

Article

Total Synthesis of Loroxanthin

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Abstract: The first total synthesis of loroxanthin (**1**) was accomplished by Horner-Wadsworth-Emmons reaction of C₂₅-apocarotenal **8** having a silyl-protected 19-hydroxy moiety with C₁₅-phosphonate **25** bearing a silyl-protected 3-hydroxy- ϵ -end group. Preparation of apocarotenal **8** was achieved via Stille coupling reaction of alkenyl iodide **10** with alkenyl stannane **9**, whereas phosphonate **25** was prepared through treatment of ally alcohol **23** with triethyl phosphite and ZnI₂. The ally alcohol **23** was derived from the known (3*R*,6*R*)-3-hydroxy C₁₅-aldehyde **20**, which was obtained by direct optical resolution of racemate **20** using a semi-preparative chiral HPLC column.

Keywords: carotenoids; loroxanthin; total synthesis; Stille-coupling; Horner-Wadsworth-Emmons reaction; optical resolution

1. Introduction

Loroxanthin (**1**) (Figure 1), one of the in-chain hydroxylated carotenoids [1], has been isolated from various green algae and is sometimes found as Δ^2 -fatty acid esters of the C19-hydroxy moiety [2–5]. It is presumed to be biosynthesized by C19-hydroxylation of lutein (**2**) and to be a biosynthetic precursor of siphonaxanthin (**4**), which is a major photosynthetic pigment of green algae [1,6,7]. The 3',6'-*trans*-configuration of the ϵ -end group in **1** was determined [8] by comparison of its ¹H-NMR spectrum with that of lutein (**2**), while the absolute configurations at C3 and C6' in **1** have been assigned as 3*R*,6'*R* [8] from the close resemblance of its circular dichroism (CD) spectrum with that of synthetic (3*R*,6'*R*)-loroxanthin model compound **3** [9]. However, compound **3** lacks a hydroxy group at C3' and thus its stereostructure has remained in dispute. Although some biological activities of **1** have been reported [10,11], its properties and functions are not yet well understood due to its limited availability from natural sources. Thus, interest in its function and structure prompted us to undertake the first total synthesis of **1**.

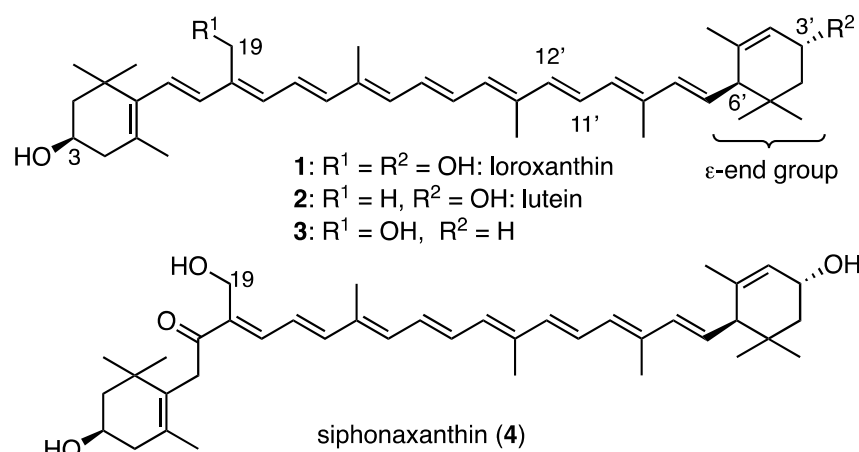


Figure 1. Structures of loroxanthin (**1**) and related carotenoids.



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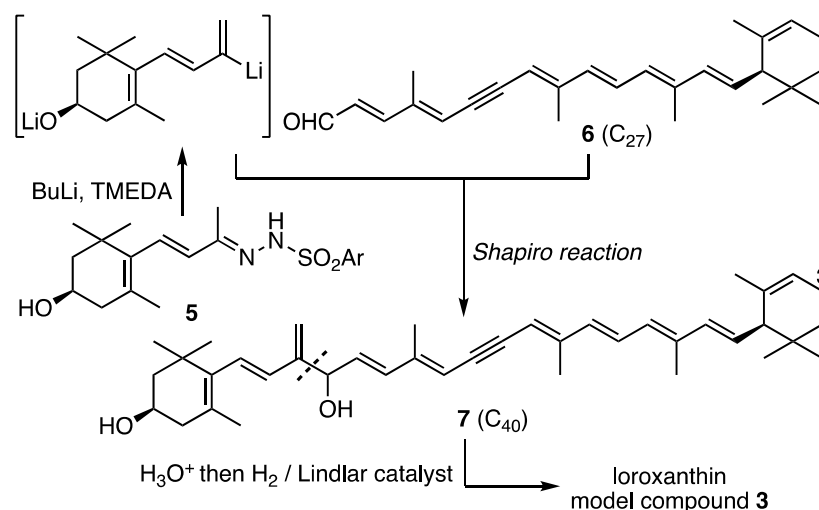
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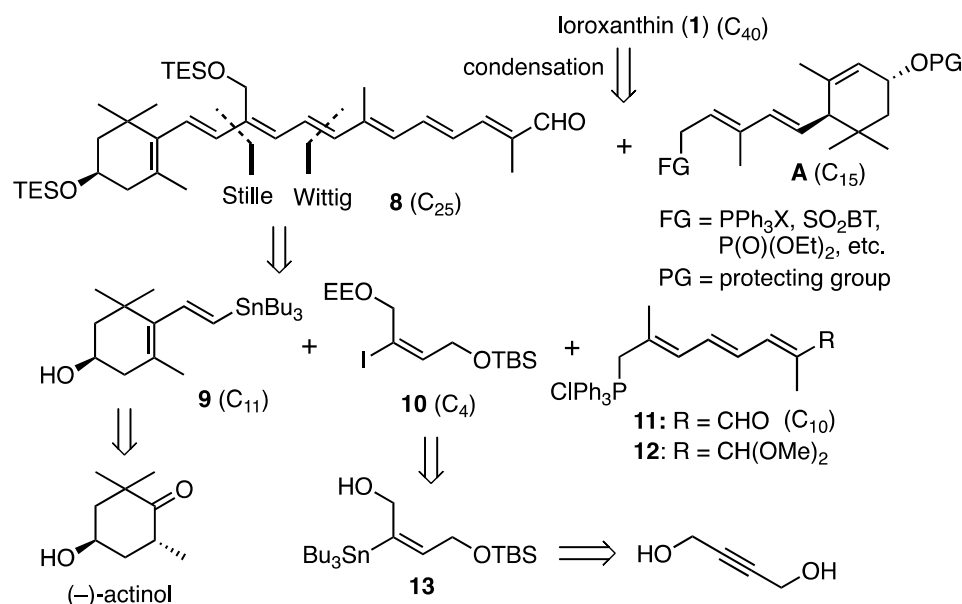
2. Results and Discussion

Loroxanthin model compound **3** was previously synthesized by utilizing the Shapiro reaction of C₁₃-(arylsulfonyl)hydrazone **5** with C₂₇-polyenal **6** and subsequent acid-promoted allylic rearrangement of the resulting adduct **7** and following Lindlar reduction [9] as shown in Scheme 1. However, this procedure cannot be applicable to the synthesis of loroxanthin itself, because the 3'-hydroxy-ε-end moiety of loroxanthin (**1**) is labile to the acidic conditions [12,13]. Moreover, many stereoisomers were produced during the conversion of compound **7** into compound **3**.



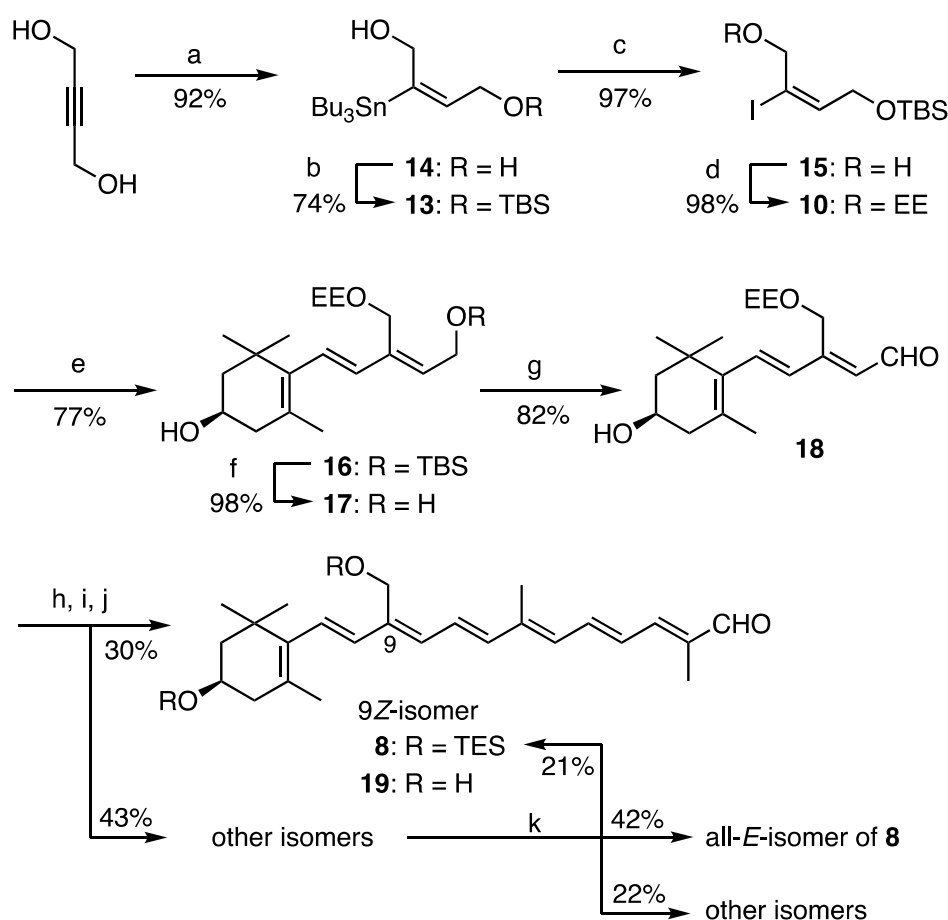
Scheme 1. Previous synthesis of loroxanthin model compound **3**.

Hence, we planned to synthesize loroxanthin (**1**) by the condensation of C₂₅-apocarotenal **8** with an appropriate C₁₅-building block **A** having a 3-hydroxy-ε-end group at the C11'–C12' double bond position on **1** as shown in Scheme 2. The apocarotenal **8** was expected to be prepared by a three-component connection, which involves the Stille coupling reaction of previously reported C₁₁-alkenyl stannane **9** [14] with the C₄-alkenyl iodide **10** and the Wittig reaction with the C₁₀-phosphonium salt **12** [15]. The compound **10** would be converted from the alkenyl stannane **13**, which was previously prepared from 1,4-butyne-1,3-diol [16,17].



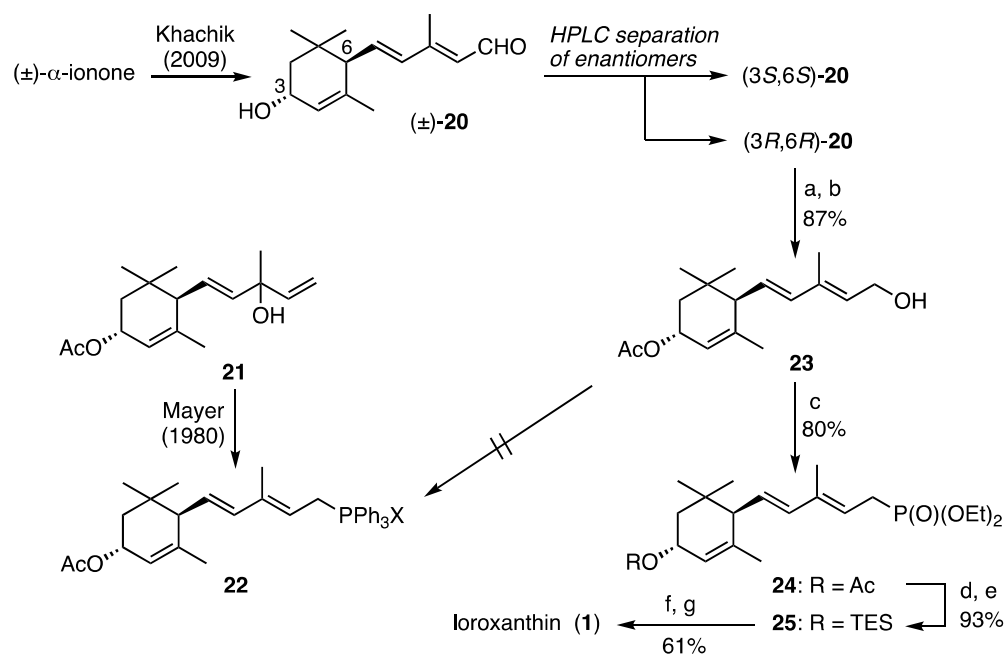
Scheme 2. Our synthetic plan of loroxanthin (**1**).

First, the C₂₅-apocarotenal **8** was prepared as shown in Scheme 3. According to the reported method [16,17], the *O*-*tert*-butyldimethylsilyl (TBS)-protected alkenyl stannane **13** was prepared by Pd-catalyzed stereoselective hydrostannylation of 1,4-butanediol and subsequent regioselective silylation of the resulting dihydroxy alkenyl stannane. The silylation yield improved (63% to 74%) by changing the reaction solvent from the reported *N,N*-dimethylformamide (DMF) to CH₂Cl₂. The alkenyl stannane **13** was treated with I₂ to provide the labile alkenyl iodide **15**, which was promptly reacted with ethyl vinyl ether in the presence of pyridinium *p*-toluenesulfonate (PPTS) to give the 1-ethoxyethyl (EE)-protected alkenyl iodide **10** in a high yield. Stille coupling reaction of this alkenyl iodide **10** with the C₁₁-alkenyl stannane **9** [14] under Baldwin's conditions [18] [Pd(PPh₃)₄, CsF, CuI] gave the desired coupling product **16** in a good yield. Desilylation of compound **16** by treatment with tetrabutylammonium fluoride (TBAF) and subsequent MnO₂ oxidation of the resulting alcohol **17** provided the aldehyde **18**. The Wittig condensation of C₁₅-aldehyde **18** with C₁₀-phosphonium salt **12** [15] in the presence of NaOMe as a base, followed by acidic treatment and subsequent protection of the hydroxy groups on the resulting condensed products **19** with triethylsilyl (TES) groups to yield 9*Z* (all-*trans*)-C₂₅-apocarotenal **8** (30% from **18**), accompanied by some stereoisomers (mainly contained 9*Z*,11*Z*-isomer: 42% from **18**). Palladium-catalyzed isomerization [19] of the latter, with careful observation of reaction progress by HPLC, afforded the desired 9*Z*-isomer of **8** (21%) along with its all-*E* (9-*cis*)-isomer (42%). The preference for 9*E* (9-*cis*)-isomer indicates its higher thermodynamic stability over the 9*Z* (9-*trans*)-isomer (Supplementary Materials).



Scheme 3. Preparation of C₂₅-apocarotenal **8**. Reagents and conditions: a, Bu₃SnH, PdCl₂(PPh₃)₂, /CH₂Cl₂; b, TBSCl, imidazole/CH₂Cl₂; c, I₂/CH₂Cl₂; d, ethyl vinyl ether, PPTS/CH₂Cl₂; e, **9**, Pd(PPh₃)₄, CsF, CuI/DMF; f, TBAF/THF; g, MnO₂/Et₂O; h, **12**, NaOMe/CH₂Cl₂; i, aq. HCl/THF–MeOH; j, TESCl, Et₃N, DMAP/CH₂Cl₂; k, PdCl₂(MeCN)₂, Et₃N/CH₃CN [16–19].

Next, the preparation of C₁₅-building block **A** (Scheme 2) having a 3-hydroxy- ϵ -end group was investigated. Mayer and Rüttimann reported [20] the preparation of the optically active phosphonium salt **22** (Scheme 4) for the total synthesis of lutein (**2**). They described that treatment of the tertiary allyl alcohol **21** with aqueous (aq.) hydrogen bromide afforded the unstable primary allyl bromide, which was reacted with triphenylphosphine, followed by treatment of the resulting phosphonium bromide **22** (X = Br) with NaCl solution to yield the phosphonium chloride **22** (X = Cl).



Scheme 4. Preparation of C₁₅-phosphonate **25** and its application for total synthesis of lutein (**1**). Reagents and conditions: a, Ac₂O, Et₃N, DMAP/CH₂Cl₂; b, NaBH₄/MeOH; c, ZnI₂, P(OEt)₃/THF/reflux; d, NaOMe/MeOH; e, TESCl, Et₃N, DMAP/CH₂Cl₂; f, **8**, NaN(TMS)₂/THF; g, TBAF/THF [13,20].

Several attempts to prepare the phosphonium salt **22** from the allyl alcohol **23** were disappointingly unsuccessful, whereas the phosphonate **25** could be prepared as an efficient building block **A** as shown in Scheme 4. Their precursor (3*R*,6*R*)-allyl alcohol **23** was derived from the known (3*R*,6*R*)-aldehyde **20** [13]. Khachik and Chang obtained (3*R*,6*R*)-**20** by lipase-mediated kinetic acetylation of racemate **20** [13]. We found that both enantiomers of **20** can be separated using a chiral HPLC column (CHIRALPAK IF; Daicel, Tokyo, Japan) and EtOH–tertiary butyl methyl ether (TBME) (1:9) as an eluent with high efficiency [Figure 2a]. Thus, direct optical resolution of racemate **20** was performed using a semi-preparative chiral column as shown in Figure 2b. Approximately 1 g of the racemate **20** could be separated into each pure enantiomer in 5 h by repeated injection of 70 mg of sample at 20-min intervals. Next, after protecting of the hydroxy group of (3*R*,6*R*)-**20** with an acetyl group, the resulting compound was reduced to the allyl alcohol **23**. Referring to Wiemer’s method [21], this was treated with triethyl phosphite and ZnI₂ under refluxing dry tetrahydrofuran (THF) to give phosphonate **24** in a good yield. The reaction time under reflux conditions was shortened from overnight (12 h) as described in the literature [21] to 30 min. TES-protected phosphonate **25** was obtained by alcoholysis of the acetyl group of **24** and subsequent silylation of the resulting hydroxy group.

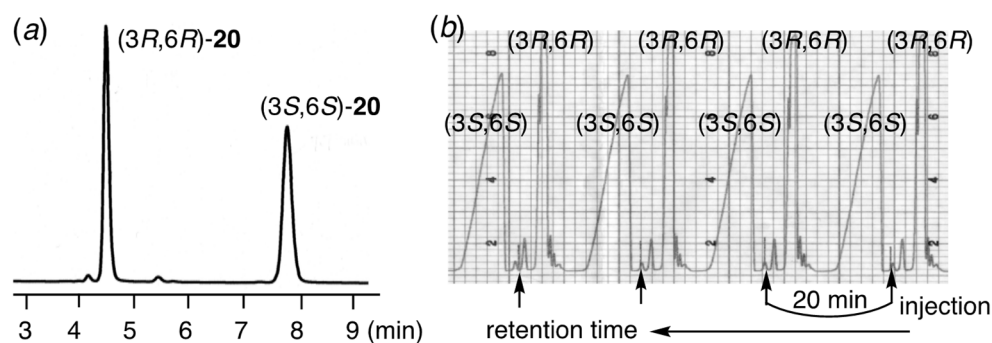


Figure 2. HPLC separation of enantiomers of 3-hydroxy C_{15} -aldehyde **20**. (a) Analytical conditions: column: CHIRALPAK IF 0.46×25 cm (Daicel, Tokyo, Japan), eluent: EtOH-TBME (1:9), flow rate: 1.0 mL/min, detection: 280 nm; (b) Preparative conditions: column: CHIRALPAK IF 2.0×25 cm (Daicel, Tokyo, Japan), eluent: EtOH-TBME (1:9), flow rate: 6.0 mL/min, detection: 280 nm.

Finally, Horner-Wadsworth-Emmons reaction of apocarotenal **8** with phosphonate **25** in the presence of sodium bis(trimethylsilyl)amide [$\text{NaN}(\text{TMS})_2$] followed by desilylation with TBAF afforded loroxanthin (**1**) stereoselectively in 61% yield in two steps. Total yield of **1** from alkenyl stanane **9** including isomerization recovery of apocarotenal **8** was 15% over 9 steps and that from (3*R*,6*R*)-aldehyde was 39% over 7 steps. Its ^1H -NMR spectral data were in good agreement with the reported data [8]. While the CD spectrum of the natural product was reported to be non-conservative with a weak positive Cotton effect around 250 nm [8], that of the synthetic product showed a relatively clear curve as shown in Figure 3. Good similarity with the reported spectrum of (3*R*,3'*R*,6'*R*)-lutein (**2**) [13] having the same configuration was observed.

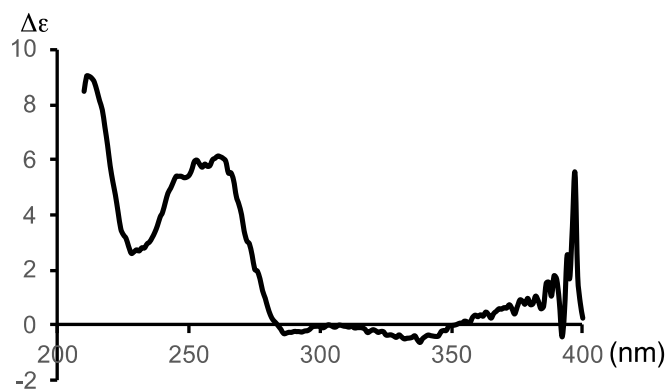


Figure 3. CD spectrum of synthetic loroxanthin in EPA [Et_2O -isopentane-EtOH (5:5:2)] solution.

In summary, the first total synthesis of loroxanthin (**1**) was accomplished via stereoselective condensation of C_{25} -apocarotenal **8** with C_{15} -phosphonate **25**. Preparation of apocarotenal **8** was achieved via Stille coupling reaction of alkenyl iodide **10** with alkenyl stanane **9**, whereas phosphonate **25** was prepared through treatment of ally alcohol **23** with triethyl phosphite and ZnI_2 . The phosphonate **25** would be a versatile building block for carotenoids with 3-hydroxy- ϵ -end group such as lutein (**3**) and siphonaxanthin (**4**). Recent our achievement of the total synthesis of 19-deoxysiphonaxanthin, siphonaxanthin biosynthetic precursor, also proves usefulness of phosphonate **25** [22]. This method will provide a material needed for investigating the biological functions of **1**.

3. Experimental Section

3.1. General

UV-VIS spectra were recorded on a JASCO V-650 instrument (JASCO, Tokyo, Japan), with ethanol solutions. IR spectra were measured on a Perkin-Elmer spectrum 100 FT-

IR spectrometer (Perkin-Elmer, Yokohama, Japan), with chloroform solutions. ^1H - and ^{13}C -NMR spectra were determined on a Varian Gemini-300 or a Varian NMR System AS 500 superconducting FT-NMR spectrometer (Varian Inc., Palo Alto, CA, USA), with CDCl_3 solutions. The chemical shifts are expressed in ppm relative to tetramethylsilane (TMS) ($\delta = 0$) as internal standard for ^1H -NMR and CDCl_3 ($\delta = 77.0$) for ^{13}C -NMR. J values are given in Hz. Mass spectra were taken on a Thermo Fisher Scientific Exactive spectrometer (Thermo Fisher Scientific, Bremen, Germany).

CD spectra on a JASCO J-820 circular dichroism spectrometer (JASCO, Tokyo, Japan). The concentrations were calculated using $\log \epsilon = 5.0$ at main λ_{max} (in EPA). Optical rotations were measured on a JASCO P-2200 polarimeter (JASCO, Tokyo, Japan).

Flash column chromatography (CC) was performed on using Kanto Silica Gel 60 N. Preparative HPLC was carried out on a Shimadzu LC-6A with a UV-VIS detector (Shimadzu, Kyoto, Japan). Preparative HPLC was carried out on a JASCO PU-2080 with a UV-VIS detector (JASCO, Tokyo, Japan). HPLC analyses were performed on Shimadzu-LC-20AT instrument (Shimadzu, Kyoto, Japan) with a photodiode array detector (GL-Sciences, Tokyo, Japan).

All operations were carried out under nitrogen or argon. Evaporation of the extract or the filtrate was carried out under reduced pressure. In solvent extraction procedure, organic layer was dried over anhydrous Na_2SO_4 . Ether refers to diethyl ether, and hexane to *n*-hexane. NMR assignments are given using the carotenoid numbering system.

3.2. Synthesis of C_{25} -Apocarotenal 8

(*E*)-7-Iodo-2,2,3,3,10-pentamethyl-4,9,11-trioxa-3-silatrdec-6-ene (**10**). To a cooled (0°C) solution of I_2 (3.79 g, 14.9 mmol) in dry CH_2Cl_2 (40 mL) was slowly added a solution of the alkenyl stanane **13** [17] (7.00 g, 14.2 mmol) in dry CH_2Cl_2 (10 mL) and the reaction mixture was stirred at 0°C for 10 min (min). 10% aq. $\text{Na}_2\text{S}_2\text{O}_3$ (20 mL) was added and the mixture was stirred at room temperature (rt) for 5 min. After CH_2Cl_2 was evaporated off, the mixture was diluted with AcOEt and washed brine, dried and evaporated. The residue was purified by flash CC [KF-SiO_2 (1:9), AcOEt-hexane, 15:85 to 2:8] to give the labile alkenyl iodide **15** (4.54 g, 97%) as a colorless oil: δ_{H} (300 MHz) 0.08 (6H, s, $\text{SiCH}_3 \times 2$), 0.89 (9H, s, *tert*-Bu), 2.52 (1H, t, J 6.5, OH), 4.21 (2H, td, J 0.5, 6.3, CH_2OTBS), 4.28 (2H, qd-like, J 1, 6.6, CH_2OH), 6.45 (1H, tt, J 1.5, 6.3, =CH); δ_{C} (75 MHz) −5.33 ($\text{C} \times 2$), 18.23, 25.78 ($\text{C} \times 3$), 61.19, 66.61, 104.67, 141.50.

To a cooled (0°C) solution of the compound **15** (4.54 g, 13.8 mmol) and ethyl vinyl ether (4.13 mL, 41.5 mmol) in dry CH_2Cl_2 (40 mL) was added PPTS (174 mg, 0.69 mmol) and the reaction mixture was stirred at rt for 40 min. Saturated aq. NaHCO_3 (20 mL) was added and the mixture was stirred at rt for 5 min. After CH_2Cl_2 was evaporated off, the mixture was diluted with AcOEt and washed brine, dried and evaporated. The residue was purified by flash CC (SiO_2 , AcOEt-hexane, 1:9) to give the EE-protected alkenyl iodide **10** (5.42 g, 98%) as a colorless oil: δ_{H} (300 MHz) 0.07 (6H, s, $\text{SiCH}_3 \times 2$), 0.89 (9H, s, *tert*-Bu), 1.22 (3H, t, J 7.2, OCH_2CH_3), 1.36 (3H, d, J 5.4, CHCH_3), 3.53 and 3.68 (each 1H, qd, 7.2, 9.3, OCH_2CH_3), 4.22 (4H, m, $\text{OCH}_2 \times 2$), 4.77 (1H, q, J 5.4, CHCH_3), 6.51 (1H, tt, J 1.5, 6.3, =CH); δ_{C} (75 MHz) −5.30 ($\text{C} \times 2$), 15.26, 18.23, 19.67, 25.80 ($\text{C} \times 3$), 60.51, 61.08, 67.02, 98.52, 99.46, 144.03; HRMS (ESI) m/z calcd for $\text{C}_{14}\text{H}_{29}\text{O}_3\text{INaSi}$ [$\text{M} + \text{Na}$] $^+$ 423.0823, found 428.0823.

(1*R*)-4-[(1*E*,3*Z*)-5-*tert*-Butyldimethylsilyloxy-3-(1-ethoxyethoxymethyl)penta-1,3-dien-1-yl]-3,5,5-trimethylcyclohex-3-en-1-ol (**16**). To a degassed solution of the C_{11} -alkenyl stanane **9** (910 mg, 2.00 mmol) and the alkenyl iodide **10** (960 mg, 2.40 mmol) in DMF (20 mL) were added CsF (608 mg, 4.00 mmol) and $\text{Pd}(\text{PPh}_3)_4$ (232 mg, 0.20 mmol) and CuI (76 mg, 0.40 mmol). After being stirred at 45°C for 1.5 h (h), the mixture was diluted with water and extracted with AcOEt. The organic layer was washed with brine, dried and evaporated to give the residue, which was purified by flash CC [KF-SiO_2 (1:9), AcOEt-hexane, 3:7] to give the coupling product **16** (673 mg, 77%) as a pale yellow oil: $[\alpha]_{\text{D}}^{22}$ −64.6 (c 1.00, MeOH); $\nu_{\text{max}}/\text{cm}^{-1}$ 3606 and 3459 (OH); δ_{H} (300 MHz) 0.09 (6H, s, $\text{SiCH}_3 \times 2$), 0.91 (9H, s, *tert*-Bu), 1.05 (6H, s, *gem*- CH_3), 1.22 (3H, t, J 7.2, OCH_2CH_3), 1.32 (3H, d, J 5.4, CHCH_3),

1.46 (1H, t, *J* 12, 2- H_{ax}), 1.71 (3H, br s, 5- CH_3), 1.76 (1H, ddd, *J* 2, 3.5, 12, 2- H_{eq}), 2.02 (1H, br dd, *J* 9.5, 16.5, 4- H_{ax}), 2.36 (1H, br dd, *J* 6, 16.5, 4- H_{eq}), 3.51 and 3.63 (each 1H, qd, 7.2, 9.3, OCH_2CH_3), 3.99 (1H, m, 3-H), 4.21 and 4.30 (each 1H, d, *J* 11.4, CH_2OEE), 4.40 (2H, d, *J* 6.5, CH_2OTBS), 4.73 (1H, q, *J* 5.4, $CHCH_3$), 5.73 (1H, t, *J* 6.5, 10-H), 5.95 (1H, d, *J* 16, 8-H), 6.23 (1H, br d, *J* 16, 7-H); δ_C (75 MHz) –5.18 ($C \times 2$), 15.31, 18.36, 19.68, 21.44, 25.94 ($C \times 3$), 28.54 and 28.56 (split), 30.12, 37.02, 42.31, 48.27, 59.72, 59.91, 60.06, 65.01, 98.59, 125.87, 126.59 and 126.62 (split), 134.04, 134.70, 135.14 and 135.17 (split), 137.47; HRMS (ESI) *m/z* calcd for $C_{25}H_{46}O_4NaSi$ [$M + Na$]⁺ 461.3058, found 461.3062.

(1*R*)-4-[(1*E*,3*Z*)-3-(1-ethoxyethoxymethyl)-5-hydroxypenta-1,3-dien-1-yl]-3,5,5-trimethylcyclohex-3-en-1-ol (**17**). To a cooled (0 °C) solution of the compound **16** (1.90 g, 4.33 mmol) in dry THF (17 mL) was added TBAF (1.0 M in THF; 5.85 mL, 5.85 mmol) and the mixture was stirred at rt for 1 h. After being quenched by addition of saturated aq. NH_4Cl , the mixture was extracted with AcOEt. The extracts were washed with brine, dried and evaporated to give the residue, which was purified by flash CC (SiO_2 , acetone-hexane, 1:2 to 2:3) to provide the alcohol **17** (1.38 g, 98%) as a pale brown oil: $[\alpha]_D^{23}$ –83.8 (c 1.02, MeOH); ν_{max}/cm^{-1} 3608 and 3430 (OH); δ_H (300 MHz) 1.04 and 1.05 (each 3H, s, *gem*- CH_3), 1.23 (3H, t, *J* 7.2, OCH_2CH_3), 1.34 (3H, d, *J* 5.5, $CHCH_3$), 1.46 (1H, t, *J* 12, 2- H_{ax}), 1.70 (3H, br s, 5- CH_3), 1.76 (1H, ddd, *J* 2, 3.5, 12, 2- H_{eq}), 2.02 (1H, br dd, *J* 9.5, 17, 4- H_{ax}), 2.36 (1H, br dd, *J* 5.5, 17, 4- H_{eq}), 3.55 and 3.63 (each 1H, qd, 7.2, 9.3, OCH_2CH_3), 3.98 (1H, m, 3-H), 4.22 and 4.33 (each 1H, dd, *J* 7, 13, CH_2OH), 4.35 (2H, s, CH_2OEE), 4.80 (1H, q, *J* 5.4, $CHCH_3$), 5.91 (1H, t, *J* 7, 10-H), 5.96 (1H, d, *J* 16, 8-H), 6.29 (1H, br d, *J* 16, 7-H); δ_C (75 MHz) 15.15, 19.42, 21.40, 28.51 and 28.55 (split), 30.10, 36.98 and 37.01 (split), 42.23, 48.13, 58.35, 59.15, 59.60, 64.92, 97.82 and 97.87 (split), 126.11 and 126.14 (split), 127.53, 132.69, 134.96 and 135.02 (split), 136.84, 137.35; HRMS (ESI) *m/z* calcd for $C_{19}H_{32}O_4Na$ [$M + Na$]⁺ 347.2193, found 347.2196.

(2*Z*,4*E*)-3-(1-ethoxyethoxymethyl)-5-[(*R*)-4-hydroxy-2,6,6-trimethylcyclohex-1-en-1-yl]penta-2,4-dienal (**18**). MnO_2 (2.5 g) was added to a stirred solution of the alcohol **17** (490 mg, 1.51 mmol) in Et_2O (15 mL) at rt. After being stirred at rt for 1.5 h, the mixture was filtered through a pad of Celite and the filtrate was concentrated. The resulting mixture was purified by flash CC (SiO_2 , acetone-hexane, 1:2) to give the aldehyde **18** (400 mg, 82%) as a yellow oil: $[\alpha]_D^{25}$ –75.7 (c 1.00, MeOH); ν_{max}/cm^{-1} 3606 and 3462 (OH), 1663 (conj. CO), 1609 ($C=C$); δ_H (300 MHz) 1.09 (6H, br s, *gem*- CH_3), 1.22 (3H, t, *J* 7.2, OCH_2CH_3), 1.37 (3H, d, *J* 5.4, $CHCH_3$), 1.49 (1H, t, *J* 12, 2- H_{ax}), 1.75 (3H, br s, 5- CH_3), 1.78 (1H, ddd, *J* 2, 3.5, 12, 2- H_{eq}), 2.06 (1H, br dd, *J* 9.5, 17.5, 4- H_{ax}), 2.41 (1H, br dd, *J* 5.5, 17.5, 4- H_{eq}), 3.51 and 3.62 (each 1H, qd, *J* 7, 9, OCH_2CH_3), 4.00 (1H, m, 3-H), 4.67 (2H, s, CH_2OEE), 4.80 (1H, q, *J* 5.4, $CHCH_3$), 6.01 (1H, d, *J* 8, 10-H), 6.13 (1H, d, *J* 16, 8-H), 6.80 (1H, br d, *J* 16, 7-H), 10.18 (1H, d, *J* 8, CHO); δ_C (75 MHz) 15.26, 19.62, 21.57, 28.69, 30.12, 37.07, 42.51, 48.21, 59.15, 60.57, 64.72, 99.13, 129.40, 129.86, 133.48, 135.79, 136.96, 153.14, 191.55; HRMS (ESI) *m/z* calcd for $C_{19}H_{30}O_4Na$ [$M + Na$]⁺ 345.2036, found 345.2039.

2,7-Dimethyl-11-triethylsilyloxymethyl-13-[(*R*)-2,6,6-trimethyl-4-triethylsilyloxycyclohex-1-en-1-yl]trideca-2,4,6,8,10,12-hexaenal (**8**). An acidic solution (1.5 mL) prepared from *p*-TsOH (500 mg) and H_3PO_4 (725 mg) in MeOH (40 mL) and methyl orthoformate (1.90 mL, 17.4 mmol) was added to a solution of the C_{10} -phosphonium chloride **11** [15] (2.58 g, 5.78 mmol) in THF (2 mL) and MeOH (20 mL). The reaction mixture was stirred at rt for 2 h and neutralized with NaOMe (28% in MeOH) until just before the red color of an ylide appeared to give a solution of the Wittig salt **12**. To this solution were added a solution of the aldehyde **18** (790 mg, 2.45 mmol) in CH_2Cl_2 (5 mL) and NaOMe (28% in MeOH; 1.67 mL, 8.65 mmol) at rt. After being stirred at rt for 30 min, the mixture was poured into saturated aq. NH_4Cl and extracted with AcOEt. The extracts were washed with brine and concentrated. The resulting mixture were dissolved in THF (25 mL) and MeOH (5 mL) and 5% aq. HCl was added to it. After being stirred at rt for 20 min, the mixture was diluted with AcOEt and washed with brine, dried and evaporated. The resulting residue was purified by flash CC (SiO_2 , MeOH-acetone- CH_2Cl_2 , 2:20:80) to provide the isomeric mixture of the dihydroxy apocarotenal **19**, a part of which was purified by preparative

HPLC (COSMOSIL 5SL-II 2 × 25 cm (Nacalai tesque, Kyoto, Japan); MeOH-AcOEt-hexane, 1.5:30:60) to provide the pure 9Z-apocarotenal of **19** as orange foam.

A solution of the above isomeric mixture of **19**, Et₃N (1.76 mL, 12.2 mmol) and dimethylaminopyridine (DMAP) (19 mg, 0.16 mmol) in dry CH₂Cl₂ (30 mL) was added TESCl (1.27 mL, 7.6 mmol) at 0 °C and the mixture was stirred at rt for 20 min. After addition of saturated aq NaHCO₃ (5 mL), CH₂Cl₂ was evaporated off and the resulting mixture was diluted with AcOEt and washed with brine, dried and evaporated. The residue was purified by flash CC (SiO₂, AcOEt-hexane, 1:4) and then preparative HPLC (COSMOSIL 5SL-II 2 × 25 cm (Nacalai tesque, Kyoto, Japan); AcOEt-hexane, 6:94) to provide the 9Z-isomer of di-TES-apocarotenal **8** (445 mg, 30% from **18**) and the other isomeric mixture of **8** (642 mg, 43% from **18**) as an orange foam, respectively.

To a solution of the latter isomeric mixture (642 mg) of **8** in MeCN (40 mL) was added to a solution of PdCl₂(MeCN)₂ (13 mg), Et₃N (7 µL) in MeCN (8.8 mL) and water (1.2 mL). After being stirred at rt for 3.5 h, the mixture was concentrated and purified by flash CC (SiO₂, AcOEt-hexane, 1:4) and then preparative HPLC (COSMOSIL 5SL-II 2 × 25 cm (Nacalai tesque, Kyoto, Japan); AcOEt-hexane, 6:94) to provide the 9Z-isomer of apocarotenal **8** (136 mg, 21%) and the all-*E*-isomer of **8** (271 mg, 42%).

9Z-Isomer of 19: λ_{max}(EtOH)/nm 422; ν_{max}/cm^{−1} 3608 and 3454 (OH), 1658 (conj. CO), 1610, 1597 and 1548 (C=C); δ_H (500 MHz) 1.087 and 1.089 (each 3H, s, *gem*-CH₃), 1.49 (1H, t, *J* 12, 2-H_{ax}), 1.76 (3H, br s, 5-CH₃), 1.78 (1H, ddd, *J* 2, 3.5, 12, 2-H_{eq}), 1.89 (3H, br s, 13'-CH₃), 2.04 (3H, br s, 13-CH₃), 2.06 (1H, br dd, *J* 10, 17, 4-H_{ax}), 2.40 (1H, br dd, *J* 5.5, 17, 4-H_{eq}), 4.01 (1H, m, 3-H), 4.57 (2H, s, CH₂OH), 6.07 (1H, d, *J* 16, 8-H), 6.26 (1H, d, *J* 12, 10-H), 6.34 (1H, br d, *J* 11.5, 14-H), 6.41 (1H, br d, *J* 16, 7-H), 6.45 (1H, d, *J* 15, 12-H), 6.71 (1H, dd, *J* 12, 14.5, 15'-H), 6.86 (1H, dd, *J* 12, 15, 11-H), 6.96 (1H, br d, *J* 11.5, 14'-H), 7.02 (1H, dd, *J* 12, 14.5, 15-H), 9.46 (1H, s, CHO); δ_C (125 MHz) 9.64 (13'-CH₃), 13.11 (13-CH₃), 21.68 (5-CH₃), 28.77 and 30.31 (*gem*-CH₃), 37.15 (C1), 42.57 (C4), 48.40 (C2), 57.41 (CH₂OH), 64.99 (C3), 126.11 (C11), 127.06 (C5), 127.68 (C7), 128.09 (C15'), 132.07 (C14), 132.73 (C10), 135.25 (C8), 137.33 (C13'), 137.37 (C15), 137.57 (C6), 138.90 (C12), 138.96 (C9), 141.15 (C13), 148.61 (C14'), 194.48 (CHO); HRMS (ESI) *m/z* calcd for C₂₅H₃₅O₃ [M+H]⁺ 383.2586, found 383.2587.

9Z-Isomer of 8: λ_{max}(EtOH)/nm 420; ν_{max}/cm^{−1} 1661 (conj. CO), 1610, 1596 and 1548 (C=C); δ_H (500 MHz) 0.62 and 0.66 (each 6H, q, *J* 8, SiCH₂ × 6), 0.981 and 0.986 (each 9H, t, *J* 8, SiCH₂CH₃ × 6), 1.06 and 1.07 (each 3H, s, *gem*-CH₃), 1.51 (1H, t, *J* 12, 2-H_{ax}), 1.67 (1H, ddd, *J* 2, 3.5, 12, 2-H_{eq}), 1.73 (3H, br s, 5-CH₃), 1.88 (3H, br s, 13'-CH₃), 2.03 (3H, br s, 13-CH₃), 2.10 (1H, br dd, *J* 10, 17, 4-H_{ax}), 2.25 (1H, br dd, *J* 5, 17, 4-H_{eq}), 3.95 (1H, m, 3-H), 4.54 (2H, s, CH₂O), 6.04 (1H, d, *J* 16, 8-H), 6.21 (1H, d, *J* 12, 10-H), 6.32 (1H, br d, *J* 11.5, 14-H), 6.39 (1H, br d, *J* 16, 7-H), 6.40 (1H, d, *J* 15, 12-H), 6.70 (1H, dd, *J* 11.5, 14, 15'-H), 6.91 (1H, dd, *J* 12, 15, 11-H), 6.96 (1H, br d, *J* 11.5, 14'-H), 7.02 (1H, dd, *J* 11.5, 14, 15-H), 9.46 (1H, s, CHO); δ_C (125 MHz) 4.50 (C × 3), 4.93 (C × 3), 6.84 (C × 3), 6.87 (C × 3), 9.60, 12.95, 21.63, 28.62, 30.19, 37.14, 43.22, 48.93, 57.81, 65.31, 127.11, 127.27, 127.68, 128.11, 131.49, 131.67, 135.46, 137.06, 137.52, 137.60, 137.86, 139.62, 141.43, 148.75, 194.46; HRMS (ESI) *m/z* calcd for C₃₇H₆₃O₃Si₂ [M + H]⁺ 611.4310, found 611.4319.

all-*E*-Isomer of 8: λ_{max}(EtOH)/nm 417; ν_{max}/cm^{−1} 1660 (conj. CO), 1610, 1602 and 1555 (C=C); δ_H (500 MHz) 0.63 and 0.66 (each 6H, q, *J* 8, SiCH₂ × 6), 0.987 and 0.991 (each 9H, t, *J* 8, SiCH₂CH₃ × 6), 1.06 and 1.08 (each 3H, s, *gem*-CH₃), 1.53 (1H, t, *J* 12, 2-H_{ax}), 1.69 (1H, ddd, *J* 2, 3.5, 12, 2-H_{eq}), 1.76 (3H, br s, 5-CH₃), 1.89 (3H, br s, 13'-CH₃), 2.04 (3H, br s, 13-CH₃), 2.11 (1H, br dd, *J* 9.5, 17, 4-H_{ax}), 2.28 (1H, br dd, *J* 5.5, 17, 4-H_{eq}), 3.97 (1H, m, 3-H), 4.42 (2H, s, CH₂O), 6.21 (1H, br d, *J* 16, 7-H), 6.32 (1H, br d, *J* 12, 14-H), 6.35 (1H, br d, *J* 12, 10-H), 6.41 (1H, d, *J* 15, 12-H), 6.50 (1H, d, *J* 16, 8-H), 6.69 (1H, dd, *J* 12, 14.5, 15'-H), 6.87 (1H, dd, *J* 12, 15, 11-H), 6.96 (1H, br d, *J* 12, 14'-H), 7.03 (1H, dd, *J* 11.5, 14, 15-H), 9.46 (1H, s, CHO); δ_C (125 MHz) 4.50 (C × 3), 4.93 (C × 3), 6.83 (C × 3), 6.87 (C × 3), 9.58, 13.10, 21.70, 28.62, 30.22, 37.04, 43.13, 48.78, 63.81, 65.27, 126.18, 126.99, 127.36, 127.50, 127.95, 128.18, 131.26, 136.97, 137.41, 137.60, 137.81, 138.31, 141.46, 148.81, 194.43; HRMS (ESI) *m/z* calcd for C₃₇H₆₃O₃Si₂ [M+H]⁺ 611.4310, found 611.4320.

3.3. Synthesis of C₁₅-Phosphonate 25

(3*R*,6*R*)-3-Hydroxy C₁₅-aldehyde **20**. According to the Khachik's method, racemic 3-hydroxy C₁₅-aldehyde **20** was synthesized starting from commercially available α -ionone and its enantiomers were directly separated using a semi-preparative chiral HPLC column [CHIRALPAK IF 2.0 $\times$ 25 cm (Daicel, Tokyo, Japan)] as shown in Figure 2b. Spectral data of the resulting enantiomers were identical with those reported [13].

(1*R*,4*R*)-4-[(1*E*,3*E*)-5-hydroxy-3-methylpenta-1,3-dien-1-yl]-3,5,5-trimethylcyclohex-2-en-1-yl acetate (**23**). Ac₂O (1.22 mL, 12.9 mmol) was added dropwise to a stirred solution of the (3*R*,6*R*)-aldehyde **20** (1.01 g, 4.3 mmol) in dry CH₂Cl₂ (18 mL), Et₃N (3 mL, 21.5 mmol) and DMAP (0.05 g, 0.43 mmol) at rt for 15 min. The resulting mixture was poured into saturated aq. NaHCO₃ and extracted with AcOEt and washed with brine. The organic layer was dried and evaporated to give the crude aldehyde, which was dissolved in MeOH (16 mL) and NaBH₄ (0.165 g) was added to it at 0 °C. After being stirred at 0 °C for 10 min, the reaction was quenched by addition of saturated aq. NH₄Cl. The resulting mixture was evaporated and the mixture was extracted with AcOEt and washed with brine, dried and evaporated to give a residue, which was purified flash CC (acetone-hexane, 3:7) to provide the allylic alcohol **23** (1.05 g, 87 % from **20**) as a pale yellow viscous oil: $[\alpha]_D^{24} +335.4$ (c 1.08, CHCl₃); $\nu_{\max}/\text{cm}^{-1}$ 3610 and 3447 (OH), 1720 (CO), 1623 and 1645 (C=C); δ_H (300 MHz) 0.87 and 0.99 (each 3H, s, *gem*-CH₃), 1.45 (1H, dd, *J* 5.5, 14, 2-H), 1.64 (3H, br s, 5-CH₃), 1.78 (3H, br s, 9-CH₃), 1.83 (1H, dd, *J* 5.5, 14, 2-H), 2.04 (3H, s, CH₃COO), 2.38 (1H, br d, *J* 9.5, 6-H), 4.28 (2H, d, *J* 7, 11-H₂), 5.32 (1H, m, 3-H), 5.41 (1H, dd, *J* 9.5, 15.5, 7-H), 5.49 (1H, m, 4-H), 5.62 (1H, br t, *J* 7, 10-H), 6.08 (1H, d, *J* 15.5, 8-H); δ_C (75 MHz) 12.71, 21.41, 22.85, 25.13, 28.86, 33.23, 39.45, 54.55, 59.19, 68.80, 119.98, 128.54, 128.77, 135.90, 136.75, 140.21, 170.92; HRMS (ESI) *m/z* calcd for C₁₇H₂₆O₃Na [M + Na]⁺ 301.1774, found 301.1774.

(1*R*,4*R*)-4-[(1*E*,3*E*)-5-diethoxyphosphoryl-3-methylpenta-1,3-dien-1-yl]-3,5,5-trimethylcyclohex-2-en-1-yl acetate (**24**). To a stirred suspension of ZnI₂ (1.69 g, 5.29 mmol) in dry THF (2.6 mL) was added dropwise P(OEt)₃ (1.84 mL, 10.6 mmol) and a solution of the alcohol **23** (0.98 g, 3.52 mmol) in dry THF (5.0 mL) at rt. After being stirred at 85 °C for 30 min, the resulting mixture was diluted with H₂O and AcOEt. The resulting mixture was filtered through a pad of Celite and the resulting mixture was poured into saturated aq. NaHCO₃ and extracted with AcOEt. The extracts were washed with brine, dried and evaporated to give a residue, which was purified by flash CC (AcOEt-hexane, 3:7) to provide phosphonate **24** (1.13 g, 81%) as a colorless oil: $[\alpha]_D^{24} +251.1$ (c 0.93, CHCl₃); $\nu_{\max}/\text{cm}^{-1}$ 1720 (CO); δ_H (300 MHz) 0.86 and 0.99 (each 3H, s, *gem*-CH₃), 1.31 (6H, t, *J* 7, OCH₂CH₃ $\times$ 2), 1.45 (1H, dd, *J* 5.5, 13.5, 2-H), 1.63 (3H, br s, 5-CH₃), 1.77 (3H, dd, *J* 1, 4, 9-CH₃), 1.83 (1H, dd, *J* 6, 13.5, 2-H), 2.04 (3H, s, CH₃COO), 2.36 (1H, br d, *J* 9.5, 6-H), 2.76 (2H, dd, *J* 8, 23, CH₂P), 4.04–4.17 (4H, m, OCH₂ $\times$ 2), 5.31 (1H, m, 3-H), 5.35 (1H, ddd, *J* 2, 9.5, 15.5, 7-H), 6.09 (1H, dd, *J* 1, 15.5, 8-H); δ_C (75 MHz) 12.71 (*J*_{CP} 2.3), 16.36 (*J*_{CP} 6.3, C $\times$ 2), 21.38, 22.83, 25.12, 26.74 (*J*_{CP} 139.4), 28.85, 33.19 (*J*_{CP} 1.7), 39.43, 54.51, 61.85 (*J*_{CP} 6.8, C $\times$ 2), 68.75, 118.40 (*J*_{CP} 11.9), 119.93, 127.53 (*J*_{CP} 4.0), 136.65 (*J*_{CP} 5.1), 137.38 (*J*_{CP} 14.9), 140.24, 170.81; HRMS (ESI) *m/z* calcd for C₂₁H₃₅O₅NaP [M + Na]⁺ 421.2114, found 421.2114.

Diethyl {(2*E*,4*E*)-3-methyl-5-[(1*R*,4*R*)-2,6,6-trimethyl-4-triethylsilyloxycyclohex-2-en-1-yl]penta-2,4-dien-1-yl}phosphonate (**25**). To a solution of phosphonate **24** (0.83 g, 2.09 mmol) was added MeOH (25 mL), and NaOMe (28% NaOMe, 1.6 mL, 8.36 mmol) at rt and the mixture was stirred at rt for 30 min. The resulting mixture was poured into saturated aq. NH₄Cl and extracted with AcOEt. The extracts were washed with brine, dried and evaporated to give the crude alcohol. After TESCl (0.45 mL, 2.68 mmol) was added dropwise to a stirred solution of the crude alcohol (0.796 g, 2.23 mmol) in dry CH₂Cl₂ (9 mL), Et₃N (0.93 mL, 6.69 mmol) and DMAP (13.6 mg, 0.11 mmol) at 0 °C. After being stirred at 0 °C for 15 min. The resulting mixture was evaporated and the mixture was extracted with AcOEt and washed with brine, dried and evaporated to give a residue, which was purified flash CC (acetone-hexane, 3:7) to provide TES-protected phosphonate **25** (0.915 g, 93% from **24**) as a colorless oil: $[\alpha]_D^{24} +137.5$ (c 1.00, CHCl₃); δ_H (300 MHz) 0.62 (6H, q, *J* 7.5, SiCH₂CH₃ $\times$ 3), 0.82 and 0.94 (each 3H, s, *gem*-CH₃), 0.98 (9H, t, *J* 7.5,

SiCH₂CH₃ × 3), 1.31 (6H, t, *J* 7 Hz, OCH₂CH₃ × 2), 1.39 (1H, dd, *J* 8, 13, 2-H), 1.57 (3H, br s, 5-CH₃), 1.70 (1H, dd, *J* 6, 13, 2-H), 1.77 (3H, br d, *J* 4, 9-CH₃), 2.38 (1H, br d, *J* 10, 6-H), 2.70 (2H, dd, *J* 8, 23, CH₂P), 4.04–4.16 (4H, m, OCH₂ × 2), 4.25 (1H, m, 3-H), 5.35 (1H, ddd, *J* 2, 10, 15.5, 7-H), 5.43 (1H, br s, 4-H), 6.08 (1H, d, *J* 15.5, 8-H); δ_C (75 MHz) 4.87 (C × 3), 6.84 (C × 3), 12.75 (*J*_{CP} 2.3), 16.39 (*J*_{CP} 6.2, C × 2), 22.76, 23.36, 26.77 (*J*_{CP} 138.9), 29.53, 34.16 (*J*_{CP} 1.1), 45.66, 54.46, 61.86 (*J*_{CP} 6.8, C × 2), 66.05, 117.99 (*J*_{CP} 12.0), 125.69, 128.27 (*J*_{CP} 4.0), 136.48, 136.73 (*J*_{CP} 5.1), 137.49 (*J*_{CP} 14.3); HRMS (ESI) *m/z* calcd for C₂₅H₄₇O₄NaPSi [M + Na]⁺ 493.2874, found 493.2865.

3.4. Synthesis of Loroxanthin (1)

To a solution of the TES-protected apocarotenal **8** (245 mg, 0.40 mmol) and the TES-protected phosphonate **25** (226 mg, 0.48 mmol) in dry THF (15 mL) were added NaN(TMS)₂ (1.0 M in THF; 0.96 mL, 0.96 mmol) at −40 °C. After being stirred at −40 °C for 30 min, the mixture was poured into saturated aq. NH₄Cl and extracted with AcOEt. The organic layer was washed with brine, dried and evaporated to give the residue was purified by flash CC (AcOEt-hexane, 8:92) to give the condensed product (247 mg, 67%) as a red viscous oil. This was dissolved in dry THF (10 mL) and TBAF (1.0 M in THF; 1.04 mL, 1.04 mmol) was added to it at rt. After being stirred at rt for 15 min, the mixture was poured into saturated aq. NH₄Cl and extracted with AcOEt. The organic layer was washed with brine, dried and evaporated to give the residue was purified by flash CC (MeOH-CH₂Cl₂-acetone, 2:85:15 to 3:80:15) to give loroxanthin (**1**) (143 mg, 61% from apocarotenal **8**) as red solids: λ_{max}(EtOH)/nm 268, 423sh, 447, 476; δ_H (500 MHz) 0.85 and 1.00 (6H, s, 1'-gem-CH₃), 1.08 (6H, s, 1-gem-CH₃), 1.37 (1H, dd, *J* 6.5, 13, 2'-H), 1.48 (1H, t, *J* 12, 2-H_{ax}), 1.63 (3H, br s, 5'-CH₃), 1.75 (3H, br s, 5-CH₃), 1.77 (1H, overlapped, 2-H_{eq}), 1.84 (1H, dd, *J* 6, 13, 2'-H), 1.91 (3H, br s, 9'-CH₃), 1.97 (6H, br s, 13-CH₃ and 13'-CH₃), 2.05 (1H, br dd, *J* 9, 17, 4-H_{ax}), 2.39 (1H, br dd, *J* 5.5, 17, 4-H_{eq}), 2.41 (1H, br d, *J* 10, 6'-H), 4.00 (1H, m, 3-H), 4.25 (1H, m, 3'-H), 4.55 (2H, br s, 9-CH₂), 5.44 (1H, dd, *J* 10, 15, 7'-H), 5.55 (1H, br s, 4'-H), 6.05 (1H, d, *J* 16, 8-H), 6.14 (1H, br d, *J* 12, 10'-H), 6.14 (1H, d, *J* 15, 8'-H), 6.24 (1H, d, *J* 11.5, 10-H), 6.26 (1H, br d, *J* 10, 14'-H), 6.29 (1H, br d, *J* 10, 14-H), 6.34 (1H, br d, *J* 16, 7-H), 6.36 (1H, d, *J* 14.5, 12'-H), 6.43 (1H, d, *J* 14.5, 12-H), 6.62 (1H, dd, *J* 12, 14.5, 11'-H), 6.61–6.66 (2H, m, 15-H and 15'-H), 6.71 (1H, dd, *J* 11.5, 14.5, 11-H); δ_C (125 MHz) 12.82 (13-CH₃ and 13'-CH₃), 13.10 (9'-CH₃), 21.66 (5-CH₃), 22.85 (5'-CH₃), 24.25 (1'-CH₃), 28.74 (1-CH₃), 29.49 (1'-CH₃), 30.29 (1-CH₃), 34.02 (C1'), 37.13 (C1), 42.54 (C4), 44.63 (C2'), 48.39 (C2), 54.95 (C6'), 57.40 (9-CH₂), 65.02 (C3), 65.90 (C3'), 123.47 (C11), 124.50 (C4'), 125.07 (C11'), 126.52 (C7 or C12'), 126.62 (C5), 128.85 (C7'), 129.83 (C15 or C15'), 130.74 and 130.76 (C10' and C15 or C15'), 132.41 (C14'), 133.31 (C10), 133.76 (C14), 135.26 (C9'), 135.46 (C8), 136.04 (C13), 136.90 (C13'), 137.24 (C9), 137.46 (C7 or C12'), 137.65 (C6), 137.69 (C8'), 137.93 (C5'), 139.86 (C12); HRMS (APCI) *m/z* calcd for C₄₀H₅₅O₃ [M − H][−] 583.4157, found 583.4151.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/md20110658/s1>, Figures S1–S20: ¹H- and ¹³C-NMR spectra of loroxanthin (**1**), compounds **8** (9*E*- and 9*Z*-isomers), **10**, **15–19**, and **23–25**.

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