z*: 230 ($M+Na^+$), 119 (base peak). HRMS (ESI+) *m/z*: Found 229.0204 (Calcd for $C_8H_{15}BrNaO$ ($M+Na^+$)

229.0202). (*R*,*E*)-**13**, $[\alpha]_D^{29}$ –6.94 (*c* 1.00, $CHCl_3$).

(*S*,*E*)-[7-(*tert*-Butyldiphenylsilyloxy)oct-4-enyl]triphenylphosphonium bromide (*S*,*E*)-4. To a solution of TBDPSOTf (3.2 mmol, 1.2 g) in DCM (4 mL) was added a solution of (*S*,*E*)-**13** (1.3 mmol, 270 mg) in DCM (3 mL) and 2,6-lutidine (4.0 mmol, 0.5 mL) at 0 °C under N_2 atmosphere. After being stirred for 2 h at 0 °C, the reaction mixture was quenched with saturated aqueous sodium hydrogen carbonate and extracted with $CHCl_3$. The combined organic layer was washed with saturated aqueous NH_4Cl, dried over anhydrous sodium sulfate, filtrated, and evaporated under reduced pressure. The crude product was purified by column chromatography with silica gel (hexane / AcOEt = 15: 1) to afford (*S*,*E*)-(8-bromooct-4-en-2-yloxy)*tert*-butyldiphenylsilane (570 mg, 97%). $[\alpha]_D^{25}$ –20.9 (*c* 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.67–7.66 (4H, m), 7.44–7.35 (6H, m), 5.41 (1H, dtt, *J* = 1.1, 7.0, 15.3 Hz), 5.28 (1H, dtt, *J* = 1.2, 6.6, 15.3 Hz), 3.85 (1H, sext, *J* = 6.0 Hz), 3.37 (2H, t, *J* = 6.8 Hz), 2.19–2.05 (4H, m), 1.86 (2H, quin, *J* = 6.8 Hz), 1.05 (9H, s), 1.05 (3H, d, *J* = 6.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 135.9, 135.8, 134.7, 134.5, 130.4, 129.5, 129.4, 128.2, 127.5, 127.4, 69.5, 42.6, 33.3, 32.3, 30.9, 28.8, 27.0, 22.9, 19.2, 18.7. IR (film) cm^{-1}: 3070, 3050, 2960, 2930, 2895, 2800, 1590. MS (CI) *m/z*: 445 ($M+H^+$), 283 (base peak). HRMS (CI) *m/z*: Found 445.1579 (Calcd for $C_{24}H_{34}OSiBr$ ($M+H^+$) 445.1562). (*R*,*E*)-compound. $[\alpha]_D^{29}$ +20.4 (*c* 1.00, $CHCl_3$). A solution of (*S*,*E*)-(8-bromooct-4-en-2-yloxy)-*tert*-butyldiphenylsilane (4.0 mmol, 1.8 g) and PPh_3 (20 mmol, 5.3 g) in acetonitrile (80 mL) was refluxed for 48 h. After being cooled at rt, the resulting mixture was evaporated acetonitrile with hexane several times under reduced pressure, and recrystallized from Et_2O to afford (*S*,*E*)-**4** (2.4 g, 84%). $[\alpha]_D^{25}$ –14.54 (*c* 1.02, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.85–7.76 (9H, m), 7.70–7.62(10H, m), 7.42–7.31 (6H, m), 5.36 (1H, dt, *J* = 7.0, 15.3 Hz), 5.23 (1H, dt, *J* = 6.6, 15.3 Hz), 3.85–3.76 (3H, m), 2.32 (2H, dt, *J* = 7.0, 7.1 Hz), 2.15–2.02 (2H, m), 1.71–1.61 (2H, m), 1.00–0.98 (12H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 135.6, 134.9 (d, *J* = 2.9 Hz), 134.5, 134.2, 133.5 (d, *J* = 10.1 Hz), 130.4 (d, *J* = 12.5 Hz), 130.3, 129.3, 128.8, 127.3, 118.1 (d, *J* = 85.9 Hz), 69.2, 42.5, 32.9, 32.7, 26.8, 22.7, 22.3, 21.7, 19.0. IR (KBr) cm^{-1}: 3070, 3050, 2960, 2930, 2890, 2860, 2790, 1590. MS (ESI+) *m/z*: 627 ($M–Br^+$, base peak). HRMS (ESI+) *m/z*: Found 627.3212 (Calcd for $C_{42}H_{48}OPSi$ ($M–Br^+$) 627.3211). (*R*,*E*)-**4**, $[\alpha]_D^{29}$ +15.0 (*c* 1.00, $CHCl_3$).

(*Z*)-13-[(4*S*)-2-Phenyl-1,3-dioxan-4-yl]tridec-12-en-1-ol 14. To a solution of **9** (7.7 mmol, 1.5 g) in DCM (15 mL) was added pyridine (11 mmol, 0.9 mL) and DMP (10 mmol, 4.3 g) at rt under Ar atmosphere. After being stirred for 90 min, the reaction mixture was filtered and evaporated under reduced pressure. The residue was purified by column chromatography with silica gel (hexane / AcOEt = 1: 1) to afford aldehyde (990 mg). To a solution of (12-hydroxydodecyl)triphenylphosphonium bromide (**8**) (6.7 mmol, 3.5 g) in THF (50 mL) was added *t*-BuOK (1.0 M in THF, 15 mmol, 15 mL) dropwise at –50 °C under N_2 atmosphere. After being stirred for 1.5h, a solution of aldehyde (990 mg) in THF (10 mL) was dropwise

added at –50 °C. The reaction mixture was stirred for additional 2 h at rt, quenched with H_2O, and extracted with Et_2O. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtrated, and evaporated under reduced pressure. The crude product was purified by column chromatography with silica gel (hexane / AcOEt = 4: 1) to afford **14** (1.4 g, 51%). $[\alpha]_D^{25}$ +63.9 (*c* 0.60, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.51–7.49 (2H, m), 7.37–7.31 (3H, m), 5.58 (1H, s), 5.56–5.47 (2H, m), 4.68 (1H, ddd, *J* = 2.5, 7.0, 11.2 Hz), 4.28 (1H, dd, *J* = 3.8, 11.5 Hz), 4.02 (1H, dt, *J* = 2.5, 11.5 Hz), 3.62 (2H, t, *J* = 6.6 Hz), 2.18–2.07 (2H, m), 2.01–1.91 (1H, m), 1.57–1.47 (3H, m), 1.44–1.27 (18H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 138.6, 133.0, 129.3, 128.7, 128.1, 126.1, 101.2, 73.6, 66.9, 62.9, 32.7, 31.5, 29.5, 29.4, 29.2, 27.9, 25.7. IR (film) cm^{-1}: 3300, 3200, 3040, 3070, 3090, 2920, 2850. MS (EI) *m/z*: 360 (M^+), 106 (base peak). HRMS (EI) *m/z*: Found 360.2669 (Calcd for $C_{23}H_{36}O_3$ (M^+) 360.2664).

13-[(4*R*)-2-Phenyl-1,3-dioxan-4-yl]tridecanal 5. A solution of **14** (1.4 mmol, 500 mg) and Pd fibroin (50 mg) in AcOEt (14 mL) was stirred at rt for 24 h under H_2 atmosphere (1 atm). The reaction mixture was filtered with celite and was concentrated under reduced pressure. The crude product was purified by column chromatography with silica gel (hexane / AcOEt = 4: 1) to afford 13-[(4*R*)-2-phenyl-1,3-dioxan-4-yl]tridecan-1-ol (490mg, 97%). $[\alpha]_D^{27}$ +16.2 (*c* 0.60, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.50–7.48 (2H, m), 7.37–7.31 (3H, m), 5.50 (1H, s), 4.23 (1H, dd, *J* = 4.0, 11.4 Hz), 3.95 (1H, dt, *J* = 2.6, 12.2 Hz), 3.84–3.77 (1H, m), 3.60 (2H, t, *J* = 6.6 Hz), 1.84–1.73 (1H, m), 1.72–1.62 (1H, m) 1.56–1.43 (4H, m), 1.39–1.24 (20H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 138.9, 128.6, 128.2, 126.0, 101.1, 77.3, 67.1, 63.1, 36.0, 31.3, 29.6, 29.4, 25.7, 25.0. IR (film) cm^{-1}: 3420, 3360, 2920, 2850. MS (EI) *m/z*: 362 (M^+, base peak). HRMS (EI) *m/z*: Found 362.2836 (Calcd for $C_{23}H_{38}O_3$ (M^+) 362.2821). To a solution of 13-[(4*R*)-2-phenyl-1,3-dioxan-4-yl]tridecan-1-ol (1.4 mmol, 500 mg) in DCM (30 mL) was added pyridine (1.9 mmol, 0.2 mL) and DMP (1.8 mmol, 760 mg) at rt under Ar atmosphere. After being stirred for 1 h, the reaction mixture was quenched with aqueous sodium carbonate and sodium thiosulfate and extracted with $CHCl_3$. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtrated, and evaporated under reduced pressure. The crude product was purified by column chromatography with silica gel (hexane / AcOEt = 6: 1) to afford **5** (440 mg, 89%). $[\alpha]_D^{27}$ +17.3 (*c* 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.74 (1H, s), 7.50–7.47 (2H, m), 7.37–7.25 (3H, m), 5.49 (1H, s), 4.25 (1H, dd, *J* = 4.4, 11.4 Hz), 3.94 (1H, dd, *J* = 2.5, 12.1 Hz), 3.83–3.77 (1H, m), 2.40 (2H, dt, *J* = 1.3, 7.4 Hz), 1.83–1.73 (1H, m), 1.71–1.52 (3H, m), 1.51–1.41 (2H, m), 1.38–1.23 (18H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 202.6, 138.8, 128.3, 127.9, 125.8, 100.9, 77.1, 66.9, 43.7, 35.9, 31.2, 29.4, 29.2, 28.9, 24.8, 21.8. IR (film) cm^{-1}: 3420, 2930, 2860, 2720, 1720. MS (ESI+) *m/z*: 383 (M+Na^+). HRMS (ESI+) *m/z*: Found 383.2562 (Calcd for $C_{23}H_{36}NaO_3$ (M+Na^+) 383.2580).

***tert*-Butyldiphenyl[(2*S*,4*E*,8*Z*)-21-{(4*R*)-2-phenyl-1,3-dioxan-4-yl}henicosa-4,8-dien-2-yloxy]silane**

(23*S*)-15. To a solution of (*S*)-**4** (1.3 mmol, 920 mg) in THF (30 mL) was added *n*-BuLi (1.6 M in THF, 1.6 mmol, 1 mL) dropwise at –50 °C under N_2 atmosphere. After being stirred for 1 h at –50 °C, a solution of **5** (1.0 mmol, 360 mg) in THF (10 mL) was added dropwise at –50 °C. The reaction mixture was stirred for additional 2 h at rt, quenched with H_2O, and extracted with Et_2O. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtrated, and evaporated under reduced pressure. The crude product was purified by column chromatography with silica gel (hexane / AcOEt = 15: 1) to afford (23*S*)-**15** (660 mg, 93%). $[\alpha]_D^{23}$ –3.60 (*c* 0.30, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.69–7.66 (4H, m), 7.51–7.48 (2H, m), 7.43–7.31 (9H, m), 5.50 (1H, s), 5.36–5.33 (4H, m), 4.26 (1H, ddd, *J* = 1.2, 5.0, 11.3 Hz), 3.95 (1H, ddd, *J* = 2.6, 11.5, 12.2 Hz), 3.86–3.78 (2H, m), 2.19–1.96 (8H, m), 1.87–1.66 (2H, m), 1.57–1.22 (24H, m), 1.05–1.03 (12H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 138.9, 135.9, 134.8, 134.5, 132.3, 130.2, 129.4 129.1, 128.6, 128.2, 127.4, 126.7, 126.0, 101.1, 77.3, 69.6, 67.1, 42.8, 36.0, 32.8, 31.3, 29.7, 29.6, 29.5, 29.3, 27.6, 27.2, 27.0, 25.0, 22.9, 19.2. IR (film) cm^{-1}: 3070, 2930, 2855, 1560, 1530. MS (EI) *m/z*: 708 (M^+), 190 (base peak). HRMS (EI) *m/z*: Found 708.4940 (Calcd for $C_{47}H_{68}O_3Si$ (M^+) 708.4938). (23*R*)-**15** 69%, $[\alpha]_D^{20}$ +20.2 (*c* 1.11, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.69–7.66 (4H, m), 7.51–7.48 (2H, m), 7.43–7.31 (9H, m), 5.50 (1H, s), 5.36–5.33 (4H, m), 4.26 (1H, ddd, *J* = 1.3, 4.9, 11.3 Hz), 3.95 (1H, dd, *J* = 2.3, 11.9 Hz), 3.88–3.78 (2H, m), 2.28–1.92 (8H, m), 1.85–1.74 (1H, m), 1.71–1.65 (1H, m), 1.56–1.43 (3H, m), 1.39–1.24 (20H, m), 1.05–1.03 (12H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 138.9, 135.9, 135.8, 134.5, 132.3, 130.2, 129.4, 129.1, 128.6, 128.2, 127.4, 126.7, 126.0, 101.1, 77.0, 69.6, 67.1, 42.8, 36.0, 32.8, 32.6, 32.5, 31.6, 31.3, 29.7, 29.6, 29.3, 29.2, 27.3, 27.2, 27.0, 25.0, 22.9, 22.6, 19.2, 14.1. IR (film) cm^{-1}: 3070, 3040, 3000, 2960, 2920, 2850, 1590. MS (ESI+) *m/z*: 731 (M+Na^+). HRMS (ESI+) *m/z*: Found 731.4835 (Calcd for $C_{47}H_{68}NaO_3Si$ (M+Na^+) 731.4835).

(3*R*,16*Z*,20*E*,23*S*)-3-Benzyloxy-23-(*tert*-butyldiphenylsilyloxy)tetracosa-16,20-dien-1-ol (23*S*)-16. To a solution of (23*S*)-**15** (0.5 mmol, 330 mg) in toluene (30 mL) was added DIBAL (1.0 M in hexane, 7.1 mmol, 7.1 mL) dropwise at –40 °C under N_2 atmosphere. After being stirred for 6 h at –40 °C, the reaction mixture was quenched with H_2O and extracted with Et_2O. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtrated, and evaporated under reduced pressure. The crude product was purified by column chromatography with silica gel (hexane / AcOEt = 4: 1) to afford (23*S*)-**16** (310 mg, 94%). $[\alpha]_D^{26}$ –25.4 (*c* 1.20, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.70–7.66 (4H, m), 7.43–7.25 (11H, m), 5.36–5.33 (4H, m), 4.60 (1H, d, *J* = 11.4 Hz), 4.48 (1H, d, *J* = 11.4 Hz), 3.85–3.73 (3H, m), 3.66–3.61 (1H, m), 2.42 (1H, br), 2.15–1.97 (8H, m), 1.83–1.53 (4H, m), 1.38–1.24 (18H, m), 1.05–1.03 (12H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 138.4, 135.9, 135.8, 134.8, 134.5, 132.3, 130.2, 129.4, 129.4, 128.4, 127.8, 127.7, 127.4, 126.7, 78.7, 70.9, 69.9, 60.8, 42.7, 35.8, 33.4, 32.8, 29.8, 29.6, 29.3, 27.3, 27.2, 27.0, 25.1, 22.9, 19.2. IR (film) cm^{-1}: 3400, 3070, 2930, 2860, 1750, 1560, 1530. MS (ESI+) *m/z*: 711

($M+H^+$), 387 (base peak). HRMS (ESI+) *m/z*: Found 711.5193 (Calcd for $C_{47}H_{71}O_3Si$ ($M+H^+$) 711.5173). (23*R*)-**16** 83%, $[\alpha]_D^{27}$ –2.2 (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.70–7.66 (4H, m), 7.43–7.27 (11H, m), 5.39–5.31 (4H, m), 4.60 (1H, d, *J* = 11.5 Hz), 4.48 (1H, d, *J* = 11.5 Hz), 3.88–3.70 (3H, m), 3.67–3.61 (1H, m), 2.42 (1H, br), 2.20–1.93 (8H, m), 1.86–1.49 (4H,m), 1.37–1.26 (18H, m), 1.05–1.03 (12H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 138.4, 135.9, 135.8, 134.8, 134.5, 132.3, 130.2, 129.4, 129.1, 128.4, 127.8, 127.7, 127.4, 126.7, 78.7, 70.9, 69.6, 42.7, 35,8, 33.4, 32.8, 29.8, 29.7, 29.6, 29.3, 27.3, 27.2, 27.0, 25.1, 22.9, 19.2. IR (film) cm^{-1}: 3450, 3070, 2930, 2860, 1650. MS (ESI+) *m/z*: 733 ($M+Na^+$), 387 (base peak). HRMS (ESI+) *m/z*: Found 733.4985 (Calcd for $C_{47}H_{70}NaO_3Si$ ($M+Na^+$) 733.4992).

(3*R*,16*Z*,20*E*,23*S*)-3-Benzyloxy-23-(*tert*-butyldiphenylsilyloxy)tetracosa-16,20-dienoic acid (23*S*)-17. To a solution of oxalyl chloride (1.9 mmol, 0.2 mL) in DCM (3 mL) was added a solution of DMSO (3.9 mmol, 0.3 mL) in DCM (3 mL) dropwise at –78 °C under N_2 atmosphere. After being stirred for 30 min, the resulting mixture was added (23*S*)-**16** (0.4 mmol, 310 mg) in DCM (3 mL) and stirred for 1 h at –78 °C. Et_3N (2.2 mmol, 220 mg) was added and the whole mixture was warmed to rt, stirred for additional 30 min, quenched with H_2O, and extracted with $CHCl_3$. The combined organic layer was dried over anhydrous sodium sulfate, filtrated, and evaporated under reduced pressure. The residue was dissolved in THF (15 mL) and poured into a solution of $NaClO_2$ and sulfamic acid in water. After being stirred for 15 min, the reaction mixture was quenched with saturated aqueous sodium hydrogen carbonate and extracted with AcOEt. The combined organic layer was dried over anhydrous sodium sulfate, filtrated, and evaporated under reduced pressure. The crude product was purified by column chromatography with silica gel (hexane / AcOEt = 4: 1) to afford (23*S*)-**17** (270 mg, 85%). $[\alpha]_D^{34}$ –61.7 (*c* 1.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.70–7.66 (4H, m), 7.43–7.26 (11H, m), 5.39–5.30 (4H, m), 4.57 (2H, s), 3.88–3.82 (2H, m), 2.62 (1H, dd, *J* = 6.9, 15.5 Hz), 2.58 (1H, dd, *J* = 5.2, 15.5 Hz), 2.19–1.97 (8H, m), 1.70–1.51 (2H, m), 1.38–1.03 (20H, m), 0.89–0.88 (12H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 175.8, 138.0, 135.9, 135.9, 134.8, 134.5, 132.3, 130.2, 129.4, 129.1, 128.4, 127.8, 127.7, 127.4, 126.7, 75.7, 71.5, 69.6, 42.8, 39.3, 34.1, 32.8, 29.7, 29.6, 29.3, 27.3, 27.2, 27.0, 25.1, 22.9, 19.2. IR (film) cm^{-1}: 2930, 2855, 1710, 1560, 1520. MS (ESI+) *m/z*: 725 ($M+H^+$), 509 (base peak). HRMS (ESI+) *m/z*: Found 725.5000 (Calcd for $C_{47}H_{69}O_4Si$ ($M+H^+$) 725.4965). (23*R*)-**17** 76%, $[\alpha]_D^{29}$ +10.6 (*c* 0.8, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.70–7.66 (4H, m), 7.43–7.26 (11H, m), 5.39–5.30 (4H, m), 4.57 (2H, s), 3.88–3.82 (2H, m), 2.62 (1H, dd, *J* = 6.9, 15.5 Hz), 2.58 (1H, dd, *J* = 5.2, 15.5 Hz), 2.19–1.97 (8H, m), 1.70–1.51 (2H, m), 1.38–1.03 (20H, m), 0.89–0.88 (12H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 177.2, 138.2, 135.8, 134.7, 132.2, 130.2, 129.4, 129.3, 129.0, 128.3, 127.8, 127.6, 127.4, 127.3, 126.7, 75.7, 71.5, 69.6, 42.7, 396, 34.2, 32.7, 29.7, 29.6, 29.5, 29.3, 27.4, 27.2, 27.1, 25.1, 22.8, 19.2. IR (film) cm^{-1}: 2920, 2860, 1710. MS (ESI+) *m/z*: 747 ($M+Na^+$), 509 (base peak). HRMS (ESI+) *m/z*: Found 747.4831 (Calcd for $C_{47}H_{68}NaO_4Si$ ($M+Na^+$) 747.4785).

(3*R*,16*Z*,20*E*,23*S*)-3-Benzyloxy-23-hydroxytetracosa-16,20-dienoic acid (23*S*)-3. To a solution of (23*S*)-**17** (1.1 mmol, 820 mg) in THF (30 mL) was added TBAF (1.0 M in THF, 10 mmol, 10 mL) dropwise at 0 °C under Ar atmosphere. After being stirred for 48 h, the reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with AcOEt. The combined organic layer was dried over anhydrous sodium sulfate, filtrated, and evaporated under reduced pressure. The crude product was purified by column chromatography with silica gel (hexane / AcOEt = 4: 1) to afford (23*S*)-**3** (440 mg, 79%). $[\alpha]_D^{26}$ –0.30 (*c* 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.34–7.28 (5H, m), 5.57–5.30 (4H, m), 4.57 (2H, s), 3.87 (1H, quin, *J* = 6.0 Hz), 3.83–3.75 (1H, m), 2.62 (2H, dd, *J* = 6.9, 15.5 Hz), 2.56 (2H, dd, *J* = 5.2, 15.5 Hz), 2.23–1.96 (8H, m), 1.71–1.52 (2H, m), 1.28–1.26 (20H, m), 1.19 (3H, d, *J* = 6.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 175.0, 138.3, 133.8, 130.4, 128.8, 128.2, 127.7, 127.5, 126.2, 75.9, 71.4, 67.8, 67.1, 42.4, 39.5, 34.2, 32.6, 29.6, 29.5, 29.2, 29.0, 27.2, 27.0, 25.5, 25.1, 22.4. IR (film) cm^{-1}: 3520, 2930, 2860, 1650. MS (ESI+) *m/z*: 509 (M+Na$^+$), 468 (base peak). HRMS (ESI+) *m/z*: Found 509.3612 (Calcd for $C_{31}H_{50}NaO_4$ (M+Na$^+$) 509.3607). (23*R*)-**3** 66%, $[\alpha]_D^{26}$ –2.20 (*c* 0.50, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.38–7.27 (5H, m), 5.59–5.51 (1H, m), 5.46–5.30 (3H, m), 4.57 (2H, s), 3.87 (1H, quin, *J* = 6.1 Hz), 3.81–3.73 (1H, m), 2.63 (2H, dd, *J* = 6.7, 15.8 Hz), 2.56 (2H, dd, *J* = 5.4, 15.8 Hz), 2.24–2.17 (1H, m), 2.14–1.94 (7H, m), 1.71–1.52 (2H, m), 1.43–1.26 (20H, m), 1.19 (3H, d, *J* = 6.3 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 175.1, 137.9, 134.1, 130.5, 128.8, 128.4, 127.8, 126.2, 75.7, 71.5, 67.1, 42.4, 39.1, 32.7, 29.6, 29.5, 29.3, 27.2, 27.0, 25.0, 22.5. IR (film) cm^{-1}: 3420, 2920, 2860, 1710. MS (ESI+) *m/z*: 509 (M+Na$^+$), 468 (base peak). HRMS (ESI+) *m/z*: Found 509.3599 (Calcd for $C_{31}H_{50}NaO_4$ (M+Na$^+$) 509.3607).

(3*R*,16*Z*,20*E*,23*S*)-3-Benzyloxytetracosa-16,20-dien-23-olide (23*S*)-18. To a solution of MNBA (0.01 mmol, 33 mg) and DMAP (0.22 mmol, 27 mg) in DCM (33 mL) was added a solution of (23*S*)-**3** (0.07 mmol, 36 mg) in THF (46 mL) with syringe pump for 9 h at rt under N_2 atmosphere. After being stirred for additional 1 h, the reaction mixture was quenched with saturated aqueous sodium hydrogen carbonate and extracted with $CHCl_3$. The combined organic layer was dried over anhydrous sodium sulfate, filtrated, and evaporated under reduced pressure. The crude product was purified by column chromatography with silica gel (hexane / AcOEt = 20: 1) to afford (23*S*)-**18** (27 mg, 79%). $[\alpha]_D^{27}$ –6.39 (*c* 1.20, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.34–7.27 (5H, m), 5.52–5.31 (4H, m), 4.98–4.90 (1H, m), 4.56 (1H, d, *J* = 11.4 Hz), 4.52 (1H, d, *J* = 11.4 Hz), 3.89–3.83 (1H, m), 2.65 (1H, dd, *J* = 5.9, 14.8 Hz), 2.43 (1H, dd, *J* = 7.0, 14.8 Hz), 2.23 (2H, dt, *J* = 5.5, 6.2 Hz), 2.10–1.99 (6H, m), 1.57 (2H, m), 1.41–1.24 (20H, m), 1.21 (3H, d, *J* = 6.3 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.3, 138.6, 133.4, 130.4, 129.1, 128.3, 127.8, 127.6, 125.2, 76.0, 71.3, 70.6, 39.9, 39.1, 33.9, 32.8, 29.0, 28.6, 28.4, 28.2, 27.3, 26.7, 24.4, 19.5. IR (film) cm^{-1}: 2920, 2860, 1730. MS (EI) *m/z*: 468 (M$^+$), 91 (base peak). HRMS (EI) *m/z*: Found 468.3629 (Calcd for $C_{31}H_{48}O_3$ (M$^+$) 468.3603). (23*R*)-**18** 67%, $[\alpha]_D^{22}$ +5.26 (*c* 1.40, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.34–7.27 (5H, m),

5.48 (1H, dt, *J* = 6.2, 15.3 Hz) 5.40–5.30 (3H, m), 4.97–4.89 (1H, m), 4.58 (1H, d, *J* = 11.5 Hz), 4.51 (1H, d, *J* = 11.5 Hz), 3.86–3.80 (1H, m), 2.65 (1H, dd, *J* = 5.5, 13.9 Hz), 2.44 (1H, dd, *J* = 7.3, 14.2 Hz), 2.24 (2H, sext, *J* = 7.2 Hz), 2.12–1.96 (6H, m), 1.61–1.53 (2H, m), 1.44–1.25 (20H, m), 1.20 (3H, d, *J* = 6.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.9, 138.5, 133.5, 130.4, 129.1, 128.3, 127.7, 127.5, 125.0, 7.58, 71.1, 70.6, 40.1, 39.0, 33.7, 32.7, 29.0, 28.6, 28.5, 28.4, 28.3, 27.2, 26.7, 24.2, 19.3. IR (film) cm^{-1}: 2920, 2860, 1730. MS (ESI+) *m/z*: 468 (M+Na$^+$). HRMS (ESI+) *m/z*: Found 491.3500 (Calcd for $C_{31}H_{47}NaO_3$ (M+Na$^+$) 491.3501).

(3*R*,16*Z*,20*E*,23*S*)-3-Hydroxytetracosa-16,20-dien-23-olide (23*S*)-2. To a solution of (23*S*)-**18** (0.07 mmol, 33 mg) and 2-methyl-2-butene (3.5 mmol, 245 mg) in DCM (15 mL) was added dropwise a solution of $TiCl_4$ (0.35 mmol, 60 mg) in DCM (1 mL) at 0 °C under Ar atmosphere. After being stirred for 15 min, the reaction mixture was quenched with H_2O and extracted with $CHCl_3$. The combined organic layer was dried over anhydrous sodium sulfate, filtrated, and evaporated under reduced pressure. The crude product was purified by column chromatography with silica gel (hexane / AcOEt = 4: 1) to afford (23*S*)-**2** (28 mg, 99%). $[\alpha]_D^{30}$ –28.1 (*c* 0.70, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.54–5.31 (4H, m), 5.04–4.96 (1H, m), 3.98–3.95 (1H, m), 2.87 (1H, br), 2.49 (1H, dd, *J* = 3.6, 16.0 Hz), 2.40 (1H, dd, *J* = 8.4, 16.0 Hz), 2.33–2.19 (2H, m), 2.10–2.00 (6H, m), 1.59–1.28 (22H, m), 1.24 (3H, d, *J* = 6.3 Hz). ^{13}C NMR (100MHz, $CDCl_3$) δ: 172.4, 133.5, 130.3, 128.9, 125.1, 70.7, 67.9, 41.5, 39.0, 35.8, 32.7, 29.2, 28.4, 28.3, 28.1, 28.03, 28.0, 27.8, 27.1, 26.9, 24.5, 19.6. IR (film) cm^{-1}: 3440, 2920, 2860, 1720, 1650. MS (ESI+) *m/z*: 379 (M+H$^+$), 401 (base peak, M+Na$^+$). HRMS (ESI+) *m/z*: Found 379.3212 (Calcd for $C_{24}H_{43}O_3$ (M+H$^+$) 379.3210). (23*R*)-**2** 83%, $[\alpha]_D^{24}$ +10.8 (*c* 0.87, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.50 (1H, dt, *J* = 6.0, 15.3 Hz), 5.42–5.32 (3H, m), 5.04–4.96 (1H, m), 3.95–3.94 (1H, m), 2.91 (1H, br), 2.51 (1H, dd, *J* = 4.4, 15.8 Hz), 2.43 (1H, dd, *J* = 7.5, 15.8 Hz), 2.35–2.19 (2H, m), 2.13–1.97 (6H, m), 1.55–1.28 (22H, m), 1.24 (3H, d, *J* = 6.3 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 172.3, 133.7, 130.6, 129.0, 124.9, 70.8, 68.2, 41.2, 39.0, 36.0, 33.7, 29.1, 28.6, 28.4, 28.3, 28.1, 28.0, 27.9, 27.8, 27.1, 26.9, 24.5, 19.6. IR (film) cm^{-1}: 3440, 2920, 2860, 1730. MS (ESI+) *m/z*: 401 (base peak, M+Na$^+$). HRMS (ESI+) *m/z*: Found 401.3041 (Calcd for $C_{24}H_{42}NaO_3$ (M+Na$^+$) 401.3032).

(3*R*,16*Z*,20*E*,23*S*)-Eushearilide (23*S*)-1 To a solution of (23*S*)-**2** (0.1 mmol, 40 mg) in toluene (1 mL) was added a solution of 2-chloro-2-oxo-1,3,2- dioxaphosphorane (5.3 mmol, 750 mg) in toluene (1 mL) at 0 °C under N_2 atmosphere. After being stirred for 15 min, Et_3N (2.1 mmol, 210 mg) was added to the reaction mixture, stirred for additional 18 h, quenched with H_2O, and extracted with AcOEt. The combined organic layer was dried over anhydrous sodium sulfate, filtrated, and evaporated under reduced pressure. The residue was dissolved in a (2 mL) and liquid Me_3N (2 mL) was added. After the reaction mixture was stirred for 18 h at 70 °C with sealed tube, and evaporated under reduced pressure. The residue was filtered with

amino silica gel ($CHCl_3$ / hexane = 5: 1 to $CHCl_3$ / MeOH = 3: 1) and purified by column chromatography with Sephadex^{TM} LH-20 to afford (23*S*)-**1** (26 mg, 52%). $[\alpha]_D$ –12.0 (*c* 0.34, MeOH). ^{1}H NMR (400 MHz, CD_3OD) δ: 5.50 (1H, dt, *J* = 6.5, 15.2 Hz), 5.42–5.31 (3H, m), 4.92–4.85 (1H, m), 4.58–4.49 (1H, m), 4.29–4.23 (2H, m), 3.64–3.61 (2H, m), 3.22 (9H, s), 2.82 (1H, dd, *J* = 4.7, 15.0 Hz), 2.51 (1H, dd, *J* = 8.3, 15.0 Hz), 2.31–2.20 (2H, m), 2.14–1.98 (6H, m), 1.68–1.62 (2H, m), 1.43–1.28 (20H, m), 1.20 (3H, d, *J* = 6.3 Hz). ^{13}C NMR (100 MHz, CD_3OD) δ: 172.0, 134.7, 131.3, 130.2, 126.5, 74.1 (d, *J* = 6.0 Hz), 72.0, 67.6, 60.3 (d, *J* = 5.0 Hz), 54.7, 41.6 (d, *J* = 3.3 Hz), 40.2, 36.1 (d, *J* = 5.1 Hz), 33.9, 30.0, 29.8, 29.7, 29.6, 29.4, 29.2, 28.4, 27.5, 25.4, 19.8. IR (film) cm^{-1}: 3380, 2920, 2860, 1720, 1650. MS (ESI+) *m/z*: 544 ($M+H^+$), 304 (base peak). HRMS (ESI+) *m/z*: Found 544.3793 (Calcd for $C_{29}H_{55}NO_6P$ ($M+H^+$) 544.3767). (23*R*)-**1** 35%, $[\alpha]_D^{21}$ –1.79 (*c* 0.39, MeOH). ^{1}H NMR (400 MHz, CD_3OD) δ: 5.56–5.47 (1H, m), 5.43–5.31 (3H, m), 4.92–4.86 (1H, m), 4.58–4.50 (1H, m), 4.28–4.22 (2H, m), 3.64–3.61 (2H, m), 3.21 (9H, s), 2.82 (1H, dd, *J* = 4.6, 14.4 Hz), 2.53 (1H, dd, *J* = 8.5, 14.4 Hz), 2.34–2.19 (2H, m), 2.15–1.98 (6H, m), 1.68–1.61 (2H, m), 1.50–1.40 (20H, m), 1.20 (3H, d, *J* = 6.3 Hz). ^{13}C NMR (100 MHz, CD_3OD) δ: 171.8, 134.8, 131.3, 130.3, 126.4, 74.1 (d, *J* = 6.0 Hz), 72.3, 67.5, 60.3 (d, *J* = 5.0 Hz), 54.7, 42.1 (d, *J* = 3.3 Hz), 40.1, 36.1 (d, *J* = 5.1 Hz), 33.8, 30.0, 29.9, 29.8, 29.7, 29.4, 29.2, 28.4, 27.5, 25.4, 19.7. IR (film) cm^{-1}: 3380, 2920, 2860, 1720. MS (ESI+) *m/z*: 544 ($M+H^+$), 304 (base peak). HRMS (ESI+) *m/z*: Found 544.3785 (Calcd for $C_{29}H_{55}NO_6P$ ($M+H^+$) 544.3767).

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