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Total Synthesis of Biselyngbyaside

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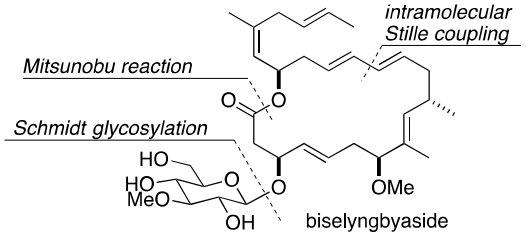


Abstract: The first total synthesis of biselyngbyaside, an 18-membered macrolide glycoside, was achieved. The glycoside bond was introduced using the Schmidt method before construction of the 18-membered ring due to the instability of the conjugated diene and the β-hydroxy ester moiety. The macrolactone ring was constructed using the Mitsunobu reaction followed by intramolecular the Stille coupling reaction.

Introduction:

Biselyngbyaside (**1**, Figure 1), an 18-membered macrolide glycoside, was isolated from the marine cyanobacterium *Lyngya* sp. collected at Okinawa[1]. Biselyngbyaside and its aglycone biselyngbyolide B (**2**)[2] show growth-inhibitory activity against HeLa and HL60 cells. Furthermore, **1** inhibited RANKL-induced osteoclastogenesis and induced apoptosis of mature osteoclasts at a low concentration[3]. Recently, we investigated whether they inhibit the ATPase activities of SERCA1a and 2a, and determined the X-ray crystal structures with SERCA1a[4]. The X-ray crystal structures showed that the 1,3-diene moiety and the side chain of biselyngbyasides play important roles in their interaction with SERCA. In fact, the activities of biselyngbyaside C[2, 5], in which the 1,3-diene moiety is modified, against HeLa cells and SERCA1a are much weaker than those of **1** and **2** (Figure 1). The growth-inhibitory activity may depend on the affinity to SERCAs. However, the role of the sugar moiety and the differences is IC_{50} values and K_i values between biselyngbyaside and biselyngbyolide B have not been clarified. Because of the instability of the 18-membered ring structure of biselyngbyasides, it is difficult to synthesize their artificial analogs using natural products. Therefore, little is known about the structure-activity relationships, especially on the sugar moiety. Synthetic studies of biselyngbyasides have been reported by several groups[6] and total syntheses of biselyngbyolide B were achieved by Goswami's group[7a] and our group[7b]. However, the total synthesis of biselyngbyaside and its analogs with a sugar moiety has not yet been achieved. Herein, we report the first total synthesis of

biselyngbyaside.

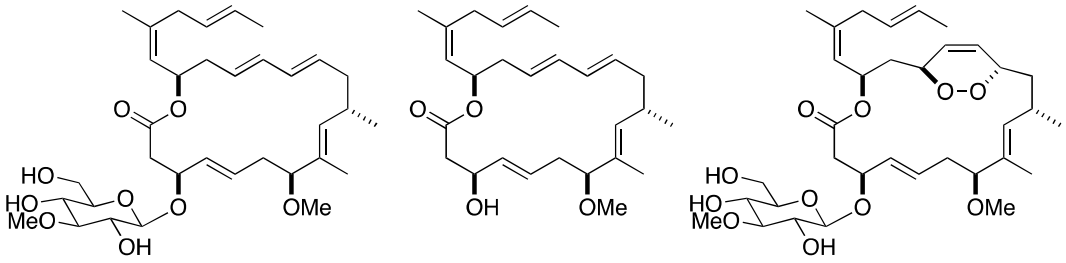


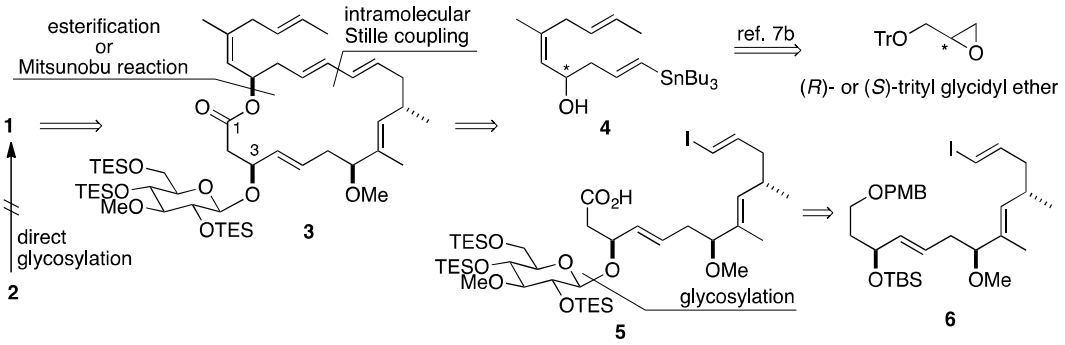
Figure 1. Structures and biological activities of biselyngbyasides. IC_{50} is the growth-inhibitory activities against HeLa cells. K_i is the ATPase-inhibitory activity against SERCA1a.

Result and Discussion:

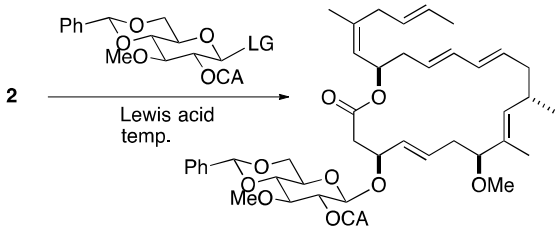
To synthesize biselyngbyaside, we first tried a direct conversion to glycoside from its aglycone biselyngbyolide B. However, even with the use of various conditions[9-12] (see Table 1) for the glycosylation reaction the glycoside bond could not be constructed. First, we employed imidate sugar as a glycosyl donor[9]. No desired products were obtained and the starting material was recovered at low temperature or decomposed at high temperature. Although we tested mild activator (Au catalysts[10] (entry 3 and 4), NIS[11a] (entry 5), NBS[11b-c] (entry 6), Ag catalysts[12] (entry 7 to 9)), no desired compounds were detected. Possible explanations for why direct glycosylation did not work include the sensitivity of the macrolactone ring system under the reaction conditions and the low reactivity of the C3 hydroxy group. Especially, intramolecular hydrogen bonding between the C3 hydroxy group and the C1 carbonyl oxygen interfere with functionalization of alcohol[13].

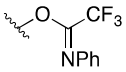
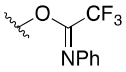
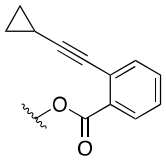
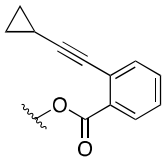
Based on the results described above, our retrosynthetic analysis is shown in Scheme 1. The macrolactone ring was planned to be constructed using an intramolecular Stille coupling reaction. The cyclization precursor **3** would be obtained from stannane **4**[7b] and carboxylic acid **5**. Their two components could be connected *via* esterification or a Mitsunobu reaction. The stannane **4** was derived from the chiral glycidol derivative[7b]. The glycoside moiety could be introduced before the connection of stannane and vinyl iodide.

Scheme 1. Retrosynthetic Analysis of Biselyngbyaside



Tabale 1. Glycosylation Reaction of Biselyngbyolide B



entry	Leaving group	Lewis acid	Temp	results
1[9]		BF_3•OEt_2	–78 ˚C	no reaction
2[9]		BF_3•OEt_2	–40 ˚C	decomposed
3[10]		Ph_3AuNTf_2	–15 ˚C	no reaction
4[10]		Ph_3AuNTf_2	rt	decomposed
5[11a]	SPh	NIS/AgOTf	–15 ˚C	decomposed
6[11b-c]	SPh	NBS	rt	decomposed
7[12a]	F	$AgClO_4/SnCl_2$	0 ˚C	decomposed
8[12b-c]	F	$AgClO_4/Cp_2HfCl_2$	–15 ˚C	no reaction
9[12b-c]	F	$AgOTf/Cp_2HfCl_2$	–15 ˚C	no reaction

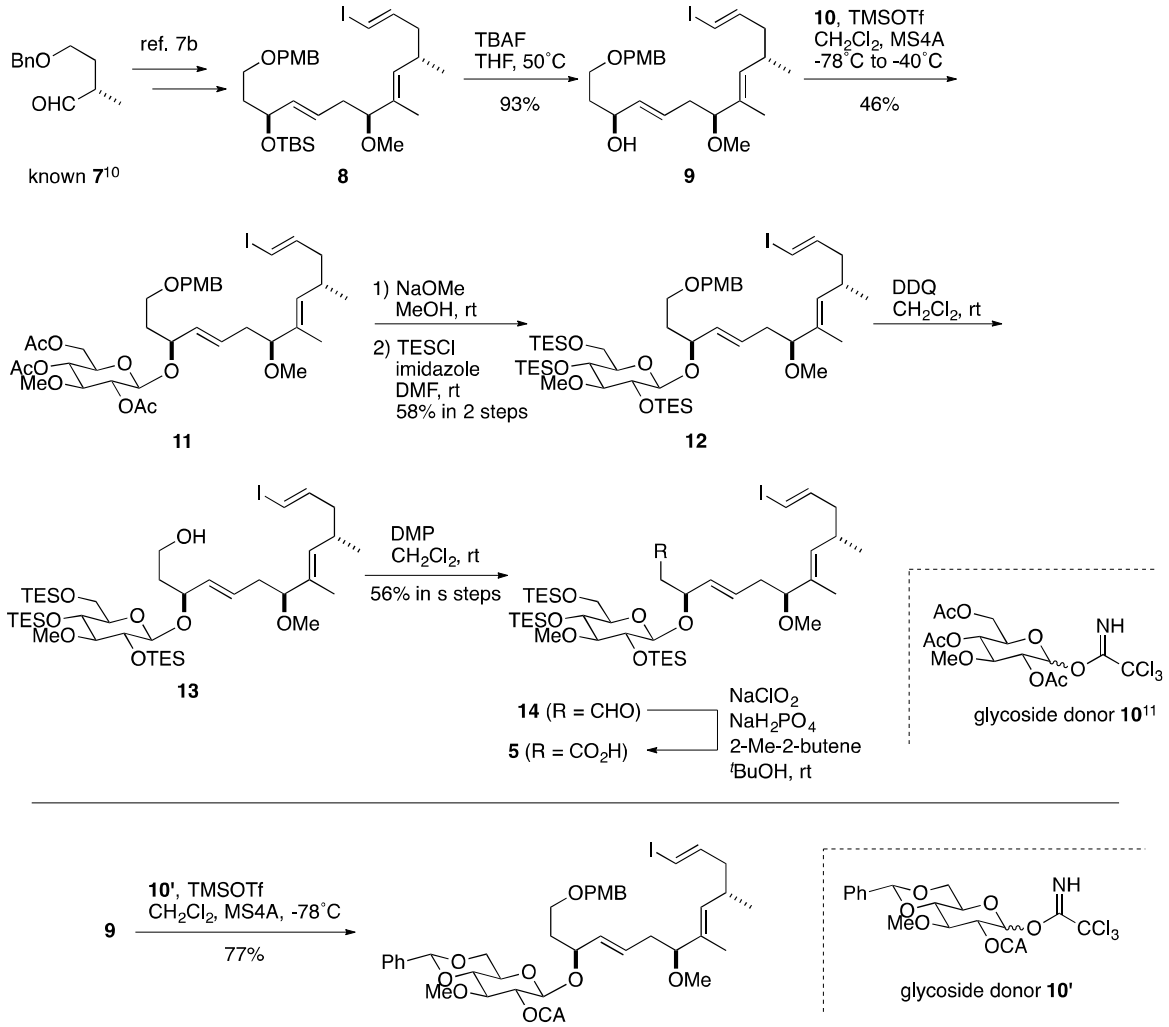
All reactions were performed with activated MS4A. LG: leaving group, CA: chloroacetyl

The synthesis of carboxylic acid **5** was started from known aldehyde **7**[14], which was synthesized from

1,3-propanediol in 7 steps (Scheme 2). Aldehyde **7** was converted to vinyl iodide **8** in 14 steps[7b]. The TBS group was removed using tetrabutylammonium fluoride (93%) to obtain the alcohol **9**. Next, we tried the glycosylation reaction. At first, we used glycoside donor **10'**, which was protected by chloroacetyl group (C2 position) and benzylidene acetal (C4 and C6 position), and the desired glycoside was obtained in good yield (77%). Glycosylation of alcohol **9** was much faster than that of **2** because of the effect of the β-carbonyl group (see Tabale 1 entry 1). Unfortunately, the chloroacetyl group could not be removed at the last stage. Thus, we selected to change the protecting group after glycosylation reaction.

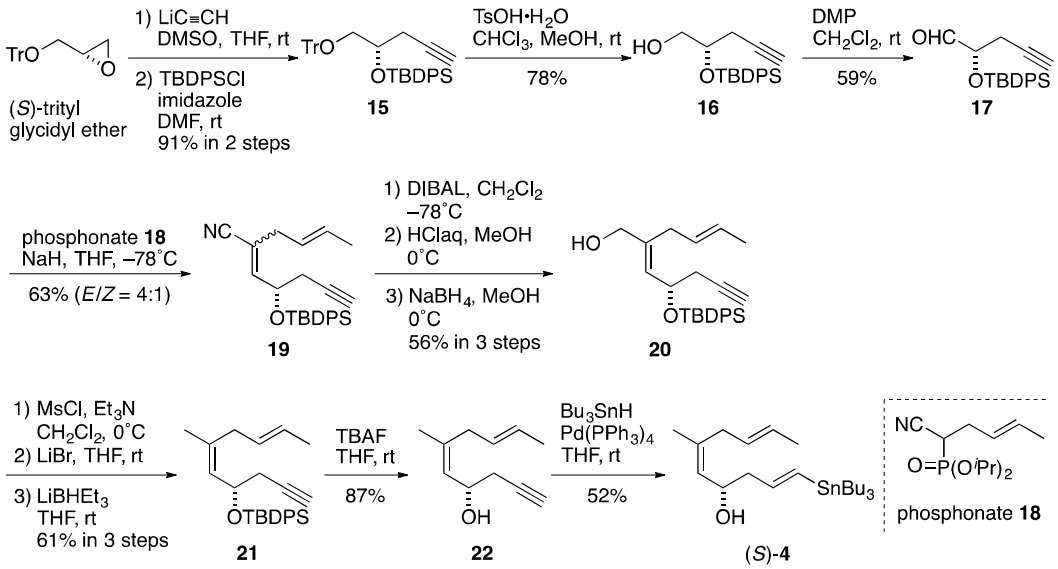
The alcohol **9** and glycoside donor **10**[15] were connected using Schmidt conditions[8] (46%). In this glycosylation reaction, only β-glycoside was obtained due to the effect of the neighboring acetyl group, and the stereochemistry of the anomeric carbon was determined by the coupling constant of the anomer proton ($J_{1\text{-}2}$ = 7.8 Hz). At this stage, the acetyl protecting groups on the sugar moiety should be exchanged with TES groups, which can be removed under mild conditions in the last stage of synthesis. So, the acetyl groups were removed by methanolysis and the resulting triol was converted to TES ether **12** (58% in 2 steps). The PMB group was cleaved by DDQ and the primary alcohol **13** was oxidized in two steps, using Dess-Martin periodinane[16] (56% in 2 steps) and Pinnick conditions to give carboxylic acid **5**.

Scheme 2. Synthesis of Carboxylic Acid **5**



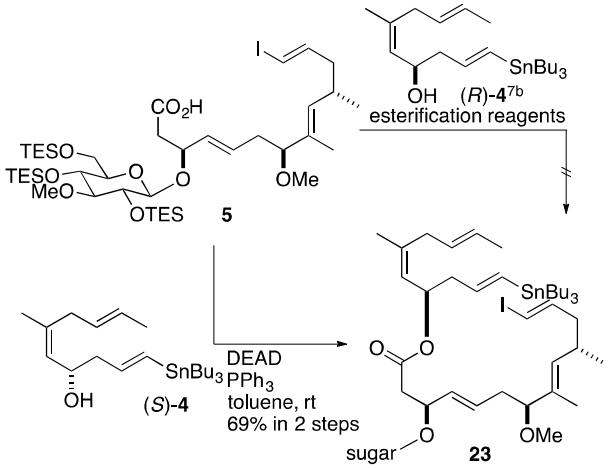
The synthetic route to stannane (*S*)-**4** is shown in Scheme 3. Previously, we synthesized stannane (*R*)-**4** from (*R*)-trityl glycidyl ether[7b]. Therefore, we prepared (*S*)-**4** from (*S*)-trityl glycigyl ether using same method. The commercially available glycidol derivative was treated with lithium acetylide followed by protection of the secondary alcohol to give TBDPS ether **15** (91% in 2 steps). The trityl group was removed (78%) and the obtained alcohol **16** was oxidized by Dess-Martin periodinane to synthesize aldehyde **17** (59%). Next, the side chain moiety was introduced using the corresponding phosphonate **18** with sodium hydride (63%) to afford alkene **19** as an inseparable mixture of isomers (*E*/*Z* = 4:1). The nitrile group in **19** was converted by a three-step procedure: i) DIBAL reduction, ii) hydrolysis in the presence of acid catalyst, and iii) sodium borohydride reduction to give alcohol **20**. In our previous study[7b], partial isomerization of the olefin occurred, but an examination of the reaction conditions greatly improved the results without isomerization of the olefin. The undesired isomer could be completely removed in this stage. Deoxygenation of the alcohol **20** gave good results in the reaction with methanesulfonyl chloride, lithium bromide and lithium triethyl borohydride (61% in 3 steps) to provide **21**. Finally, the TBDPS group in **21** was removed by tetrabutylammonium fluoride (87%) and the hydrostannation of **22** using tributyltin hydride with palladium catalyst gave (*S*)-**4**.

Scheme 3. Synthesis of Stannane **4**



To connect the two components [carboxylic acid **5** and stannane (*R*)-**4**[7b] (Scheme 4)], we tried the esterification reaction. In the synthesis of biselyngbyolide B[7b], Shiina esterification[17] proceeded smoothly and the corresponding ester was obtained in good yield. However, with the use of carboxylic acid **5** with a sugar moiety, the desired ester could not be obtained at all. Although we tried various conditions for esterification (using Yamaguchi reagent, EDCI or CDI as a condensation reagent, and DMAP, DMAPO or DMAP•HCl as a catalyst), only the starting material was recovered. Therefore, we selected the Mitsunobu reaction[18] between stannane (*S*)-**4** and carboxylic acid **5** to obtain ester **23**. As a result, the Mitsunobu reaction proceeded smoothly under the usual reaction conditions using diethyl azodicarboxylate with triphenylphosphine (69% in 2 steps).

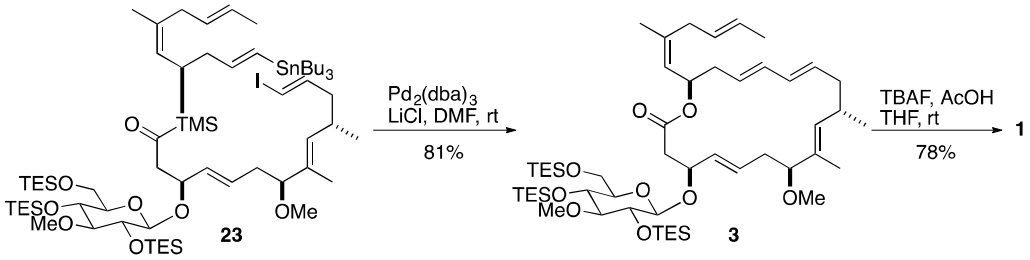
Scheme 4. Connection of carboxylic acid **5** and stannane **4**



Finally, the 18-membered ring structure was constructed using an intramolecular Stille coupling reaction[19], similar to the synthesis of biselyngbyolide B, to obtain TES-protected biselyngbyaside **3** (81%)

(Scheme 5). Three TES groups were cleaved by tetrabutylammonium fluoride in the presence of acetic acid to provide biselyngbyaside (**1**) (78%). The spectroscopic data (^{1}H and ^{13}C NMR, HRMS) and optical rotation for the synthetic biselyngbyaside were fully consistent with those of the natural product[1].

Scheme 5. Completion of the Synthesis



We next investigated the bioactivities of the synthetic compounds (Table 1). Synthetic biselyngbyaside (**1**) exhibited growth-inhibitory activity against HeLa cells (IC_{50} 0.72 μM). In contrast, the protected biselyngbyaside **3** completely lost bioactivity (IC_{50} >30 μM). The results showed that the bulky TES groups lowered the affinity with SERCA. This result was supported by a docking simulation study using the Glide program[20]. The protected compounds **3** did not provide any docking poses using SERCA1a as a template (PDB ID: 4YCM[4]).

Table 1. Bioactivities of Synthetic Compounds

compounds	IC_{50} values (HeLa)
natural **1** [4]	2.5 μM
synthetic **1**	0.63 ± 0.13 μM
3	> 30 μM

Conclusion:

In conclusion, we achieved the first total synthesis of biselyngbyaside using a Schmidt glycosylation reaction in the early stage followed by the Mitsunobu reaction and the intramolecular Stille coupling reaction. In addition, we found that biselyngbyaside with protected sugar did not inhibit the growth of HeLa cells. The results showed that the sugar moiety also plays important roles in bioactivity.

Experimental Section:

General Information:

Chemicals and solvent were the best grade available and were used as received from commercial sources. Optical rotations were measured with a JASCO DIP-1000 polarimeter. ^{1}H NMR spectra were recorded on a JEOL JNM-AL400 (400 MHz), a JEOL JNM-A400 (400 MHz) or a JEOL JNM-ECX400 (400 MHz) instrument. Chemical shifts are reported δ values in parts per million relative to the residual solvent signal ($CHCl_3$: δ = 7.26 ppm; CD_3OD: δ = 3.31 ppm) and coupling constants are in hertz (Hz). The following abbreviations are used for spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and

br = broad. ^{13}C NMR spectra were recorded on a JEOL JNM-AL400 (100 MHz), a JEOL JNM-A400 (100 MHz) or a JEOL JNM-ECX400 (100 MHz) instruments using $CDCl_3$ or CD_3OD as a solvent. Chemical shifts are reported in parts per million from the solvent signal ($CDCl_3$:77.16 ppm; CD_3OD: 49.00 ppm). IR spectra were recorded on a recorded on a JASCOFT/IR-4200 instrument and reported in wavenumbers (cm^{-1}). High-resolution mass spectra were recorded by electrospray ionization (ESI) using time-of-flight (TOF) on a LCT premier EX spectrometer (Waters). Both TLC analysis and preparative TLC were conducted on E. Merck precoated silica gel 60 F254. Wako gel 60N and Nacalai Tesque silica gel 60 were used for column chromatography unless otherwise noted. Organic solvents for moisture-sensitive reactions were distilled from the following drying agents: THF (Na-benzophenone ketyl), toluene (Na), CH_2Cl_2 (P_2O_5), MeOH (calcium hydride). Anhydrous DMF was used as obtained from commercial supply. All moisture-sensitive reactions were performed under an atmosphere of nitrogen, and the starting materials were azeotropically dried with benzene befor use.

Synthesis of Biselyngbaside:

(3S,4E,7S,8E,10S,12E)-13-iodo-7-methoxy-1-((4-methoxybenzyl)oxy)-8,10-dimethyltrideca-4,8,12-trien-3-ol (**9**): To a solution of TBS ether **8** (27.4 mg, 43.6 μmol) in THF (0.3 mL) was added 1 M solution of TBAF (0.1 mL, 0.1 mmol). The reaction was stirred at 50 ˚C for 14 h, then quenched by addition of saturated aqueous NH_4Cl and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography on SiO_2 (hexane/EtOAc 3:1 to 2:1) to give alcohol **9** (20.8 mg, 40.4 μmol, 93%) as a colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.3 Hz, 2H), 6.87 (d, *J* = 8.3 Hz, 2H), 6.42 (dt, *J* = 14.7, 7.3 Hz, 1H), 6.00 (d, *J* = 14.7 Hz, 1H), 5.61-5.50 (m, 2H), 5.10 (d, *J* = 9.3 Hz, 1H), 4.44 (s, 2H), 4.30 (m, 1H), 3.80 (s, 3H), 3.66 (m, 1H), 3.61 (m, 1H), 3.43 (t, *J* = 6.8 Hz, 1H), 3.15 (s, 3H), 2.79 (brs, 1H, OH), 2.51 (m, 1H), 2.34 (m, 1H), 2.18 (m, 1H), 2.03 (m, 1H), 1.97 (m, 1H), 1.83-1.78 (m, 2H), 1.52 (s, 3H), 0.98 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4, 145.1, 134.5, 134.1, 133.4, 130.2, 129.5, 127.4, 114.0, 87.1, 75.6, 73.1, 71.8, 68.4, 55.8, 55.4, 43.6, 36.9, 36.8, 31.9, 20.9, 11.0; IR (neat) 3447, 2922, 2858, 2357, 2341, 1611, 1510, 1457, 1363, 1300, 1246, 1173, 1092, 1035, 950, 820 cm^{-1}; HRMS-ESI: Exact mass calcd for $C_{24}H_{35}INaO_4$ $[M+Na]^+$: 537.1478; found 537.1440; $[\alpha]_D^{24.5}$ +14.5 (c 0.88, $CHCl_3$).

(2R,3R,4S,5R,6R)-2-(acetoxymethyl)-6-(((3S,4E,7S,8E,10S,12E)-13-iodo-7-methoxy-1-((4-methoxybenzyl)oxy)-8,10-dimethyltrideca-4,8,12-trien-3-yl)oxy)-4-methoxytetrahydro-2H-pyran-3,5-diyl diacetate (**11**): To a mixture of alcohol **9** (45.5 mg, 88.4 μmol), imidate **10** (48.6 mg, 105 μmol) and MS4A (339.3 mg) were added CH_2Cl_2 and stirred at room temperature for 30 min, then cooled to –78 ˚C. The solution was added 55 mM solution of TMSOTf (0.15 mL, 8.3 μmol). The reaction was stirred at –78 ˚C for 1 h and at –40 ˚C for 1.5 h, then quenched by addition of Et_3N and filtered. The filtrate was concentrated *in vacuo* and the residue was purified column chromatography on SiO_2 (hexane/EtOAc 3:1 to 2:1) to give glycoside **11** (33.3 mg, 40.8 μmol, 46%) as a colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.8 Hz, 2H) 6.86 (d, *J* = 8.8 Hz, 2H), 6.42

(dt, *J* = 14.2, 7.1 Hz, 1H), 5.98 (d, *J* = 14.2 Hz, 1H), 5.63 (m, 1H), 5.27 (dd, *J* = 8.3 Hz, 15.6 Hz, 1H), 5.11 (d, *J* = 9.8 Hz, 1H), 5.06 (dd, *J* = 9.8 Hz, 9.8 Hz, 1H), 4.98 (dd, J = 7.8, 9.3 Hz, 1H), 4.45 (d, *J* = 7.8 Hz, 1H), 4.40 (d, *J* = 7.8 Hz, 1H), 4.29 (m, 1H), 4.20 (dd, *J* = 4.9, 12.2 Hz, 1H), 4.09 (dd, *J* = 2.4, 12.2 Hz, 1H), 3.80 (s, 3H), 3.55-3.43 (m, 5H), 3.38 (s, 3H), 3.15 (s, 3H), 2.51 (m, 1H), 2.37 (m, 1H), 2.14 (m, 1H), 2.09 (s, 3H), 2.09 (s, 3H), 2.05 (s, 3H), 2.03-1.94 (m, 2H), 1.87 (m, 1H), 1.74 (m, 1H), 1.54 (s, 3H), 0.99 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 170.0, 169.3, 159.2, 144.9, 133.8, 133.7, 131.6, 131.0, 130.9, 129.3, 113.9, 113.8, 97.7, 86.9, 81.5, 76.1, 75.7, 72.8, 72.0, 71.9, 69.1, 66.4, 62.6, 58.4, 55.9, 55.4, 43.6, 37.6, 35.8, 31.8, 21.1, 21.0, 20.9, 20.8; IR (neat) 2953, 2932, 2868, 1750, 1612, 1513, 1456, 1437, 1373, 1302, 1226, 1173, 1155, 1092, 1038, 970, 904, 823, 599 cm^{-1} HRMS-ESI: Exact mass calcd for $C_{37}H_{53}INaO_{12}$ $[M+Na]^+$: 839.2479; found 839.2462; $[\alpha]_D^{24.6}$ +0.1 (c 1.37, $CHCl_3$).

(((2R,3R,4S,5R,6R)-2-(((3S,4E,7S,8E,10S,12E)-13-iodo-7-methoxy-1-((4-methoxybenzyl)oxy)-8,10-dimethyltrideca-4,8,12-trien-3-yl)oxy)-4-methoxy-6-(((triethylsilyl)oxy)methyl)tetrahydro-2H-pyran-3,5-diyl)bis(oxy))bis(triethylsilane) (**12**): To a solution of glycoside **11** (33.3 mg, 40.8 μmol) in MeOH (0.5 mL) was added 2 M solution of NaOMe in MeOH (0.5 mL, 1 mmol) and stirred at room temperature for 12 h, then quenched by addition of DOWEX 50W and filtered. The filtrate was concentrated *in vacuo* to give triol (26.8 mg) as a colorless oil. The solution of triol in DMF (0.3 mL) was added imidazole (48.3 mg, 0.71 mmol) and TESCl (0.05 mL, 0.30 mmol). After stirring at room temperature for 3.5 h, the reaction was quenched by addition of H_2O and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography on SiO_2 (hexane/EtOAc 15:1 to 10:1) to give TES ether **12** (24.3 mg, 23.5 μmol, 58% in 2 steps) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.8 Hz, 2H), 6.86 (d, *J* = 8.8 Hz, 2H), 6.43 (dt, *J* = 14.6, 7.8 Hz, 1H), 5.98 (d, *J* = 14.6 Hz, 1H), 5.58 (dt, *J* = 14.6, 6.8 Hz, 1H), 5.28 (dd, *J* = 8.8, 14.6 Hz, 1H), 5.10 (d, *J* = 9.8 Hz, 1H), 4.41 (s, 2H), 4.29 (dd, *J* = 7.8, 14.1 Hz, 1H), 4.23 (d, *J* = 7.3 Hz, 1H), 3.80 (s, 3H), 3.69 (dd, *J* = 4.9, 11.2 Hz, 1H), 3.52 (s, 3H), 3.52-3.44 (m, 3H), 3.39 (dd, *J* = 5.9, 7.3 Hz, 1H), 3.34 (dd, *J* = 7.8, 7.8 Hz, 1H), 3.15 (s, 3H), 3.06 (m, 1H), 2.93 (dd, *J* = 8.8, 8.8 Hz, 1H), 2.50 (m, 1H), 2.36 (m, 1H), 2.14 (m, 1H), 2.04-1.95 (m, 3H), 1.77 (m, 1H), 1.52 (s, 3H), 0.99-0.93 (m, 27H), 0.67-0.54 (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 145.0, 133.8, 133.7, 132.3, 131.1, 130.9, 129.4, 129.3, 113.8, 98.2, 88.5, 86.9, 77.1, 75.8, 74.4, 72.7, 70.9, 67.3, 62.4, 61.8, 55.8, 55.4, 43.6, 37.3, 35.8, 31.9, 20.7, 11.2, 7.1, 7.0, 5.3, 5.2, 4.7 IR (neat) 2952, 2911, 2875, 2359, 1614, 1540, 1513, 1457, 1417, 1375, 1302, 1246, 1095, 1041, 1006, 971, 852, 815, 741 cm^{-1} HRMS-ESI: Exact mass calcd for $C_{49}H_{89}INaO_9Si_3$ $[M+H]^+$: 1055.4757; found 1055.4751; $[\alpha]_D^{26.8}$ –2.4 (c 1.22, $CHCl_3$)

(3S,4E,7S,8E,10S,12E)-13-iodo-7-methoxy-3-(((2R,3R,4S,5R,6R)-4-methoxy-3,5-bis((triethylsilyl)oxy)-6-(((triethylsilyl)oxy)methyl)tetrahydro-2H-pyran-2-yl)oxy)-8,10-dimethyltrideca-4,8,12-trien-1-ol (**13**): To a solution of TES ether **12** (26.6 mg, 25.7 μmol) in CH_2Cl_2 was added 1 M solution of pH 7 phosphate buffer (1 mL) and DDQ (13.6 mg, 59.9 μmol) and stirred at room temperature for 20 min. The reaction mixture was

added DDQ (13.7 mg, 60.4 μmol) and stirred at room temperature for 1.5 h and added DDQ (28.9 mg, 127 μmol). After stirring at room temperature for 1 h, the reaction was quenched by addition of saturated aqueous solution of $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography on SiO_2 (hexane/EtOAc 10:1 to 5:1) to give alcohol **13** (17.4 mg) as a mixture with anisaldehyde: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.43 (dt, *J* = 14.6, 7.8 Hz, 1H), 5.98 (d, *J* = 14.6 Hz, 1H), 5.58 (dt, *J* = 15.6, 7.3 Hz, 1H), 5.42 (dd, *J* = 8.3, 15.6 Hz, 1H), 5.11 (d, *J* = 9.3 Hz, 1H), 4.31 (dt, *J* = 13.7, 7.8 Hz, 1H), 4.21 (d, *J* = 7.8 Hz, 1H), 3.85 (dd, *J* = 2.0, 11.2 Hz, 1H), 3.65-3.61 (m, 2H), 3.52 (s, 3H), 3.42 (dd, *J* = 6.8, 6.8 Hz, 1H), 3.37 (dd, *J* = 8.8, 9.0 Hz, 1H), 3.35 (dd, *J* = 7.8, 8.8 Hz, 1H), 3.18 (m, 1H), 3.16 (s, 3H), 2.95 (dd, *J* = 9.0, 9.0 Hz, 1H), 2.72 (brs, 1H, OH), 2.51 (m, 1H), 2.36 (m, 1H), 2.16 (m, 1H), 2.05-1.95 (m, 2H), 1.73-1.71 (m, 2H), 1.53 (d, *J* = 1.0 Hz, 3H), 0.99-0.94 (m, 27H), 0.69-0.58 (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.0, 133.8, 133.5, 132.8, 131.1, 130.3, 99.6, 88.2, 86.8, 77.4, 76.1, 75.6, 62.9, 61.9, 59.4, 55.9, 55.7, 43.7, 38.3, 37.1, 31.9, 20.7, 11.2, 7.1, 6.9, 5.3, 5.3, 4.5; HRM-ESI: Exact mass calcd for $C_{41}H_{81}INaO_8Si_3$ $[M+Na]^+$: 935.4182; found 935.4214.

(3S,4E,7S,8E,10S,12E)-13-iodo-7-methoxy-3-(((2R,3R,4S,5R,6R)-4-methoxy-3,5-bis((triethylsilyl)oxy)-6-(((triethylsilyl)oxy)methyl)tetrahydro-2H-pyran-2-yl)oxy)-8,10-dimethyltrideca-4,8,12-trienal (**14**): To a solution of alcohol **13** (17.4 mg, mixture with anisaldehyde) in CH_2Cl_2 (0.5 mL) was added Dess-Martin periodinane (23.1 mg, 54.5 μmol). After stirring at room temperature for 30 min, the mixture was added Dess-Martin periodinane (21.4 mg, 50.5 μmol) and stirred at room temperature for 1 h. The reaction was quenched by addition of saturated aqueous solution of $Na_2S_2O_3$ and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with saturated aqueous solution of $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography on SiO_2 (hexane/EtOAc 10:1 to 5:1) to give aldehyde **14** (13.2 mg, 14.5 μmol, 56% in 2 steps) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.71 (t, *J* = 2.9 Hz, 1H), 6.42 (dt, *J* = 14.6, 7.3 Hz, 1H), 5.98 (d, *J* = 14.6 Hz, 1H), 5.71 (dt, *J* = 15.1, 7.3 Hz, 1H), 5.35 (dd, *J* = 8.8, 15.1 Hz, 1H), 5.11 (d, *J* = 9.3 Hz, 1H), 4.77 (ddd, *J* = 5.4, 8.8, 13.7 Hz, 1H), 4.27 (d, *J* = 7.8 Hz, 1H), 3.81 (dd, *J* = 1.5, 10.7 Hz, 1H), 3.69 (dd, *J* = 5.4, 10.7 Hz, 1H), 3.52 (s, 3H), 3.48-3.39 (m, 2H), 3.34 (dd, *J* = 7.8, 8.8 Hz, 1H), 3.15 (s, 3H), 3.10 (m, 1H), 2.94 (dd, *J* = 8.8, 8.8 Hz, 1H), 2.65 (m, 1H), 2.53-2.48 (m, 2H), 2.38 (m, 1H), 2.16 (m, 1H), 2.03 (m, 1H), 1.96 (m, 1H), 1.53 (d, *J* = 1.0 Hz, 3H), 0.99-0.90 (m, 27H), 0.69-0.55 (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.4, 145.0, 133.9, 133.6, 133.2, 129.4, 98.6, 88.3, 77.4, 77.2, 75.7, 75.6, 72.5, 70.9, 62.4, 61.9, 55.9, 49.2, 43.7, 37.3, 31.9, 20.8, 11.2, 7.1, 6.9, 5.3, 5.2, 4.7; IR (neat) 2954, 2911, 2876, 2356, 2338, 1732, 1716, 1698, 1558, 1540, 1520, 1507, 1472, 1456, 1081, 1008, 969, 808, 738 cm^{-1}; HRMS-ESI: Exact mass calcd for $C_{41}H_{79}INaO_8Si_3$ $[M+Na]^+$: 933.4025; found 933.4037; $[\alpha]_D^{24.0}$ –5.5 (c 0.66, $CHCl_3$).

(3S,4E,7S,8E,10S,12E)-13-iodo-7-methoxy-3-(((2R,3R,4S,5R,6R)-4-methoxy-3,5-bis((triethylsilyl)oxy)-6-(((triethylsilyl)oxy)methyl)tetrahydro-2H-pyran-2-yl)oxy)-8,10-dimethyltrideca-4,8,12-trienoic acid (**5**): To a

solution of aldehyde **14** (13.2 mg, 14.5 μmol) in ^{t}BuOH (1 mL) was added 2-Me-2-butene (0.5 mL), 1 M aqueous solution of NaH_2PO_4 (1 mL) and 1 M aqueous solution of $NaClO_2$ (0.5 mL). After stirring at room temperature for 40 min, the mixture was diluted with EtOAc and H_2O and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue (15.5 mg) was used to the next reaction without further purification.

(S)-tert-butyldiphenyl((1-(trityloxy)pent-4-yn-2-yl)oxy)silane (**15**): To a stirred suspension of lithium acetylide ethylenediamine complex (1.5 g, 16.3 mmol) in DMSO (10 mL) was added a solution of (*S*)-(-)-trityl glycidyl ether (2.4 g, 7.6 mmol) in THF (10 mL) at room temperature. After stirring for 2 h, the mixture was diluted with saturated aqueous solution of NH_4Cl at 0 °C, and extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with water and brine, dried over Na_2SO_4 and concentrated *in vacuo* to give crude alcohol (2.82 g) and the crude alcohol was used for the next reaction without further purification. To a solution of the crude alcohol in DMF (5 mL) was added imidazole (1.01 g, 14.8 mmol) and TBDPSCl (2.2 mL, 8.6 mmol). The reaction was stirred at room temperature for 2 h, then quenched by addition of water and extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography on SiO_2 (hexane/EtOAc 30:1 to 25:1) to give TBDPS ether 15 (4.0 g, 6.9 mmol, 91% in 2 steps) as a colorless oil: The analytical data are identical with that of enantiomer[7b)], except for the specific rotation.

(S)-2-((tert-butyldiphenylsilyl)oxy)pent-4-yn-1-ol (**16**): To a solution of TBDPS ether **15** (4.0 g, 6.9 mmol) in $CHCl_3$ (10 mL) and MeOH (10 mL) was added TsOH•H_2O (247.9 mg, 1.30 mmol). The reaction was stirred at room temperature for 1 h, then quenched by addition of saturated aqueous solution of NH_4Cl and extracted withe EtOAc (3 × 100 mL). The combined organic layers were washed with saturated aqueous solution of $NaHCO_3$, water and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography on SiO_2 (hexane/EtOAc 20:1 to 10:1 to 5:1) to give alcohol **16** (1.83 g, 5.41 mmol, 78%) as a colorless oil: The analytical data are identical with that of enantiomer[7b)], except for the specific rotation.

(S)-2-((tert-butyldiphenylsilyl)oxy)pent-4-ynal (**17**): To a solution of alcohol **16** (777.7 mg, 2.30 mmol) in CH_2Cl_2 (7 mL) was added Dess-Martin periodinane (1.95 g, 4.60 mmol). After stirring at room temperature for 30 min, the mixture was added Dess-Martin periodinane (1.88 mg, 4.43 mmol) and stirred at room temperature for 10 min. The reaction was quenched by addition of saturated aqueous solution of $Na_2S_2O_3$ and extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with saturated aqueous solution of $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography on SiO_2 (hexane/EtOAc 30:1 to 20:1) to give aldehyde **17** (455.7 mg, 1.35 mmol, 59%) as a colorless oil: The analytical data are identical with that of enantiomer[7b)], except for the specific rotation.

(S,E)-2-((E)-but-2-en-1-yl)-4-((tert-butyldiphenylsilyl)oxy)hept-2-en-6-ynenitrile (**19**): To a solution of

phosphonate **18** (404.6 mg, 1.56 mmol) in THF (12 mL) was added NaH (60% in oil, 64.2 mg, 1.61 mmol) at 0 °C and warmed to room temperature. After stirring for 15 min at room temperature, the mixture was cooled to -78 °C and added the solution of aldehyde **17** (455.7 mg, 1.35 mmol) in THF (3 mL, 1 mL). The reaction mixture was stirred at -78 °C for 3 h, diluted with saturated aqueous NH_4Cl, and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography on SiO_2 (hexane/EtOAc = 30:1) to give nitrile **19** (349.9 mg, 0.85 mmol, 63%, E/Z = ca. 4:1) as a colorless oil: The analytical data are identical with that of enantiomer[7b)], except for the specific rotation.

(S,E)-2-((E)-but-2-en-1-yl)-4-((tert-butyldiphenylsilyl)oxy)hept-2-en-6-yn-1-ol (**20**): To a solution of nitrile **19** (349.9 mg, 0.85 mmol) in CH_2Cl_2 (10 mL) cooled at -78 °C was added DIBAL (1.0 M solution in hexane, 2.5 mL, 2.5 mmol). After stirring for 10 min, the mixture was diluted with MeOH (2 mL) and warmed to room temperature. The precipitate was filtered by Celite pad and the filtrate was concentrated to give imine as a colorless oil. The solution of the imine in THF (10 mL) coold at 0 °C was added HClaq (1.0 M, 1 mL, 1 mmol). After stirring for 15 min, the mixture was diluted with saturated aqueous solution of $NaHCO_3$ and extracted with EtOAC (3 × 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* to give aldehyde. To the solution of the aldehyde in MeOH (5 mL) cooled at 0 °C was added $NaBH_4$ (43.9 mg, 1.16 mmol). The reaction mixture was stirred for 1 h, diluted with saturated aqueous solution of $NaHCO_3$ then extracted with EtOAc (3 × 20 mL). The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography on SiO_2 (hexane/EtOAc = 10:1 to 8:1) to give alcohol **20** (181.3 mg, 0.48 mmol, 56% in 3 steps) as a colorless oil: The analytical data are identical with that of enantiomer[7b)], except for the specific rotation.

tert-butyl(((S,5Z,8E)-6-methyldeca-5,8-dien-1-yn-4-yl)oxy)diphenylsilane (**21**): To a solution of alcohol **20** (181.3 mg, 0.48 mmol) in CH_2Cl_2 (2 mL) cooled at 0 °C was added Et_3N (0.3 mL, 2.16 mmol) and MsCl (0.1 mL, 1.29 mmol). After stirring for 2.5 h, the mixture was diluted with water and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* to give mesylate. The mesylate was dissolved to THF (2 mL) and added LiBr (143.3 mg, 1.65 mmol) at room temperature. The mixture was stirred for 1 h, diluted with water and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* to give bromide. To a solution of the bromide in THF (3 mL) cooled at 0 °C was added lithium triethylborohydride solution (1.0 M in THF, 1.5 mL, 1.5 mmol). The reaction mixture was warmed to room temperature and stirred for 50 min then diluted with water. The reaction mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with saturated aqueous solution of $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography on SiO_2 (hexane/EtOAc = 50:1) to give diene **21** (117.6 mg, 0.29 mmol, 61% in 3 steps) as a colorless oil: The

analytical data are identical with that of enantiomer[7b], except for the specific rotation.

(S,5Z,8E)-6-methyldeca-5,8-dien-1-yn-4-ol (**22**): To a solution of diene **21** (117.6 mg, 0.29 mmol) in THF (1.5 mL) was added TBAF solution (1.0 M in THF, 0.6 mL, 0.6 mL). After stirring for 18 h at room tempetature, the mixture was diluted with saturated aqueous solution of NH_4Cl and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography on SiO_2 (hexane/EtOAc = 10:1 to 5:1) to give alcohol **22** (41.5 mg, 0.25 mmol, 87%) as a colorless oil: The analytical data are identical with that of enantiomer[7b], except for the specific rotation.

(S,1E,5Z,8E)-6-methyl-1-(tributylstannyl)deca-1,5,8-trien-4-ol ((*S*)-**4**): To a degassed solution of alcohol **22** (41.5 mg, 0.25 mmol) in THF (1 mL) was added $Pd(PPh_3)_4$ (18.1 mg, 15.7 μmol) and Bu_3SnH (0.1 mL, 0.37 mmol). After stirring at 0 ˚C for 30 min, the solvent was removed *in vacuo*. The residue was purified by column chromatography on SiO_2 (hexane/ EtOAc 20:1 to 10:1) to give stannane (*S*)-**4** (59.3 mg, 0.13 mmol, 52%) as a colorless oil: The analytical data are identical with that of enantiomer[7b], except for the specific rotation.

(R,1E,5Z,8E)-6-methyl-1-(tributylstannyl)deca-1,5,8-trien-4-yl (3S,4E,7S,8E,10S,12E)-13-iodo-7-methoxy-3-(((2R,3R,4S,5R,6R)-4-methoxy-3,5-bis((triethylsilyl)oxy)-6-(((triethylsilyl)oxy)methyl)tetrahydro-2H-pyran-2-yl)oxy)-8,10-dimethyltrideca-4,8,12-trienoate (**23**): To a solution of stannane (*S*)-**4** (7.7 mg, 16.9 μmol), carboxylic acid **5** (15.5 mg, crude) and PPh_3 (7.8 mg, 29.7 μmol) in toluene (0.3 mL) was added 2.2 M solution of DEAD in toluene (0.02 mL, 44 μmol). After stirring at room temperature for 16 h, the mixture was diluted with EtOAc and H_2O and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography on SiO_2 (hexane/EtOAc 15:1 to 10:1) to give ester **23** (13.6 mg, 10.0 μmol, 69% in 2 steps) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.43 (dt, *J* = 14.6, 7.8 Hz, 1H) 5.98 (d, *J* = 14.6 Hz, 1H), 5.97 (d, *J* = 19.0 Hz, 1H), 5.78 (dt, *J* = 19.0, 6.3 Hz, 1H), 5.68 (dt, *J* = 14.6, 6.8 Hz, 1H), 5.55 (m, 1H), 5.44 (m, 1H), 5.31-5.25 (m, 2H), 5.11 (d, *J* = 9.3 Hz, 1H), 5.11 (d, *J* = 9.3 Hz, 1H), 4.63 (m, 1H), 4.25 (d, *J* = 7.8 Hz, 1H), 3.81 (dd, *J* = 1.0, 11.2 Hz, 1H), 3.67 (dd, *J* = 5.4, 11.2 Hz, 1H), 3.52 (s, 3H), 3.44-3.32 (m, 3H), 3.14 (s, 3H), 3.08 (m, 1H), 2.93 (dd, *J* = 8.8, 8.8 Hz, 1H), 2.83 (m, 1H), 2.71-2.66 (m, 2H), 2.53-2.41 (m, 3H), 2.37-2.29 (m, 2H), 2.13 (m, 1H), 2.03-1.97 (m, 2H), 1.67-1.41 (m, 15H), 1.35-1.21 (m, 9H), 1.00-0.80 (m, 27H), 0.71-0.59 (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 145.0, 143.6, 139.6, 133.8, 133.8, 133.5, 132.0, 129.5, 128.3, 126.6, 124.0, 98.3, 88.5, 86.7, 77.4, 75.9, 75.7, 73.7, 71.0, 70.4, 62.4, 61.8, 55.9, 43.7, 41.4, 37.6, 36.1, 31.9, 29.9, 29.3, 29.2, 27.4, 23.4, 20.7, 18.0, 13.9, 11.3, 9.5, 7.1, 7.0, 5.3, 5.2, 4.7; IR (neat) 2954, 2925, 2875, 2854, 2359, 2340, 1733, 1457, 1417, 1376, 1338, 1239, 1178, 1151, 1082, 1006, 965, 852, 813, 741, 689, 669 cm^{-1}; HRMS-ESI $C_{64}H_{121}INaO_9Si_3Sn$ $[M+Na]^+$: 1387.6283; found 1387.6252; $[\alpha]_D^{22.2}$ –0.68 (c 0.68, $CHCl_3$).

(4S,5E,8S,9E,11S,13E,15E)-8-methoxy-4-(((2R,3R,4S,5R,6R)-4-methoxy-3,5-bis((triethylsilyl)oxy)-6-(((t

riethylsilyl)oxy)methyl)tetrahydro-2H-pyran-2-yl)oxy)-9,11-dimethyl-18-((1Z,4E)-2-methylhexa-1,4-dien-1-yl) oxacyclooctadeca-5,9,13,15-tetraen-2-one (**3**): To a degassed solution of ester **23** (13.6 mg, 10.0 μmol) in DMF (6 mL) was added LiCl (3.8 mg, 90 μmol) and $Pd_2(dba)_3$ (0.6 mg, 0.7 μmol). After stirred at room temperature for 4 h, the mixture was diluted by Et_2O and H_2O and extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography on SiO_2 (hexane/EtOAc 15:1 to 10:1) to give macrolactone **3** (7.7 mg, 8.1 μmol, 81%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.03-5.89 (m, 2H), 5.59-5.25 (m, 6H), 5.07-5.00 (m, 2H), 4.54 (dt, *J* = 15.6, 7.8 Hz, 1H), 4.20 (d, *J* = 7.8 Hz, 1H), 3.81-3.74 (m, 2H), 3.66-3.55 (m, 1H), 3.52 (s, 3H), 3.38-3.31 (m, 2H), 3.15 (s, 3H), 3.05 (m, 1H), 2.96-2.09 (m, 2H), 2.75-2.63 (m, 3H), 2.43-2.14 (m, 6H), 1.89-1.81 (m, 1H), 1.70-1.42 (m, 9H), 1.34-1.17 (m, 1H), 1.08-0.83 (m, 27H), 0.73-0.57 (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 138.7, 136.6, 135.1, 133.7, 132.3, 131.8, 131.3, 130.4, 128.2, 126.9, 126.6, 123.6, 99.1, 88.2, 87.7, 77.4, 75.6, 74.2, 70.8, 70.4, 62.0, 61.8, 55.4, 41.6, 40.3, 38.0, 36.7, 35.9, 32.6, 29.9, 23.6, 22.1, 18.0, 10.2, 9.5, 7.1, 7.0, 5.3, 5.2, 4.7; IR (neat) 2953, 2932, 2915, 2878, 2360, 2342, 1733, 1558, 1540, 1507, 1456, 1088, 1007, 969, 815, 741 cm^{-1}; HRMS-ESI: Exact mass calcd for $C_{52}H_{94}NaO_9Si_3$ $[M+Na]^+$: 969.6103; found 969.6115; $[\alpha]_D^{25.8}$ –20.3 (c 0.39, $CHCl_3$).

Biselyngbyaside (**1**): To a solution of macrolactone **3** (7.2 mg, 7.6 μmol) in THF (0.3 mL) was added 1.8 M solution of AcOH in THF (0.04 mL, 72 μmol) and 1 M solution of TBAF in THF (0.06 mL, 60 μmol). The reaction was stirred at room temperature for 11.5 h and added 1 M solution of TBAF in THF (0.05 mL, 50 μmol). After stirring at room temperature for 4 h, the reaction was quenched by addition of saturated aqueous solution of NH_4Cl and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by PTLC on SiO_2 [200 x 100 x 0.5, $CHCl_3$/MeOH 5:1] to give biselyngbyaside (3.6 mg, 6.0 μmol, 78%) as a colorless oil: ^{1}H NMR (400 MHz, CD_3OD) δ 6.08-5.98 (m, 2H), 5.59-5.38 (m, 7H), 5.14 (d, *J* = 8.8 Hz, 1H), 5.12 (d, *J* = 8.8 Hz, 1H), 4.51 m, 1H), 4.26 (d, *J* = 6.8 Hz, 1H), 3.86 (dd, *J* = 2.4, 11.7 Hz, 1H), 3.74 (dd, *J* = 4.6, 11.7 Hz, 1H), 3.64 (s, 3H), 3.47 (m, 1H), 3.45 (dd, *J* = 9.3, 9.8 Hz, 1H), 3.22 (dd, *J* = 6.8, 9.3 Hz, 1H), 3.19 (m, 1H), 3.16 (s, 3H), 3.05 (dd, *J* = 9.3, 9.3 Hz, 1H), 2.93 (m, 1H), 2.76-2.68 (m, 2H), 2.57 (dd, *J* = 8.0, 14.9 Hz, 1H), 2.34-2.23 (m, 6H), 1.97 (m, 1H), 1.68 (s, 3H), 1.65 (d, *J* = 5.9 Hz, 3H), 1.56 (s, 3H), 1.04 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 172.1, 140.1, 138.5, 135.3, 133.3, 133.0, 132.8, 132.1, 131.9, 129.3, 127.9, 127.5, 124.9, 100.9, 89.1, 87.7, 77.7, 77.4, 74.6, 72.6, 70.7, 62.3, 61.0, 55.6, 43.0, 41.5, 39.6, 36.8, 36.6, 34.0, 23.6, 22.4, 18.0, 10.1; IR (neat) 2365, 2342, 1559, 1508, 1073 cm^{-1}; HRMS-ESI: Exact mass calcd for $C_{34}H_{52}O_9Na$ $[M+Na]^+$: 627.3509; found 627.3510; $[\alpha]_D^{26.3}$ –42.9 (c 0.11, $CHCl_3$).

Cell Growth Analysis:

All cells were obtained from RIKEN Cell Bank. HeLa cells were cultured at 37˚C with 5% CO_2 in DMEM (Nissui) supplemented with 10% heat-inactivated fetal bovine serum (FBS), 100 units/mL penicillin, 100 μg/mL streptomycin, 0.25 μg/mL amphotericin, 300 μg/mL L-glutamine, and 2.25 mg/mL $NaHCO_3$.

HeLa cells were seeded at 2 × 10^4 cells/well in 96-well plates (Iwaki) and cultured overnight. Various concentrations of compounds were then added, and cells were incubated for 72 h. Cell proliferation was measured by the MTT assay. Adriamycin was used as positive control (IC_{50} value 0.5 μM (HeLa cells)).

Docking Simulation:

The PDB structure 4YCM was prepared with the Protein Preparation Wizard program assuming a pH 7 and used as the starting structure for docking analysis.

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Supporting Information:

The Supporting Information is available free of charge on the ACS Publication website at DOI: XXXXX.

^{1}H and ^{13}C NMR spectra of all new compounds.

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