Stereocontrolled Total Synthesis of Fucoxanthin and its Polyene Chain-modified Derivative

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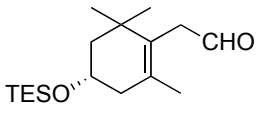
General

All commercially available reagents were used without further purification. All solvents were used after distillation. Tetrahydrofuran (THF), diethyl ether and toluene were refluxed over and distilled from sodium-benzophenone ketyl. Dichloromethane was refluxed over and distilled from P_2O_5. Dimethylformamide (DMF) was distilled from CaH_2 under reduced pressure. Preparative separation was performed by column chromatography on silica gel. ^{1}H NMR and ^{13}C NMR spectra were recorded on 400MHz or 750 MHz spectrometers and chemical shifts were represented as δ-values relative to the internal standard TMS. IR spectra were recorded on a FT-IR Spectrometer. High-resolution mass spectra (HRMS) were measured on a ESI-TOF MS.

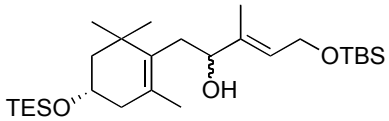
Experimental

[(4S)-4-Triethylsilyloxy-2,6,6-trimethylcyclohexyl]-acetaldehyde 8. To a solution of the alkyne (2.0 g, 6.74 mmol) in xylene (13.5 mL) were added $(Ph_3SiO)_3VO$ (300 mg, 0.34 mmol) and benzoic acid (41 mg, 0.34 mmol) was refluxed for 3 h. After evaporation off of the solvent, the residue was purified by silica gel column chromatography (from 1% to 3% ethyl acetate in hexane) afforded aldehyde **8** (1.96 g, 98%) as a yellow oil: $[\alpha]^{24}_D$ +73.3 (c 1.06, $CHCl_3$); IR (neat, cm^{-1}) 3427, 2957, 2716, 1724, 1460, 1383, 1238, 1084, 835; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.50 (t, *J* =2.3 Hz, 1H), 3.93 (m, 1H), 3.08 (t, *J* =18.4 Hz,



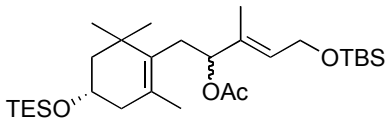
2H), 2.21 (dd, *J* =17.4, 4.6 Hz, 1H), 2.10 (ddd, *J* =16.5, 9.2, 1.3 Hz, 1H), 1.68 (ddd, *J* =12.4, 3.2, 1.8 Hz, 1H), 1.58 (s, 3H), 1.53 (dd, *J* =12.4, 11.9 Hz, 1H), 1.01 (s, 3H), 0.99 (s, 3H), 0.97 (t, *J* =8.2 Hz, 9H), 0.61 (q, *J* =7.8 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 200.9, 130.3, 128.6, 65.5, 48.7, 43.7, 43.1, 37.6, 29.6, 28.1, 20.4, 7.2, 5.2; ESI-HRMS m/z calcd for $C_{17}H_{32}O_2SiNa$ $(M+Na)^+$ 319.2069, found 319.2073.

(2*E*)-*tert*-Butyldimethyl{5-[(4'*S*)-4'-triethylsilyloxy-2',6',6'-trim ethylcyclohexenyl]-4-hydroxy-3-methylpent-2-enyloxy}silane



8a. To a solution of the vinyl iodide **10** (1.43 g, 4.57 mmol) in diethyl ether (15.0 mL) was added dropwise *tert*-butyllithium (1.57M in THF, 3.13 mL, 4.92 mmol) at -78 ºC and the mixture was stirred for 30 min. To this mixture was added dropwise a solution of the aldehyde **8** (1.04 g, 3.51 mmol) in diethyl ether (2.78 mL) at-78 ºC. After being stirred for 20 min at the same temperature, the mixture was poured into a saturated aqueous NH_4Cl, and then extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by silica gel column chromatography (from 2% to 10% ethyl acetate in hexane) afforded alcohol **8a** (1.52 g, 90%) as a mixture of C8 diastereomer as a colorless oil: $[\alpha]^{24}_D$ +23.6 (c 1.06, $CHCl_3$); IR (neat, cm^{-1}) 3508, 2959, 2127, 1632, 1458, 1361, 1253, 1109, 835; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.57 (t, *J* =6.4 Hz, 2H), 4.24 (d, *J* =5.9 Hz, 4H), 4.15 (m, 2H), 3.94 (m, 2H), 2.38 (m, 2H), 2.29-2.02 (m, 6H), 1.70-1.67 (m, 12H), 1.65-1.60 (m, 2H), 1.52 (dd, *J* =12.4, 11.9 Hz, 2H), 1.08 (s, 3H), 1.07 (s, 3H), 1.06 (s, 3H), 1.05 (s, 3H), 0.97 (t, *J* =7.8 Hz, 18H), 0.90 (s, 18H), 0.60 (q, *J* =7.8 Hz, 12H) 0.07 (s, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.9, 138.8, 133.7, 133.6, 129.6, 129.5, 125.9, 125.7, 76.6, 76.5, 65.6, 60.4, 49.9, 49.3, 43.7, 43.4, 38.2, 37.8, 34.6, 30.5, 30.3, 29.7, 29.0, 26.3, 21.3, 18.7, 12.3, 12.2, 7.2, 5.3, -4.7; ESI-HRMS m/z calcd for $C_{27}H_{54}O_3Si_2Na$ $(M+Na)^+$ 505.3509, found 505.3491.

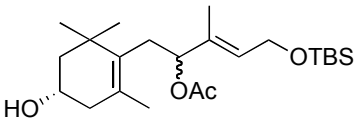
(2*E*)-*tert*-Butyldimethyl{5-[(4'*S*)-4'-triethylsilyloxy-2',6',6'-trim ethylcyclohexenyl]-4-acetoxy-3-methylpent-2-enyloxy}silane 8b.



To a solution of alcohol **8a** (100 mg, 2.90 mmol) in pyridine (0.83 mL) were added acetic anhydride (0.05 mL, 0.52 mmol) and N,N-4-dimethylaminopyridine (5 mg, 0.041 mmol) at room temperature, and the reaction mixture was stirred for 30 min at the same temperature. A saturated aqueous $CuSO_4$ solution was added, and then the resulting mixture was extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by silica gel column chromatography (from 1% to 3% ethyl acetate in hexane) afforded acetate **8b** (101 mg, 93%) as a mixture of C8 diastereomer as a

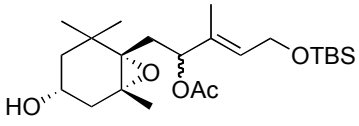
colorless oil: $[\alpha]^{24}_D$ +23.5 (c 1.05, $CHCl_3$); IR (neat, cm^{-1}) 3424, 2957, 2141, 1741, 1649, 1741, 1649, 1471, 1370, 1238, 1007, 835; NMR ($CDCl_3$, 400 MHz) δ 5.56 (t, *J* =6.0 Hz, 1H), 5.54 (t, *J* =6.0 Hz, 1H), 5.32 (dd, *J* =10.5, 3.2 Hz, 1H), 5.28 (dd, *J* =9.2, 5.0 Hz, 1H), 4.21 (d, *J* =6.0 Hz, 2H), 4.20 (d, *J* =6.0 Hz, 2H), 3.88 (m, 2H), 2.48 (dd, *J* =15.3, 11.2 Hz, 1H), 2.42 (dd, *J* =14.7, 8.7 Hz, 1H), 2.28 (dd, *J* =14.1, 4.1 Hz, 1H), 2.19-2.09 (m, 3H), 2.00 (s, 3H), 1.98 (s, 3H), 1.67-1.64 (m, 12H), 1.51-1.44 (m, 2H), 1.06 (s, 3H), 1.05 (s, 3H), 1.02 (s, 6H), 0.97 (t, *J* =7.8 Hz, 18H), 0.89 (s, 18H), 0.60 (q, *J* =7.8 Hz, 12H), 0.05 (s, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.2, 135.5, 135.4, 132.9, 132.8, 128.6, 127.3, 127.1, 78.6, 78.5, 65.7, 60.2, 49.7, 49.3, 43.5, 43.4, 38.1, 37.9, 32.2, 32.1, 30.4, 30.0, 29.4, 29.0, 26.2, 21.6, 21.5, 21.3, 21.1, 18.7, 13.1, 13.0, 7.2, 5.2, -4.7; ESI-HRMS m/z calcd for $C_{29}H_{56}O_4Si_2Na$ $(M+Na)^+$ 547.3615, found 547.3598.

(2*E*)-*tert*-Butyldimethyl{5-[(4'*S*)-4'-hydroxy-2',6',6'-trimethylcyclohexenyl]-4-acetoxy-3-methylpent-2-enyloxy}silane 11. To a solution of the acetate **8b** (101 mg, 0.19 mmol) in MeOH (0.96 mL)



was added pyridinium *p*-toluenesulfonate (5 mg, 0.019 mmol) at room temperature, and the reaction mixture was stirred for 10 min at the same temperature. A saturated aqueous $NaHCO_3$ solution was added, and then the resulting mixture was extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by silica gel column chromatography (from 5% to 50% ethyl acetate in hexane) afforded alcohol **11** (77 mg, 98%) as a mixture of C8 diastereomer as a colorless oil: $[\alpha]^{24}_D$ +32.5 (c 1.06, $CHCl_3$); IR (neat, cm^{-1}) 3362, 2955, 1740, 1471, 1371, 1240, 1113, 837; NMR ($CDCl_3$, 400 MHz) δ 5.56 (t, *J* =6.4 Hz, 1H), 5.54 (t, *J* =5.9 Hz, 1H), 5.34 (dd, *J* =10.5, 3.2 Hz, 1H), 5.29 (dd, *J* =9.2, 5.0 Hz, 1H), 4.21 (d, *J* =5.9 Hz, 2H), 4.20 (d, *J* =6.0 Hz, 2H), 3.93 (m, 2H), 2.50 (dd, *J* =15.1, 10.5 Hz, 1H), 2.43 (dd, *J* =15.2, 9.2 Hz, 1H), 2.31-2.16 (m, 4H), 2.00 (s, 3H), 1.99 (s, 3H), 1.93 (dd, *J* =16.1, 10.1 Hz, 2H), 1.68-1.66 (m, 12H), 1.47-1.40 (m, 2H), 1.09 (s, 3H), 1.07 (s, 3H), 1.02 (s, 6H), 0.90 (s, 18H), 0.05 (s, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.8 169.7, 134.9, 128.0, 126.9, 77.6, 76.3, 75.2, 68.0, 66.5, 63.3, 63.2, 63.0, 62.2, 60.0, 59.9, 43.9, 43.6, 39.9, 39.6, 36.2, 35.7, 30.7, 30.1, 26.4, 26.3, 26.1, 25.0, 24.8, 21.7, 21.4, 21.3, 18.4, 13.2, 12.7, -4.9; ESI-HRMS m/z calcd for $C_{23}H_{42}O_4SiNa$ $(M+Na)^+$ 433.2750, found 433.2741.

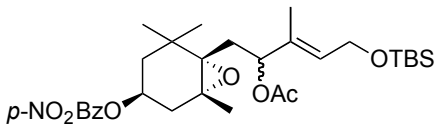
(2*E*)-*tert*-Butyldimethyl{5-[(1'*S*,2'*R*,4'*R*)-4'-hydroxy-1',2'-epoxy-2',6',6'-trimethylcyclohex-1'-yl]-4-acetoxy-3-methylpent-2-enyloxy}silane 11a. To a solution of alcohol **11** (1.08 g, 2.62 mmol) and



aluminium tri-*tert*-butoxide (645 mg, 2.62 mmol) in toluene (13.1 mL) was added

tert-butylhydroperoxide (0.95 mL, 5.24 mmol) at 0 ºC. The reaction mixture was stirred for 2 h at the room temperature. A saturated aqueous potassium sodium (+)-tartrate tetrahydrate solution was added, and then the resulting mixture was extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by silica gel column chromatography (from 5% to 50% ethyl acetate in hexane) afforded alcohol epoxide **11a** (830 mg, 74%) as a mixture of C8 epimer as a colorless oil: $[\alpha]^{24}_D$ +30.3 (c 1.05, $CHCl_3$); IR (neat, cm^{-1}) 3483, 2957, 2859, 1744, 1473, 1371, 1240, 1111, 837; NMR ($CDCl_3$, 400 MHz) δ 5.62 (t, *J* =6.0 Hz, 1H), 5.55 (t, *J* =6.0 Hz, 1H), 5.34 (dd, *J* =7.8, 4.1 Hz, 1H), 5.07 (d, *J* =9.6 Hz, 1H), 4.19 (d, *J* =6.2 Hz, 4H), 3.78 (m, 2H), 2.20-2.10 (m, 3H), 2.03 (s, 3H), 1.98 (s, 3H), 1.95 (dd, *J* =9.2, 4.1 Hz, 1H), 1.86-1.75 (m, 3H), 1.64 (d, *J* =1.0 Hz, 3H), 1.62 (d, *J* =0.9 Hz, 3H), 1.55-1.48 (m, 2H), 1.35 (s, 3H), 1.28 (s, 3H), 1.30-1.22 (m, 3H), 1.09 (s, 3H), 1.06 (s, 3H), 1.05 (s, 3H), 1.04 (s, 3H), 0.88 (s, 18H), 0.05 (s, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.3, 135.4, 135.2, 133.2, 133.0, 128.0, 127.4, 127.2, 78.6, 78.5, 65.4, 60.2, 49.2, 48.8, 42.9, 42.8, 38.1, 37.9, 32.2, 32.1, 30.4, 30.0, 29.5, 29.1, 26.2, 21.6, 21.5, 21.2, 21.1, 18.7, 13.1, 13.0, -4.7; ESI-HRMS m/z calcd for $C_{23}H_{42}O_5SiNa$ $(M+Na)^+$ 449.2699, found 449.2688.

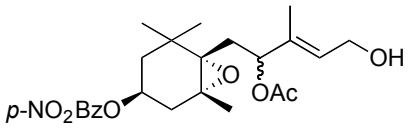
(2*E*)-*tert*-Butyldimethyl{5-[(1'*S*,2'*R*,4'*S*)-4'-*p*-nitrobenzoxy-1',2'-epoxy-2',6',6'-trimethylcyclohex-1'-yl]-4-acetoxy-3-methylpent-2-enyloxy}silane 12. To a solution of alcohol **11a**



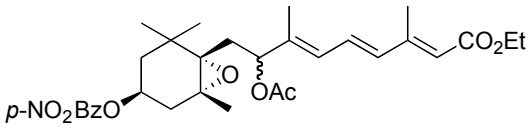
(830 mg, 1.95 mmol), *p*-nitrobenzoic acid (914 mg, 5.84 mmol) and triphenylphosphine (1.53 g, 5.84 mmol) in THF (9.73 mL) was added dropwise diisopropyl azodicarboxylate (1.46 mL, 5.84 mmol) at 0 ºC. The reaction mixture was stirred for 1 h at room temperature, and the all solvents were removed *in vacuo*. To a residue was added diethyl ether, and the precipitate was removed by filtration through a pad of Celite to give the crude products as a solution, which was concentrated *in vacuo*. Purification by short silica gel column chromatography (from 5% to 30% ethyl acetate in hexane) afforded diester **12** (784 mg, 70%) as a mixture of C8 epimer as a colorless oil: $[\alpha]^{24}_D$ -2.9 (c 1.01, $CHCl_3$); IR (neat, cm^{-1}) 2957, 2859, 1724, 1608, 1530, 1471, 1350, 1279, 1103, 837; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.27 (d, *J* =8.7 Hz, 4H), 8.15 (d, *J* =8.3 Hz, 4H), 5.64 (t, *J* =6.4 Hz, 1H), 5.57 (t, *J* =6.0 Hz, 1H), 5.43 (dd, *J* =6.2, 5.7 Hz, 1H), 5.20 (dd, *J* =10.5, 1.8 Hz, 1H), 5.15 (m, 2H), 4.20 (d, *J* =5.9 Hz, 4H), 2.55 (dd, *J* =16.0, 6.8 Hz, 2H), 2.21 (dd, *J* =15.1, 10.5 Hz, 1H), 2.06 (m, 2H), 2.04 (s, 3H), 2.01 (s, 3H), 1.98-1.79 (m, 5H), 1.66 (d, *J* =0.9 Hz, 3H), 1.64 (d, *J* =0.9 Hz, 3H), 1.40 (s, 3H), 1.35 (s, 3H), 1.22 (s, 3H), 1.20 (s, 3H), 1.13 (s, 3H), 1.11 (s, 3H), 0.89 (s, 18H), 0.05 (s, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.0, 169.9, 150.8, 136.2, 134.9, 134.8, 130.9, 128.2, 127.4, 123.8, 76.2, 75.4, 69.8, 67.7, 66.5, 62.7, 62.6, 60.1, 60.0, 41.3, 40.8, 37.2, 36.7, 35.4, 35.2, 31.9, 31.7, 31.2, 27.9, 27.7, 26.3, 26.2, 26.0, 22.9, 21.6,

21.5, 21.3, 20.8, 18.6, 14.4, 14.3, 13.2, 12.8, -4.8; ESI-HRMS m/z calcd for $C_{30}H_{45}NO_8SiNa$ $(M+Na)^+$ 598.2812, found 598.2802.

(2*E*)-5-[(1'*S*,2'*R*,4'*S*)-4'-*p*-Nitrobenzoxy-1',2'-epoxy-2',6',6'-trimethylcyclohex-1'-yl]-4-acetoxy-3-methylpenta-2-en-1-ol 12a. To a solution of diester **12** (493 mg, 0.86 mmol) in THF (3.42 mL) was added tetra-*n*-butylammonium fluoride (267 mg, 1.02 mmol) at room temperature. After being stirred for 20 min, the reaction mixture was poured into a saturated aqueous NH_4Cl solution, and then extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by silica gel column chromatography (from 30% to 60% ethyl acetate in hexane) afforded alcohol **12a** (319 mg, 81%) as a mixture of C8 epimer as a white foam: $[\alpha]^{25}_D$ -4.6 (c 1.07, $CHCl_3$); IR (neat, cm^{-1}) 3505, 2964, 2876, 1944, 1713, 1609, 1524, 1471, 1238, 1103, 972; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.27 (d, *J* =8.7 Hz, 4H), 8.15 (d, *J* =9.2 Hz, 4H), 5.73 (t, *J* =6.4 Hz, 1H), 5.66 (t, *J* =6.4 Hz, 1H), 5.42 (dd, *J* =6.9, 5.0 Hz, 1H), 5.20 (dd, *J* =10.5, 2.3 Hz, 1H), 5.15 (m, 2H), 4.18 (d, *J* =6.4 Hz, 4H), 2.55 (dd, *J* =15.6, 6.4 Hz, 2H), 2.22 (dd, *J* =15.6, 10.5 Hz, 1H), 2.06 (s, 3H), 2.02 (s, 3H), 1.98-1.78 (m, 5H), 1.71 (s, 3H), 1.69 (s, 3H), 1.54-1.44 (m, 2H), 1.41 (s, 3H), 1.35 (s, 3H), 1.22 (s, 3H), 1.20 (s, 3H), 1.13 (s, 3H), 1.10 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.2, 170.1, 164.2, 150.7, 136.8, 136.6, 136.2, 130.8, 127.2, 126.2, 123.8, 76.3, 75.6, 69.7, 67.6, 66.5, 62.7, 62.6, 59.1, 59.0, 41.3, 40.7, 37.1, 36.6, 35.3, 35.1, 31.4, 30.9, 27.8, 27.6, 26.3, 26.0, 21.5, 21.4, 21.1, 20.8, 13.0, 12.6; ESI-HRMS m/z calcd for $C_{24}H_{31}NO_8Na$ $(M+Na)^+$ 484.1947, found 484.1947.

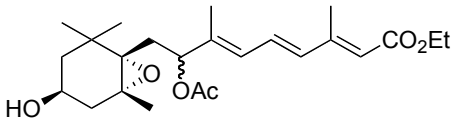


(2*E*,4*E*,6*E*)-9-[(1'*S*,2'*R*,4'*S*)-4'-*p*-Nitrobenzoxy-1',2'-epoxy-2',6',6'-trimethylcyclohex-1'-yl]-8-acetoxy-3,7-dimethylnona-2,4,6-triene-1-ynoate 13. A mixture of alcohol **12a** (319 mg, 0.69 mmol) and manganese dioxide (4.15 g) in THF (5.53 mL) was stirred at room temperature for 25 min. The precipitate was filtered through a pad of Celite, and the filtrate was concentrated *in vacuo* to afford crude aldehyde, which was used in the next reaction without further purification.



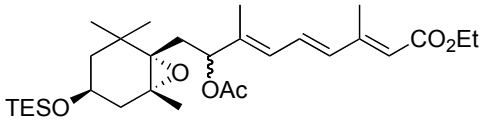
To a solution of triethyl-3-methyl-4-phosphonocrotonate (0.25 mL, 1.05 mmol) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidone (0.22 mL, 1.85 mmol) in THF (3.20 mL) was added dropwise *n*-butyllithium (1.6M in THF, 0.66 mL, 1.05 mmol) at 0 °C. After the mixture was stirred for 20 min at 0 °C, a solution of the crude aldehyde obtained above in THF (0.50 mL) was added at -78 °C. After being stirred for 5 min at room temperature, the resulting mixture was poured

into water, and extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by silica gel column chromatography (from 10% to 30% ethyl acetate in hexane) afforded trieneester **13** (286 mg, 73%) as a mixture of C8 epimer as a white foam: $[\alpha]^{25}_D$ –6.0 (c 1.01, $CHCl_3$); IR (neat, cm^{-1}) 3022, 1720, 1609, 1529, 1369, 1279, 1242, 1157, 1045, 964, 758; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.27 (d, *J* =9.2 Hz, 4H), 8.14 (d, *J* =8.7 Hz, 4H), 6.76 (dd, *J* =15.1, 11.0 Hz, 2H), 6.29 (d, *J* =15.6 Hz, 1H), 6.26 (d, *J* =15.1 Hz, 1H), 6.24 (d, *J* =10.9 Hz, 1H), 6.17 (d, *J* =11.0 Hz, 1H), 5.77 (s, 2H), 5.46 (dd, *J* =5.9, 5.9 Hz, 1H), 5.27 (dd, *J* =10.1, 2.3 Hz, 1H), 5.15 (m, 2H), 4.16 (q, *J* =6.8 Hz, 4H), 2.56 (dd, *J* =15.5, 6.8 Hz, 2H), 2.31 (s, 6H), 2.26 (dd, *J* =15.0, 10.6 Hz, 1H), 2.07 (s, 3H), 2.02 (s, 3H), 1.99-1.79 (m, 5H), 1.88 (s, 3H), 1.85 (s, 3H), 1.49 (dd, *J* =14.7, 14.7 Hz, 1H), 1.48 (dd, *J* =14.2, 14.2 Hz, 1H), 1.41 (s, 3H), 1.36 (s, 3H), 1.28 (t, *J* =7.3 Hz, 6H), 1.22 (s, 3H), 1.19 (s, 3H), 1.14 (s, 3H), 1.07 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.1, 167.3, 164.2, 152.3, 150.8, 140.0, 139.7, 137.1, 136.9, 136.2, 130.9, 130.0, 127.6, 126.7, 123.9, 119.9, 120.0, 76.7, 69.8, 67.5, 66.5, 62.7, 62.6, 60.1, 41.3, 40.7, 37.2, 36.7, 35.4, 35.2, 31.5, 31.0, 27.9, 27.6, 26.4, 26.0, 21.6, 21.5, 21.2, 20.8, 14.6, 14.1, 13.3, 13.3; ESI-HRMS m/z calcd for $C_{31}H_{39}NO_9Na$ $(M+Na)^+$ 592.2523, found 592.2533.



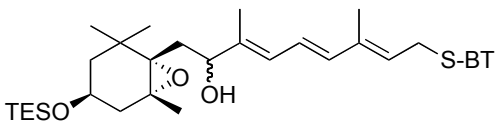
(2*E*,4*E*,6*E*)-9-[(1'*S*,2'*R*,4'*S*)-4'-Hydroxy-1',2'-epoxy-2',6',6'-trimethylcyclohex-1'-yl]-8-acetoxy-3,7-dimethylnona-2,4,6-triene-1-ynoate 13a. The triene ester **13** (1.31 g, 2.30 mmol) was dissolved in MeOH (13.8 mL), and 10% KOH aq. (1.15 mL) was added to it. After being stirred at room temperature for 5 min, the mixture was poured into a saturated aqueous NH_4Cl, and then extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by silica gel column chromatography (from 30% to 50% ethyl acetate in hexane) afforded alcohol **13a** (928 mg, 96%) as a mixture of C8 epimer as a white foam: $[\alpha]^{24}_D$ +8.7 (c 1.08, $CHCl_3$); IR (neat, cm^{-1}) 3541, 2934, 1732, 1607, 1369, 1240, 1157, 1045, 964, 758; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.75 (dd, *J* =15.1, 11.5 Hz, 2H), 6.27 (d, *J* =15.1 Hz, 1H), 6.24 (d, *J* =15.5 Hz, 1H), 6.21 (d, *J* =11.9 Hz, 1H), 6.15 (d, *J* =11.4 Hz, 1H), 5.75 (s, 2H), 5.44 (dd, *J* =7.3, 5.0 Hz, 1H), 5.24 (dd, *J* =10.1, 2.8 Hz, 1H), 4.15 (q, *J* =7.3 Hz, 4H), 3.81 (m, 2H), 2.30 (m, 1H), 2.29 (s, 6H), 2.20 (dd, *J* =15.1, 10.1 Hz, 1H), 2.06 (m, 1H), 2.04 (s, 3H), 2.01 (s, 3H), 1.85 (s, 3H), 1.83 (s, 3H), 1.71-1.54 (m, 6H), 1.63 (s, 3H), 1.31 (s, 3H), 1.27 (t, *J* =7.3 Hz, 6H), 1.17 (s, 3H), 1.15 (s, 3H), 1.05 (s, 3H), 1.00 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.2, 170.0, 167.3, 152.4, 140.2, 140.0, 136.9, 136.7, 129.8, 129.7, 127.2, 126.6, 120.0, 119.6, 76.8, 76.1, 67.1, 66.3, 64.5, 64.2, 64.0, 60.0, 47.5, 47.2, 41.5, 41.1, 35.7, 35.6, 32.1, 32.0, 29.0, 28.9, 26.1, 25.5, 21.5, 21.4, 21.2, 20.7, 14.6, 14.0, 13.7, 13.3; ESI-HRMS m/z calcd for $C_{24}H_{36}O_6Na$ $(M+Na)^+$ 443.2410, found 443.2415.

(2*E*,4*E*,6*E*)-9-[(1'*S*,2'*R*,4'*S*)-4'-Triethylsilyloxy-1',2'-epoxy-2',6',6'-trimethylcyclohex-1'-yl]-8-acetoxy-3,7-dimethylnona-2,4,6-triene-1-ynoate 14. To a solution **13a** (99



mg, 0.24 mmol) in DMF (1.19 mL) was added imidazole (32 mg, 0.48 mmol) and TESCl (0.06 mL, 0.36 mmol) at room temperature. After the reaction mixture was stirred for 10 min at the same temperature, the resulting mixture was poured into a saturated aqueous $NaHCO_3$ solution, and extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by silica gel column chromatography (from 2% to 10% ethyl acetate in hexane) afforded **14** (121 mg, 95%) as a mixture of C8 epimer as a colerless oil: $[\alpha]^{24}_D$ +6.5 (c 1.02, $CHCl_3$); IR (neat, cm^{-1}) 3447, 2963, 2116, 1736, 1610, 1458, 1370, 1238, 1153, 1066, 725; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.76 (dd, *J* =15.1, 11.0 Hz, 2H), 6.28 (d, *J* =15.1 Hz, 1H), 6.25 (d, *J* =15.6 Hz, 1H), 6.21 (d, *J* =11.9 Hz, 1H), 6.15 (d, *J* =11.0 Hz, 1H), 5.77 (s, 1H), 5.76 (s, 1H), 5.44 (dd, *J* =7.3, 4.6 Hz, 1H), 5.25 (dd, *J* =10.1, 2.8 Hz, 1H), 4.16 (q, *J* =6.9 Hz, 4H), 3.75 (m, 2H), 2.30 (d, *J* =0.9 Hz, 3H), 2.30 (d, *J* =0.9 Hz, 3H), 2.24-2.18 (m, 2H), 2.11-1.97 (m, 2H), 2.04 (s, 3H), 2.02 (s, 3H), 1.85 (d, *J* =0.9 Hz, 3H), 1.83 (d, *J* =0.9 Hz, 3H), 1.67-1.59 (m, 2H), 1.45 (ddd, *J* =13.7, 3.7, 1.8 Hz, 2H), 1.33 (s, 3H), 1.30 (s, 3H), 1.28 (t, *J* =6.8 Hz, 6H), 1.15 (s, 3H), 1.13 (s, 3H), 1.05 (s, 3H), 0.99 (s, 3H), 0.92 (t, *J* =7.7 Hz, 18H), 0.55 (q, *J* =7.8 Hz, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.1, 170.0, 167.3, 152.5, 140.3, 140.2, 136.9, 136.8, 129.9, 129.8, 127.3, 126.7, 119.7, 119.6, 76.9, 76.2, 67.2, 66.4, 64.7, 64.4, 60.0, 48.1, 47.8, 42.4, 42.1, 35.8, 35.7, 32.2, 29.1, 29.0, 26.1, 25.6, 21.6, 21.5, 21.4, 20.9, 14.7, 14.1, 13.7, 13.4, 7.2, 5.1; ESI-HRMS m/z calcd for $C_{30}H_{50}O_6SiNa$ $(M+Na)^+$ 557.3295, found 557.3274.

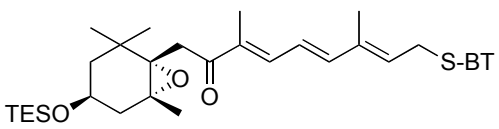
2-[(((2'*E*,4'*E*,6'*E*)-9'-(1''*S*,2''*R*,4''*S*)-4''-Triethylsilyloxy-1'',2''-epoxy-2'',6'',6''-trimethylcyclohex-1'-yl)-8'-hydroxy-3',7'-dimethylnona-2',4',6'-triene)sulfanyl]benzothiazole 15. To a solution of diester **14** (1.25 g, 2.34 mmol) in dichloromethane (11.7 mL) was added dropwise diisobutylaluminium hydride (1.0 M in toluene, 11.7 mL, 11.7 mmol) at –78 ºC. After the reaction mixture was stirred for 10 min at the same temperature, aqueous potassium sodium (+)-tartrate tetrahydrate solution was added, and then resulting mixture was extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*.



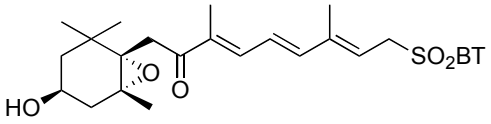
To a solution of crude diol, 2-mercaptobenzothiazole (470 mg, 2.81 mmol) and triphenylphosphine (737 mg, 2.81 mmol) in THF (11.7 mL) was added dropwise diisopropyl azodicarboxylate (0.59 mL,

3.04 mmol) at 0 ºC. The reaction mixture was stirred for 10 min at room temperature, and the all solvents were removed *in vacuo*. To a residue was added diethyl ether, and the precipitate was removed by filtration through a pad of Celite to give the crude products as a solution, which was concentrated *in vacuo*. Purification by short silica gel column chromatography (from 3% to 20% ethyl acetate in hexane) afforded thioether **15** (1.19 g, 85% for 2 steps) as a mixture of C8 epimer as a colerless oil: $[\alpha]^{24}_{D}$ -2.1 (c 1.03, $CHCl_3$); IR (neat, cm^{-1}) 3476, 2957, 2247, 1560, 1458, 1309, 1240, 1078, 1001, 908, 750; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.86 (d, *J* =7.8 Hz, 2H), 7.74 (d, *J* =7.8 Hz, 2H), 7.41 (td, *J* =8.7, 0.9 Hz, 2H), 7.29 (td, *J* =8.4, 1.4 Hz, 2H), 6.47 (dd, *J* =14.7, 11.0 Hz, 1H), 6.46 (dd, *J* =14.6, 11.0 Hz, 1H), 6.26 (d, *J* =15.5 Hz, 1H), 6.25 (d, *J* =15.2 Hz, 1H), 6.19 (d, *J* =11.0 Hz, 1H), 6.13 (d, *J* =11.0 Hz, 1H), 5.71 (t, *J* =7.8 Hz, 2H), 4.56 (d, *J* =10.5 Hz, 1H), 4.15 (d, *J* =8.2 Hz, 4H), 4.08 (d, *J* =10.0 Hz, 1H), 3.87 (s, 1H), 3.79 (m, 2H), 2.52 (d, *J* =2.7 Hz, 1H), 2.31-2.23 (m, 2H), 2.10-2.04 (m, 2H), 1.94 (s, 3H), 1.86-1.82 (m, 1H), 1.81 (s, 3H), 1.73-1.64 (m, 3H), 1.62 (s, 3H), 1.39 (s, 3H), 1.34 (s, 3H), 1.23 (dd, *J* =13.3, 9.2 Hz, 2H), 1.17 (s, 3H), 1.16 (s, 3H), 1.09 (s, 3H), 1.07 (s, 3H), 0.94 (t, *J* =7.8 Hz, 18H), 0.57 (q, *J* =7.8 Hz, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.6, 153.5, 140.3, 139.2, 136.4, 136.3, 135.6, 126.2, 124.9, 124.7, 124.6, 124.4, 121.7, 121.1, 77.6, 76.2, 74.1, 69.9, 67.9, 65.6, 65.4, 64.3, 64.1, 47.9, 47.7, 42.7, 41.8, 35.9, 35.6, 34.0, 33.0, 32.2, 29.1, 28.7, 26.6, 25.2, 21.5, 20.3, 13.5, 13.2, 12.8, 7.1, 5.0; ESI-HRMS m/z calcd for $C_{33}H_{49}NO_3S_2SiNa$ $(M+Na)^+$ 622.2821, found 622.2820.

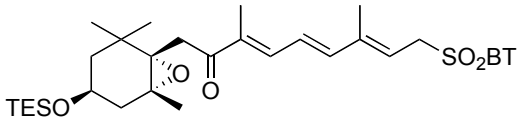
2-[(((2'*E*,4'*E*,6'*E*)-9'-(1''*S*,2''*R*,4''*S*)-4''-Triethylsilyloxy-1'',2''-epoxy-2'',6'',6''-trimethylcyclohex-1'-yl)-8'-carbonyl-3',7'-dimethylnona-2',4',6'-triene)sulfanyl]benzothiazole 15a. To a solution of thioether **15** (479 mg, 0.80 mmol) in dichloromethane (3.99 mL) was added Dess-Martin periodinane (509 mg, 1.20 mmol) at room temperature. After the reaction mixture was stirred for 10 min at the same temperature, the resulting mixture was purified by silica gel column chromatography (from 3% to 20% ethyl acetate in hexane) afforded **15a** (341 mg, 72%) as a yellow foam: $[\alpha]^{24}_{D}$ –2.0 (c 1.08, $CHCl_3$); IR (neat, cm^{-1}) 2957, 2876, 1740, 1664, 1608, 1469, 1240, 1078, 995, 756; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.87 (d, *J* =7.8 Hz, 1H), 7.75 (d, *J* =7.8 Hz, 1H), 7.42 (td, *J* =7.3, 1.4 Hz, 1H), 7.30 (td, *J* =8.2, 1.4 Hz, 1H), 7.06 (d, *J* =8.7 Hz, 1H), 6.60 (d, *J* =15.1 Hz, 1H), 6.55 (dd, *J* =15.1, 9.1 Hz, 1H) 5.95 (t, *J* =8.3 Hz, 1H), 4.18 (d, *J* =8.2 Hz, 2H), 3.75 (m, 1H), 3.61 (d, *J* =18.3 Hz, 1H), 2.51 (d, *J* =17.8 Hz, 1H), 2.19 (dd, *J* =13.7, 3.7 Hz, 1H) 1.98 (s, 3H), 1.92 (s, 3H), 1.77 (dd, *J* =13.8, 10.1 Hz, 1H) 1.42-1.30 (m, 2H), 1.18 (s, 3H), 0.99 (s, 3H), 0.94 (t, *J* =7.8 Hz, 9H), 0.92 (s, 3H), 0.90 (s, 3H), 0.58 (q, *J* =7.7 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 197.9, 165.9, 153.3, 143.8, 138.3, 138.3, 135.8, 135.5, 129.8, 126.2, 124.4, 124.1, 121.6, 121.1, 67.2, 66.8, 64.3, 48.4, 42.3, 41.0, 35.4, 31.8, 28.1, 24.6, 20.9, 12.7, 11.9, 6.9, 4.9; ESI-HRMS m/z calcd for $C_{27}H_{33}NO_5S_2Na$



$(M+Na)^+$ 538.1698, found 538.1677.

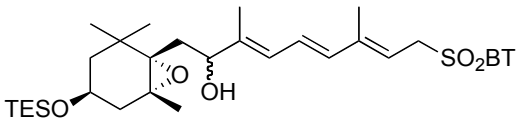


2-[(((2'*E*,4'*E*,6'*E*)-9'-(1''*S*,2''*R*,4''*S*)-4''-Hydroxy-1'',2''-epoxy-2'',6'',6''-trimethylcyclohex-1'-yl)-8'-carbonyl-3',7'-dimethylnona-2',4',6'-triene)sulfonyl]benzothiazole 16. To a solution of the thioether **15a** (53 mg, 0.089 mmol) in ethanol (1.3 mL) was added dropwise a solution of ammonium heptamolybdate tetrahydrate (11 mg, 0.0089 mmol) in hydrogen peroxide (30 wt.% in water, 0.35 mL) at 0 °C. After being stirred for 50 min at room temperature, the reaction mixture was poured into water, and then extracted with diethyl ether. The organic layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by short silica gel column chromatography (from 20% to 60% ethyl acetate in hexane) afforded the sulfone **16** (30 mg, 65%) as a yellow foam: $[\alpha]^{24.0}_D$ 1.39 (c 0.32, $CHCl_3$); IR (neat, cm^{-1}) 3444, 2926, 1660, 1609, 1471, 1329, 1150, 1053, 761; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.23 (d, *J* = 8.2 Hz 1H), 8.01 (d, *J* = 8.3 Hz 1H), 7.63 (m, 2H), 7.03 (d, *J* = 8.3 Hz, 1H), 6.56 (m, 2H), 5.72 (t, *J* = 8.2 Hz, 1H), 4.44 (d, *J* = 8.3 Hz, 2H), 3.80 (m, 1H), 3.60 (d, *J* = 18.3 Hz, 1H), 2.55 (d, *J* = 18.3 Hz, 1H), 2.31 (dd, *J* = 14.2, 3.2 Hz, 1H), 1.90 (s, 3H), 1.82 (s, 3H), 1.76 (dd, *J* = 13.7, 9.2 Hz, 1H), 1.48 (dm, *J* = 12.8 Hz, 1H), 1.33 (dd, *J* = 12.4, 10.9 Hz, 1H), 1.19 (s, 3H), 1.01 (s, 3H), 0.93 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 198.4, 165.9, 153.0, 143.8, 142.8, 138.0, 137.3, 137.0, 128.4, 128.1, 126.0, 125.8, 122.7, 118.8, 67.2, 66.4, 64.5, 60.7, 55.4, 47.4, 41.9, 41.2, 35.4, 28.4, 25.3, 21.4, 14.5, 13.2, 12.; ESI-HRMS m/z calcd for $C_{27}H_{33}NO_5S_2Na$ $(M+Na)^+$ 538.1698, found 538.1671.

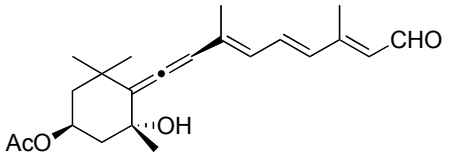


2-[(((2'*E*,4'*E*,6'*E*)-9'-(1''*S*,2''*R*,4''*S*)-4''-Triethylsiloxy-1'',2''-epoxy-2'',6'',6''-trimethylcyclohex-1'-yl)-8'-carbonyl-3',7'-dimethylnona-2',4',6'-triene)sulfonyl]benzothiazole 16a. To a solution **16** (157 mg, 0.30 mmol) in DMF (1.52 mL) was added imidazole (41 mg, 0.61 mmol) and TESCl (0.077 mL, 0.46 mmol) at room temperature. After the reaction mixture was stirred for 10 min at the same temperature, the resulting mixture was poured into a saturated aqueous $NaHCO_3$ solution, and extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by silica gel column chromatography (from 10% to 30% ethyl acetate in hexane) afforded **16a** (143 mg, 75%) as a yellow foam: $[\alpha]^{24}_D$ –2.1 (c 0.93, $CHCl_3$); IR (neat, cm^{-1}) 2984, 2878, 1742, 1664, 1473, 1373, 1242, 1047, 939; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.22 (dd, *J* =7.8, 0.9 Hz, 1H), 8.01 (dd, *J* =7.8, 0.9 Hz, 1H), 7.62 (m, 2H), 7.01 (d, *J* =8.7 Hz, 1H), 6.57 (d, *J* =15.2 Hz, 1H), 6.52 (dd, *J* =15.1, 7.8 Hz, 1H), 5.71 (t, *J* =7.3 Hz, 1H), 4.44 (d, *J* =8.2 Hz, 2H), 3.74 (m, 1H), 3.59 (d, *J* =18.3 Hz, 1H), 2.51 (d, *J*

=18.3 Hz, 1H), 2.19 (ddd, *J* =14.2, 5.0, 1.8 Hz, 1H), 1.88 (s, 3H), 1.81 (s, 3H), 1.76 (dd, *J* =13.8, 10.1 Hz, 1H), 1.39 (ddd, *J* =12.8, 3.7, 1.7 Hz, 1H), 1.33 (dd, *J* =12.9, 11.0 Hz, 1H), 0.99 (s, 3H), 0.94 (t, *J* =7.8 Hz, 9H), 0.92 (s, 3H), 0.89 (s, 3H), 0.56 (q, *J* =8.3 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 198.2, 165.8, 152.9, 143.7, 142.6, 137.7, 137.2, 137.0, 128.4 128.0, 126.0, 125.7, 122.6, 118.6, 67.3, 66.9, 64.5, 55.3, 48.6, 42.4, 41.3, 35.6, 28.3, 24.8, 21.1, 13.2, 12.2, 7.1, 5.1; ESI-HRMS m/z calcd for $C_{33}H_{47}NO_5S_2SiNa$ $(M+Na)^+$ 652.2552, found 652.2563.



2-[(((2'*E*,4'*E*,6'*E*)-9'-(1''*S*,2''*R*,4''*S*)-4''-Triethylsiloxy-1'',2''-epoxy-2'',6'',6''-trimethylcyclohex-1'-yl)-8'-hydroxy-3',7'-dimethylnona-2',4',6'-triene)sulfonyl]benzothiazole 5. To a solution **16a** (26 mg, 0.042 mmol) in THF (0.42 mL) was added $LiBH_4$ (2.7 mg, 0.13 mmol) at room temperature. After the reaction mixture was stirred for 50 min at the same temperature, the resulting mixture was poured into water, and extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by silica gel column chromatography (from 10% to 30% ethyl acetate in hexane) afforded **5** (14 mg, 51%) as a mixture of C8 epimer as a yellow foam: $[\alpha]^{24}_D$ +4.2 (c 0.67, $CHCl_3$); IR (neat, cm^{-1}) 3445, 2954, 1619, 1470, 1328, 1237, 1149, 1080; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.22 (d, *J* =7.8 Hz, 1H), 8.00 (d, *J* =7.8 Hz, 1H), 7.61 (m, 2H), 6.43 (dd, *J* =15.1, 11.0 Hz, 1H), 6.20 (d, *J* =15.1 Hz, 1H), 6.11 (d, *J* =10.5 Hz, 1H), 5.47 (t, *J* =8.3 Hz, 1H), 4.39 (d, *J* =7.8 Hz, 2H), 4.06 (d, *J* =10.1 Hz, 1H), 3.78 (m, 1H), 2.55 (d, *J* =2.3 Hz, 1H), 2.25 (dd, *J* =14.2, 3.6 Hz, 1H), 2.04 (dd, *J* =15.1, 10.0 Hz, 1H), 1.84 (td, *J* =15.0, 2.3 Hz, 1H), 1.77 (s, 3H), 1.73 (s, 3H), 1.66 (dd, *J* =14.7, 7.8 Hz, 1H), 1.58 (s, 3H), 1.48 (dm, *J* =11.4 Hz, 1H), 1.34 (s, 3H), 1.15 (dd, *J* =17.4, 11.4 Hz, 1H), 1.08 (s, 3H), 1.05 (s, 3H), 0.94 (t, *J* =7.7 Hz, 9H), 0.56 (q, *J* =7.8 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.1, 153.0, 144.5, 141.7, 137.3, 135.4, 128.3, 128.0, 126.6, 125.7, 124.5, 122.7, 114.0, 74.1, 68.1, 65.8, 64.3, 55.5, 47.7, 42.8, 35.7, 34.0, 28.8, 25.2, 20.4, 13.8, 13.2, 7.2, 5.1; ESI-HRMS m/z calcd for $C_{33}H_{49}NO_5S_2SiNa$ $(M+Na)^+$ 654.2719, found 654.2694.

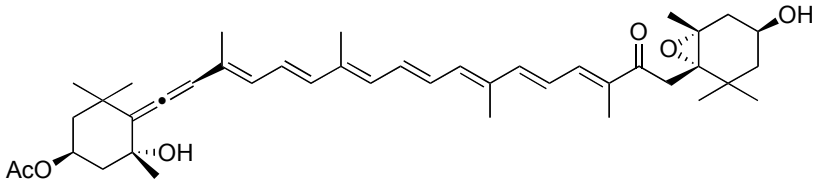


(2*E*,4*E*,6*E*)-9-[(1'*R*,2'*R*,4'*S*)-4'-Acetoxy-2'-hydroxy-2',6',6'-trimethylcyclohexylidene]-3,7-dimethylnona-2,4,6,8-tetraenal 4. A mixture of triol **17** (81 mg, 0.28 mmol) and manganese dioxide (1.11 g) in AcOEt (1.94 mL) was stirred at room temperature for 20 min. The precipitate was filtered through a pad of Celite, and the filtrate was concentrated *in vacuo* to afford crude aldehyde, which was used in the next reaction without further purification.

To a solution of crude aldehyde in pyridine (1.11 mL) were added acetic anhydride (0.039 mL, 0.42

mmol) and N,N-4-dimethylaminopyridine (3 mg, 0.028 mmol) at room temperature, and the reaction mixture was stirred for 10 min at the same temperature. A saturated aqueous $CuSO_4$ solution was added, and then the resulting mixture was extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by silica gel column chromatography (from 20% to 50% ethyl acetate in hexane) afforded acetate **4** (60 mg, 68%): $[\alpha]^{24.0}_D$ -26.3 (c 0.71, $CHCl_3$); IR (neat, cm^{-1}) 3447, 2965, 1929, 1729, 1652, 1583, 1366, 1246, 1141, 1028, 957; NMR ($CDCl_3$, 400 MHz) δ 10.1 (d, *J*= 8.2 Hz, 1H), 7.02 (dd, *J* = 15.2, 11.5 Hz, 1H), 6.34 (d, *J* = 15.1 Hz, 1H), 6.15 (d, *J* = 11.5 Hz, 1H), 6.06 (s, 1H), 5.96 (d, *J* = 8.2 Hz, 1H), 5.37 (m, 1H), 2.30 (s, 3H), 1.99 (ddd, *J* = 12.7, 4.1, 1.8 Hz, 1H), 1.86 (s, 3H), 1.50 (dd, *J* = 12.2, 12.1 Hz, 1H), 1.40 (m, 1H), 1.38 (s, 3H), 1.35 (s, 3H), 1.07 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 203.4, 191.5, 170.7, 154.9, 138.0, 135.0, 132.5, 129.5, 127.6, 118.2, 103.3, 77.9, 68.2, 46.0, 45.6, 36.1, 32.3, 31.4, 29.4, 21.7, 14.6, 13.4; ESI-HRMS m/z calcd for $C_{22}H_{30}O_4Na$ $(M+Na)^+$ 381.2042, found 381.2120.

Fucoxanthin (2). To a solution of sulfone **5** (21 mg, 0.035 mmol) and aldehyde **4** (32 mg, 0.099 mmol) in THF (0.32 mL)



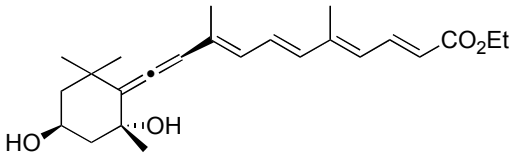
was added dropwise sodium bis(trimethylsilyl)amide (1.0M in THF, 0.16 mL, 0.16 mmol) at 0 ºC in the dark. After being stirred for 5 min at the same temperature, the reaction mixture was poured into water, and then extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by short silica gel column chromatography (from 10% to 30% ethyl acetate in hexane) in the dark afforded coupling product **18** (15.2 mg, 58%) as a mixture of the isomers in a red film.

To a solution of **18** (15.2 mg, 0.019 mmol) in dichloromethane (0.19 mL) was added Dess-Martin periodinane (10.6 mg, 0.025 mmol)at room temperature. After the reaction mixture was stirred for 20 min at the same temperature, the resulting mixture was purified by silica gel column chromatography (from 10% to 30% ethyl acetate in hexane) afforded **18a** (9.0 mg, 61%) as a red film.

To a solution of the ketone **18a** (9.0 mg, 0.012 mmol) in MeOH (0.12 mL) was added pyridinium *p*-toluenesulfonate (0.3 mg, 0.0012 mmol) at 0 ºC, and the reaction mixture was stirred for 25 min at the same temperature. A saturated aqueous $NaHCO_3$ solution was added, and then the resulting mixture was extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by silica gel column chromatography (from 30% to 60% ethyl acetate in hexane) afforded crude fucoxanthin (**2**) (5.3 mg, 70%). A solution of the obtained mixture containing *all trans*-fucoxanthin (**2**) and its *cis*-isomer in benzene was left at

room temperature under the irradiation with fluorescence light. After 3 days, the partial separation by preparative HPLC [column: Develosil CN-UG (0.6 x 25 cm); mobile phase: acetone / *n*-hexane = 1 / 8; flow rate: 2.0 mL / min.; UVdetect: 445 nm; retention time: (all-*trans*-isomer) 38 min] in the dark afforded the desired optically active fucoxanthin (**2**) (3.0 mg, 40%) as a red powder: IR (neat, cm^{-1}) 3442, 2923, 2854, 1929, 1729, 1655, 1607, 1576, 1364, 1249, 1051, 966; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.14 (d, *J* =10.1 Hz, 1H), 6.75 (dd, *J* =14.2, 11.9 Hz, 1H), 6.67 (d, *J* =15.1 Hz, 1H), 6.64 (dd, *J* =14.0, 11.4 Hz, 1H), 6.60 (dd, *J* =14.7, 11.4, Hz, 1H), 6.57 (dd, *J* =15.1, 11.0 Hz, 1H), 6.41 (d, *J* =11.4 Hz, 1H), 6.34 (d, *J* =15.1 Hz, 1H), 6.27 (d, *J* =11.7 Hz, 1H), 6.13 (d, *J* =11.5 Hz, 1H), 6.05 (s, 1H), 5.38 (m, 1H), 3.82 (m, 1H), 3.65 (d, *J* =18.4 Hz, 1H), 2.60 (d, *J* =18.4 Hz, 1H), 2.30 (m, 1H), 2.04 (s, 3H), 2.00 (m, 1H), 1.99 (s, 6H), 1.51 (m, 1H), 1.49 (m, 1H), 1.41 (m, 1H) , 1.38 (s, 3H), 1.35 (s, 3H) , 1.35 (m, 1H), 1.22 (s, 3H), 1.07 (s, 3H), 1.03 (s, 3H), 0.96 (s, 3H); ^{13}C NMR ($CDCl_3$, 100MHz) δ 202.7, 198.2, 170.4, 145.3, 139.4, 138.4, 137.4, 137.0, 135.8, 134.9, 132.9, 132.5, 129.8, 128.9, 126.0, 123.7, 117.9, 103.7, 73.0, 68.3, 67.4, 66.5, 64.7, 47.4, 45.8, 45.6, 42.0, 41.1, 36.1, 35.4, 32.4, 31.6, 30.1, 29.5, 28.5, 25.3, 21.7, 21.5, 14.3, 13.3, 13.1, 12.1; ESI-HRMS m/z Calcd for $C_{42}H_{58}O_6$ $(M+Na)^+$ 681.4131, found 681.4108.

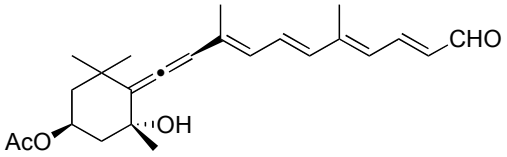
Ethyl(2*E*,4*E*,6*E*,8*E*)-11-[(1'*R*,2'*R*,4'*S*)-4'-acetoxy-2'-hydroxy-2',6',6'-trimethylcyclohexylidene]-5,9-dimethylundeca-2,4,6,8,10-pentaenoate 17a. A mixture of



triol **17** (350 mg, 1.09 mmol) and manganese dioxide (4.37 g) in AcOEt (10.93 mL) was stirred at room temperature for 30 min. The precipitate was filtered through a pad of Celite, and the filtrate was concentrated *in vacuo* to afford crude aldehyde (322 mg), which was used in the next reaction without further purification.

To a solution of ethyl diethyl phosphono acetate (0.21 mL, 1.06 mmol) in THF (5.09 mL) was added sodium hydride (0.122 mg, 3.05 mmol) at 0 ºC. After the mixture was stirred for 10 min at 0 ºC, a solution of the crude aldehyde (322 mg, 1.02 mmol) obtained above in THF (0.50 mL) was added at 0 ºC. After being stirred for 5 min at room temperature, the resulting mixture was poured into water, and extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by silica gel column chromatography (from 10% to 30% ethyl acetate in hexane) afforded tetraeneester **17a** (187 mg, 44% for 2 steps) as a yellow solid: $[\alpha]^{24.0}_D$ –15.5 (c 1.67, $CHCl_3$); IR (neat, cm^{-1}) 3733, 2960, 1929, 1698, 1617, 1571, 1454, 1368, 1136, 956; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.67 (dd, *J* = 15.1, 11.9 Hz, 1H), 6.71 (dd, *J* = 15.1, 11.4 Hz, 1H), 6.32 (d, *J* =15.1, 1H), 6.20 (d, *J* =12.4 Hz, 1H), 6.10 (d, *J* =11.4 Hz, 1H), 6.02 (s, 1H), 5.88 (d, *J* =15.1 Hz, 1H), 4.31 (m, 1H), 4.20 (q, *J* =7.3 Hz, 2H), 2.26 (ddd, *J* =12.8, 4.1, 2.3 Hz, 1H), 2.20 (s, 3H), 1.94

(ddd, *J* =12.3, 4.1, 2.3 Hz, 1H), 1.81 (s, 3H), 1.40 (dd, *J* =12.4, 11.4 Hz, 1H), 1.35 (m, 1H), 1.34 (s, 3H), 1.33 (s, 3H), 1.30 (t, *J* =7.3 Hz, 3H), 1.06 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 202.9, 167.8, 144.4, 140.7, 136.4, 134.8, 128.9, 128.5, 128.2, 120.8, 118.2, 103.3, 73.3, 64.6, 60.6, 49.7, 49.2, 36.2, 32.5, 31.7, 29.6, 14.7, 14.4, 13.5; ESI-HRMS m/z calcd for $C_{24}H_{34}O_4Na$ $(M+Na)^+$ 409.2355, found 409.2353.



(2*E*,4*E*,6*E*,8*E*)-11-[(1'*R*,2'*R*,4'*S*)-4'-Acetoxy-2'-hydroxy-2',6',6'-trimethylcyclohexylidene]-5,9-dimethylundeca-2,4,6,8,10-pentaenal 20. To a solution of ester **17a** (185 mg, 0.479 mmol) in dichloromethane (2.39 mL) was added dropwise diisobutylaluminium hydride (1.0 M in toluene, 2.87 mL, 2.87 mmol) at –78 ºC. After the reaction mixture was stirred for 5 min at the same temperature, aqueous potassium sodium (+)-tartrate tetrahydrate solution was added, and then resulting mixture was extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*.

A mixture of crude triol and manganese dioxide (2.39 g) in AcOEt (3.83 mL) was stirred at room temperature for 40 min. The precipitate was filtered through a pad of Celite, and the filtrate was concentrated *in vacuo* to afford crude aldehyde, which was used in the next reaction without further purification.

To a solution of crude aldehyde in CH_2Cl_2 (4.79 mL) were added a mixture of acetic anhydride (0.09 mL, 0.96 mmol) and triethyl amine (0.27 mL, 1.92 mmol) at room temperature and N,N-4-dimethylaminopyridine (12 mg, 0.096 mmol), and the reaction mixture was stirred for 20 min at the same temperature. A saturated aqueous $CuSO_4$ solution was added, and then the resulting mixture was extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by silica gel column chromatography (from 20% to 50% ethyl acetate in hexane) afforded aldehyde **20** (131 mg, 71%): $[\alpha]^{24.0}_D$ -18.4 (c 0.29, $CHCl_3$); IR (neat, cm^{-1}) 3446, 2964, 1929, 1727, 1666, 1567, 1365, 1250, 1125, 968; NMR ($CDCl_3$, 400 MHz) δ 9.61 (d, *J*= 7.7 Hz, 1H), 7.51 (dd, *J* = 14.7, 11.9 Hz, 1H), 6.81 (dd, *J* =15.0, 11.4 Hz, 1H), 6.36 (d, *J* =15.1 Hz, 1H), 6.34 (d, *J* =11.5 Hz, 1H), 6.17 (dd, *J* =15.1, 8.2 Hz, 1H), 6.14 (d, *J* =11.5 Hz, 1H), 6.06 (s, 1H), 5.37 (m, 1H), 2.28 (ddd, *J* =12.9, 4.1, 2.3 Hz, 1H), 2.10 (s, 3H), 2.04 (s, 3H), 1.99 (ddd, *J* =12.4, 4.1, 2.3 Hz, 1H), 1.84 (s, 3H), 1.51 (dd, *J* =12.8, 11.5 Hz, 1H), 1.41 (m, 1H), 1.38 (s, 3H), 1.36 (s, 3H), 1.07 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 203.1, 193.9, 170.7, 147.9, 146.8, 136.0, 135.9, 131.2, 129.8, 129.0, 128.2, 118.1, 103.5, 72.9, 68.2, 45.7, 45.5, 36.1, 32.3, 31.6, 29.4, 21.7, 14.5, 13.6.

C42-Fucoxanthin Derivative 3. To a solution of sulfone **5** (38.1 mg, 0.060 mmol) and aldehyde **20** (27.7 mg, 0.072 mmol) in THF (0.60 mL) was added dropwise sodium bis(trimethylsilyl)amide (1.0M in THF, 0.24 mL, 0.24 mmol) at 0 ºC in the dark. After being stirred for 5 min at the same temperature, the reaction mixture was poured into water, and then extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by short silica gel column chromatography (from 10% to 30% ethyl acetate in hexane) in the dark afforded coupling product **21** (21.9 mg, 45%) as a mixture of the isomers in a red film.

To a solution of **21** (15 mg, 0.019 mmol) in DMSO (0.13 mL) was added o-iodoxybenzoic acid (17 mg, 0.028 mmol) at room temperature. After the reaction mixture was stirred for 1 hour at the same temperature, the resulting mixture was purified by short silica gel column chromatography (from 10% to 30% ethyl acetate in hexane) afforded **21a** (5.6 mg, 38%) as a red film.

To a solution of the ketone **21a** (31 mg, 0.039 mmol) in MeOH (0.38 mL) was added pyridinium *p*-toluenesulfonate (0.9 mg, 0.0039 mmol) at 0 ºC, and the reaction mixture was stirred for 5 min at the same temperature. Water was added, and then the resulting mixture was extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by silica gel column chromatography (from 30% to 60% ethyl acetate in hexane) afforded crude C42 fucoxanthin derivative **3** (14.6 mg, 55%). A solution of the obtained mixture containing *all trans*-**3** and its *cis*-isomer in benzene was left at room temperature under the irradiation with fluorescence light. After 6 days, the partial separation by preparative HPLC [column: Develosil CN-UG (0.6 x 25 cm); mobile phase: acetone / *n*-hexane = 1 / 8; flow rate: 2.0 mL / min.; UVdetect: 460 nm; retention time: (all-*trans*-isomer) 49 min] in the dark gave crude C42 fucoxanthin derivative **3**, which was further purified by preparative HPLC [column: YMC Carotenoid C30 (1.0 x 25 cm); reverse phase: methanol; flow rate: 2.0 mL / min; UVdetect: 460 nm; retention time: (*all trans*-isomer) 15 min.] afforded the desired optically active C42 fucoxanthin derivative **3** (5.5 mg, 21%) as a red powder. The HPLC analysis from ketone **21a** to C42 derivative **3** is as shown in Fig. 2: IR (neat, cm^{-1}) 3442, 2924, 1929, 1733, 1653, 1363, 1246, 1030, 958; ^1H NMR (acetone-d6, 750 MHz) δ 7.14 (d, *J* =11.0 Hz, 1H), 6.66 (d, *J* =15.1 Hz, 1H), 6.60 (dd, *J* =13.8, 12.0 Hz, 1H), 6.60 (dd, *J* =13.8, 12.0 Hz, 1H), 6.57 (dd, *J* =15.1, 11.3, Hz, 1H), 6.49 (dd, *J* =14.4, 11.3, Hz, 1H), 6.39 (dd, *J* =14.4, 11.3 Hz, 1H), 6.35 (d, *J* =11.7 Hz, 1H), 6.10 (d, *J* =11.7 Hz, 1H), 6.05 (s, 1H), 5.38 (m, 1H), 3.81 (m, 1H),), 3.65 (d, *J* =18.2 Hz, 1H), 2.59 (d, *J* =18.2 Hz, 1H), 2.32 (dd, *J* =14.1, 3.4 Hz, 1H), 2.28 (dm, *J* =11.0 Hz, 1H), 2.04 (s, 3H), 1.99 (dm, *J* =13.8 Hz, 1H), 1.98 (s, 3H), 1.94 (s, 3H), 1.80 (s, 3H), 1.79 (dd, *J*

=13.7, 8.9 Hz, 1H), 1.50 (m, 2H), 1.40 (m, 1H) , 1.38 (s, 3H), 1.35 (s, 3H) , 1.34 (m, 1H), 1.22 (s, 3H), 1.07 (s, 3H), 1.03 (s, 3H), 0.96 (s, 3H); ^{13}C NMR ($CDCl_3$, 188MHz) δ 202.6, 197.9, 170.4, 145.0, 139.1, 136.5, 136.3, 135.4, 134.6, 133.6, 132.9, 131.1, 128.8, 128.1, 123.4, 117.6, 103.3, 72.7, 68.0, 67.1, 66.1, 64.3, 47.1, 45.4, 45.3, 41.7, 40.8, 35.8, 35.2, 32.1, 31.3, 29.2, 28.1, 25.0, 21.4, 21.2, 14.0, 12.7, 11.8; ESI-HRMS m/z Calcd for $C_{44}H_{60}O_6$ $(M+Na)^+$ 707.4288, found 707.4281.

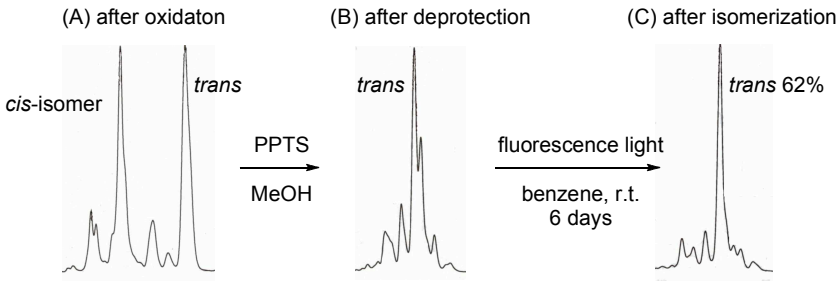


Fig. 2 HPLC analysis of C42 fucoxanthin derivative