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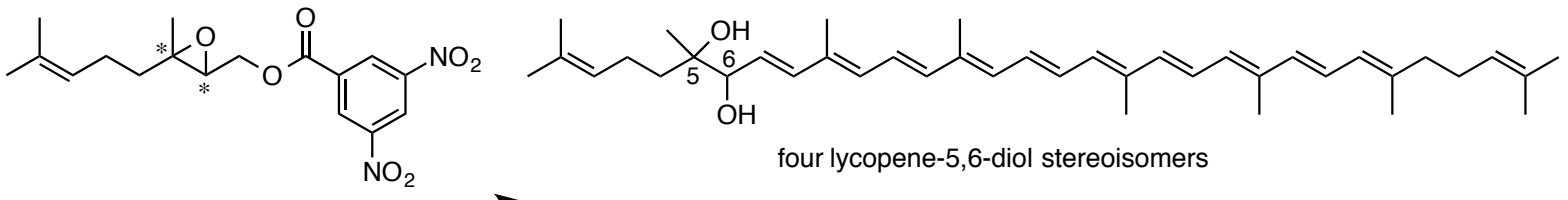
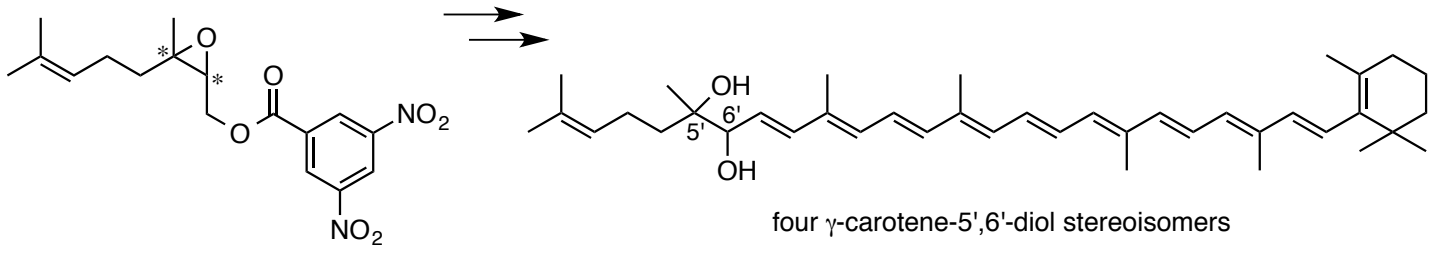


four lycopene-5,6-diol stereoisomers



four γ-carotene-5',6'-diol stereoisomers

Total synthesis of lycopene-5,6-diol and γ-carotene-5',6'-diol stereoisomers and their HPLC separation

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ABSTRACT

Lycopene-5,6-diol stereoisomers (**1a,b**) and (**2a,b**) and γ-carotene-5',6'-diol stereoisomers (**3a,b**) and (**4a,b**) were synthesized by a stepwise C_{15} + C_{10} + C_{15} double Wittig reaction strategy. The key compounds *erythro*(*anti*)-C_{15}-dihydroxy aldehydes **17a,b** and their *threo*(*syn*)-stereoisomers **23a,b** were prepared via Sharpless asymmetric epoxidation of geraniol and nerol followed by acidic hydrolysis of the epoxides in a stereospecific manner. The enantiomerically enriched *anti*-isomers were obtained by way of recrystallization of 2,3-epoxygeranyl 3,5-dinitrobenzoates **9a,b**, whereas *syn*-isomers were obtained as enantiomerically pure forms via recrystallization of dihydroxyneryl 3,5-dinitrobenzoates **21a,b**. In order to determine the absolute stereochemistry of natural products, HPLC separation methods for each enantiomers **1a,b**–**4a,b** were established by using a column carrying a chiral stationary phase.

Keywords:
Carotenoids
Lycopene-5,6-diol
γ-Carotene-5',6'-diol
Total synthesis
HPLC separation

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1. Introduction

Lycopene (Fig. 1), the major carotenoid found in tomatoes and tomato-based food products, is expected to exhibit physiological activities, especially in cancer prevention. It has been reported that lycopene exhibits excellent antioxidant activities[1] and growth-inhibitory effects on several human cancer cells.[2] Furthermore, epidemiological studies have shown that the uptake of lycopene reduces the risk of prostate cancer.[3]

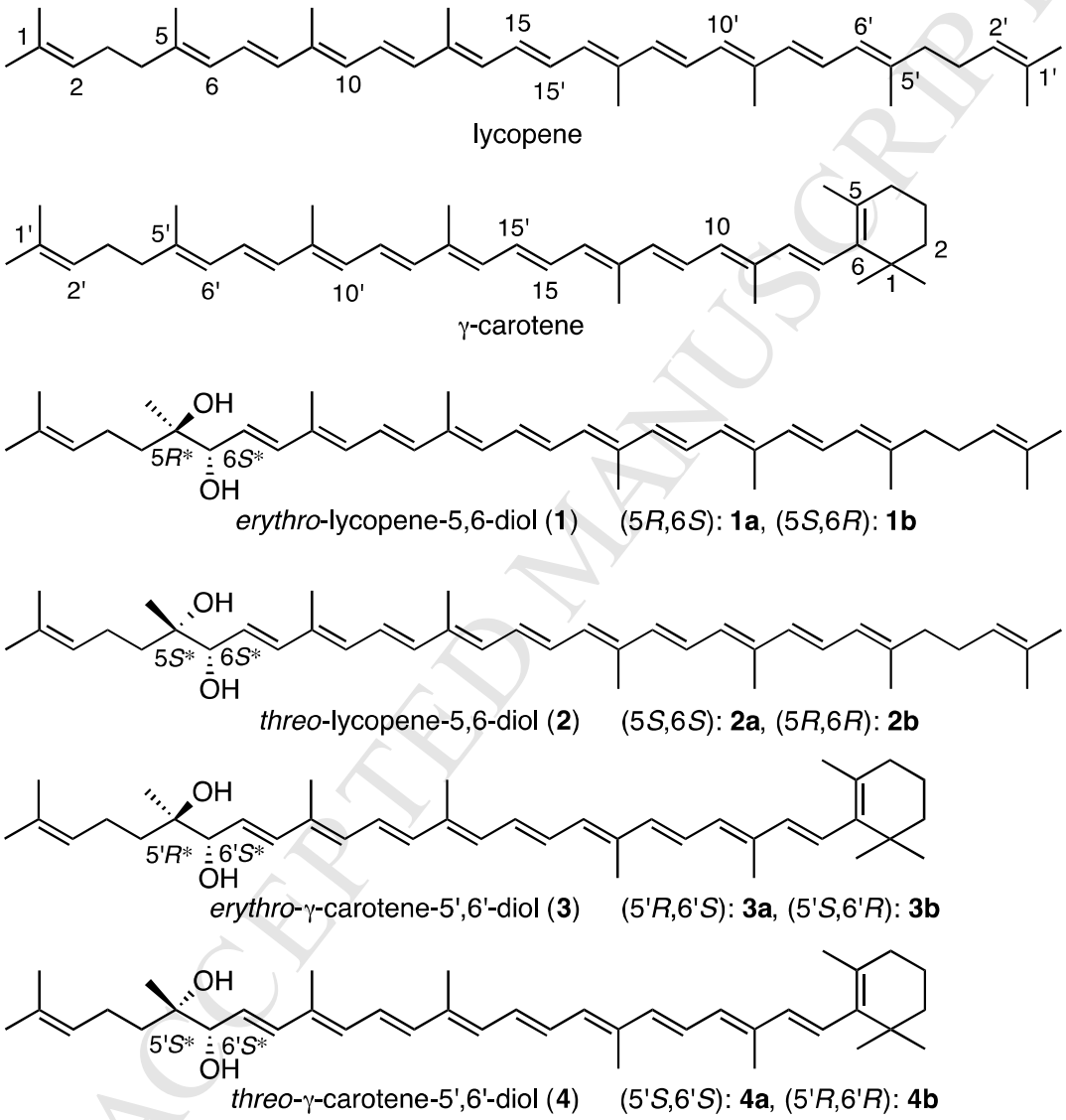


Fig. 1. Lycopene, γ-carotene and their new oxidative metabolites.

Several oxidative metabolites of lycopene, including structurally unique compounds carrying a five-membered ring end-group, have been isolated from human serum and tomato products.[4] The metabolites are considered to be formed via lycopene-5,6-epoxide as shown in Fig. 2. As lycopene is shown convincingly to be beneficial in biological and nutritional activities, biological activities of its metabolites have also attracted attention over years. In our intensive research on oxidative products of lycopene and γ-carotene, we have isolated lycopene-5,6-diols (**1**), (**2**) and γ-carotene-5',6'-diols (**3**),

(**4**) for the first time from the aril of gac *Momordica cochinichinesis*.[5] Gac is a deciduous vine that grows in South Asia and has been used traditionally as both food and folk medicine. Its aril contains lycopene with a higher content and several carotenoids. The relative stereochemistries of diol moiety in these carotenoids were estimated by NOESY and NOE difference experiments and molecular calculation using the ab initio molecular orbital method.[5] To give validation to their stereochemistries, we have employed synthetic approach. Following general description of the total synthesis of (5*S*,6*R*)-lycopene-5,6-diol (**1b**) and its (5*S*,6*S*)-isomer **2a** in the previous report,[5] we would like to report here stereospecific synthesis of the all stereoisomers of lycopene-5,6-diol (**1a**, **1b**, **2a**, **2b**) and γ-carotene-5',6'-diol (**3a**, **3b**, **4a**, **4b**) and establishment of HPLC analysis method by using a column carrying a chiral stationary phase.

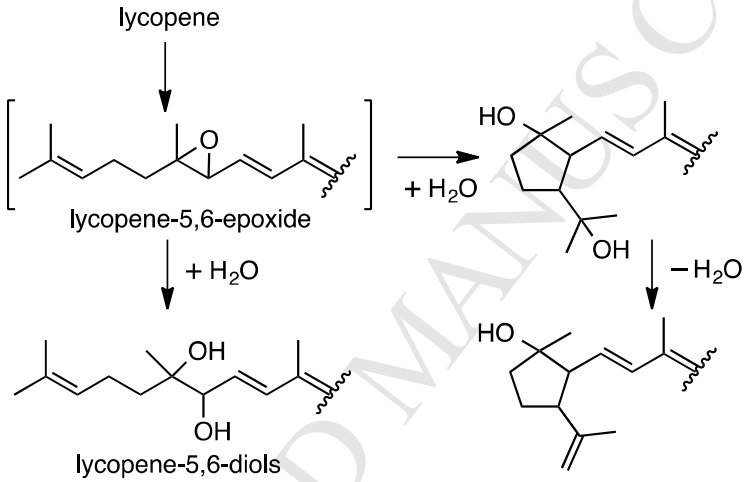
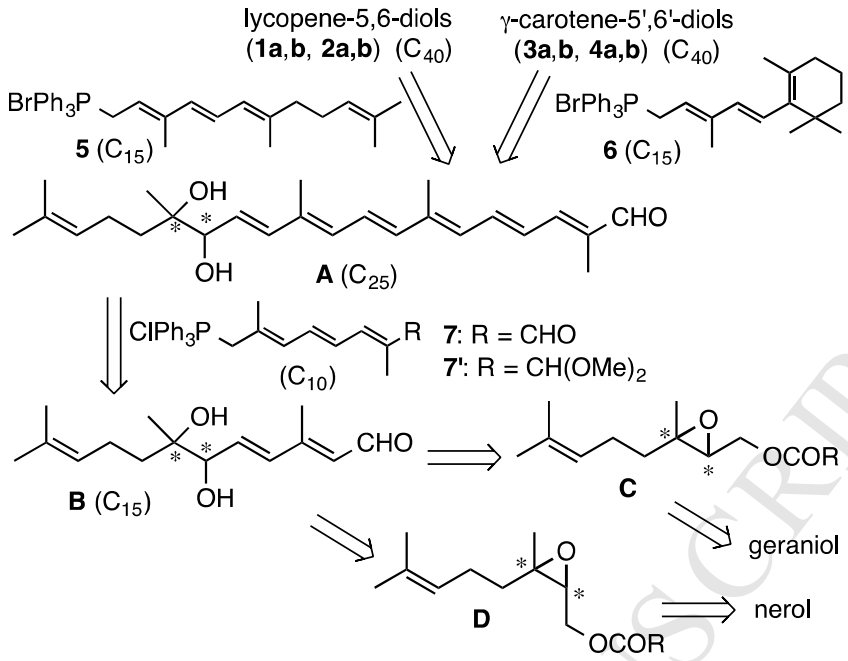


Fig. 2. Proposed metabolic pathway of lycopene.

2. Results and discussion

We planned to synthesize the all stereoisomers of lycopene-5,6-diol (**1a**,**b**, **2a**,**b**) and γ-carotene-5',6'-diol (**3a**,**b**, **4a**,**b**) by Wittig reaction of known C_{15}-phosphonium salts **5**[6] and **6**[7] with C_{25}-dihydroxy apocarotenals **A**, which would be also prepared by condensation between C_{15}-dihydroxy aldehydes **B** and C_{10}-phosphonium salt **7**[8] as shown in Scheme 1. The key C_{15}-dihydroxy aldehydes **B** having a desired stereochemistry were envisioned to prepare via Sharpless asymmetric epoxidation of geraniol and nerol and subsequent regio- and stereoselective acidic hydrolysis of epoxides **C** and **D**.



Scheme 1. Synthetic plan for lycopene-5,6-diols (**1a,b** and **2a,b**) and γ-carotene-5',6'-diols (**3a,b** and **4a,b**).

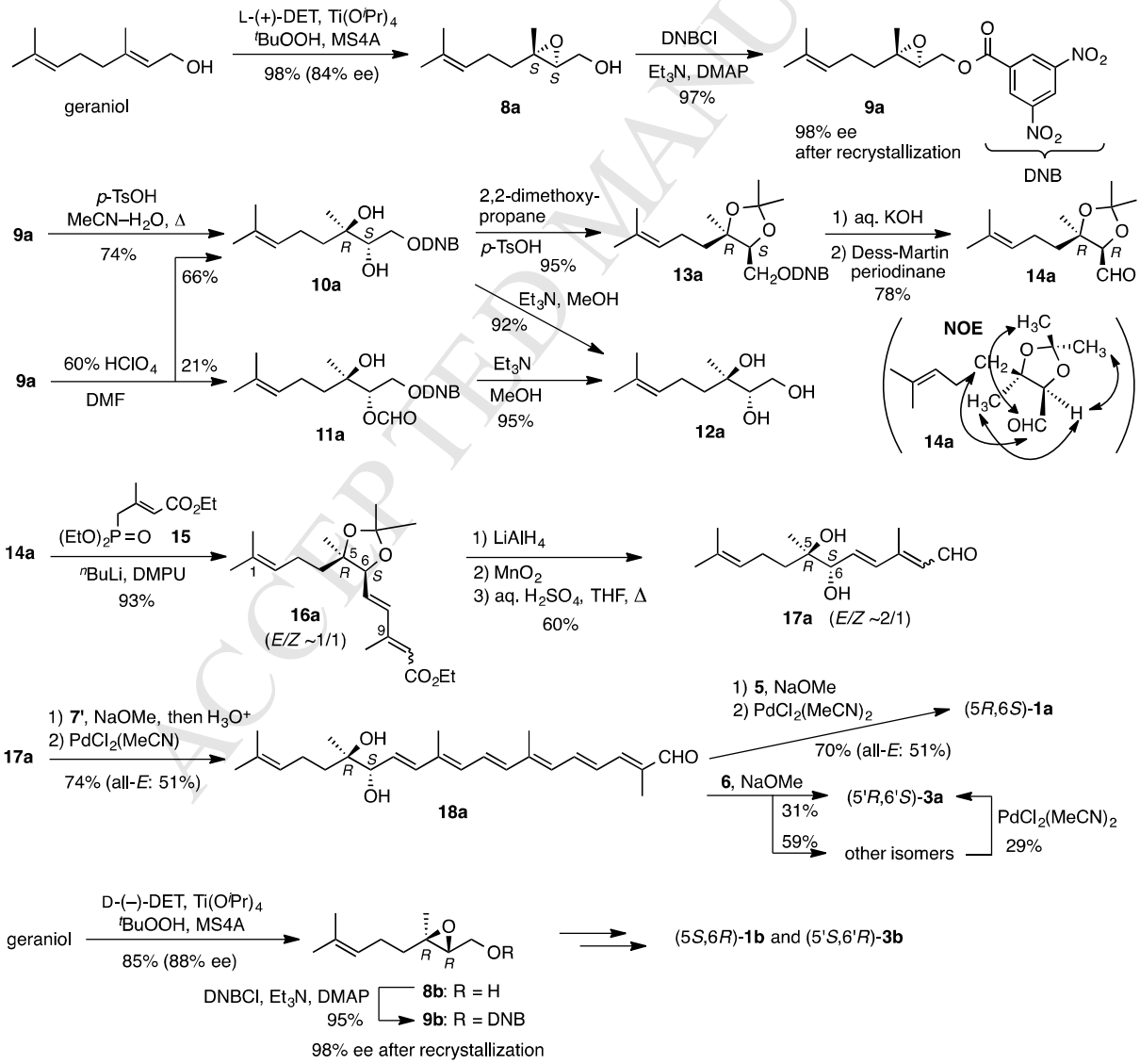
Synthetic routes for *erythro*(*anti*)-lycopene-5,6-diols (**1a,b**) and *erythro*(*anti*)-γ-carotene-5',6'-diols (**3a,b**) are shown in Scheme 2. The Sharpless asymmetric epoxidation of geraniol afforded (2*S*,3*S*)-epoxygeraniol **8a** and (2*R*,3*R*)-**8b** in good yields.[9–11] However, their reported enantiomeric purities are moderate (81–91% ee).[9–11] In order to improve them, these alcohols were subjected to 3,5-dinitrobenzoylation and subsequent recrystallization from methanol to give benzoates **9a** and **9b** as needles with 98% ee, respectively. These enantiomeric excesses were determined by HPLC analysis [CHIRALPAK ID; Daisel, EtOH–hexane (2:8), 30 °C].

The (2*S*,3*S*)-benzoate **9a** was next treated with aqueous perchloric acid in *N*,*N*-dimethylformamide (DMF)[11–13] to provide the desired *anti*-diol **10a** (66%), accompanied by its formate **11a** (21%). Their stereochemistries were confirmed by transformation into the known triol **12a**[11] by treatment with methanol in the presence of triethylamine.[14] *Anti*-configuration of **10a** was also confirmed as mentioned later. Attempted conversion of the formate **11a** to the diol **10a** was unsuccessful. Thus, the epoxide **9a** was treated with catalytic amount of *p*-tolutenesulfonic acid (*p*-TsOH) in MeCN-H_2O under heating to provide the *anti*-diol **10a** in 74% yield, accompanied by small amount of recovered epoxide. The diol **10a** was next converted into aldehyde **14a** by the sequence of acetonide-protection of the diol moiety, alkaline hydrolysis and Dess-Martin oxidation. NOESY experiments of aldehyde **14a** shown in Scheme 2 indicated that the configuration of the diol moiety in **10a** is *erythro*(*anti*) form and thus the epoxide ring of **9a** is selectively opened with inversion of configuration at the tertiary γ-position.

The C_{10}-aldehyde **14a** was then condensed with C_5-phosphonate **15**, the resulting C_{15}-dienoate **16a** was subjected to $LiAlH_4$ reduction followed by MnO_2 oxidation and subsequent acetonide-deprotection to provide an isomeric mixture (9*E*/9*Z* ~2/1)[15] of dihydroxy aldehyde **17a**

without epimerization. Without separation of the geometric isomers, the aldehyde **17a** was condensed with C_{10}-phosphonium salt **7**[8] and then briefly treated with acidic water[16] to afford an isomeric mixture of C_{25}-apocarotenal **18a**. As HPLC analysis of this mixture showed that the all-*E*-isomer was minor, the mixture was treated with a palladium catalyst[17,18] to yield a mixture in which the all-*E*-isomer constituted 51%. After purification by preparative HPLC, the resulting all-*E*-apocarotenal **18a** was condensed with phosphonium salt **5**[6] and followed by isomerization to give (5*R*,6*S*)-lycopene-5,6-diol (**1a**) in 70% yield, as a geometrical isomeric mixture (all-*E*: 51%). Crystallization from CH_2Cl_2-Et_2O-hexane afforded all-*E*-isomer of (5*R*,6*S*)-**1a** as a red powder, whose ^{1}H NMR spectral data were identical with those of natural carotenoid isolated from gac.[5] Whereas the apocarotenal **18a** was condensed with phosphonium salt **6**[7] to afford (5'*R*,6'*S*)-γ-carontene-5',6'-diol (**3a**), whose ^{1}H NMR spectral data were good accordance with those of natural carotenoid.[5]

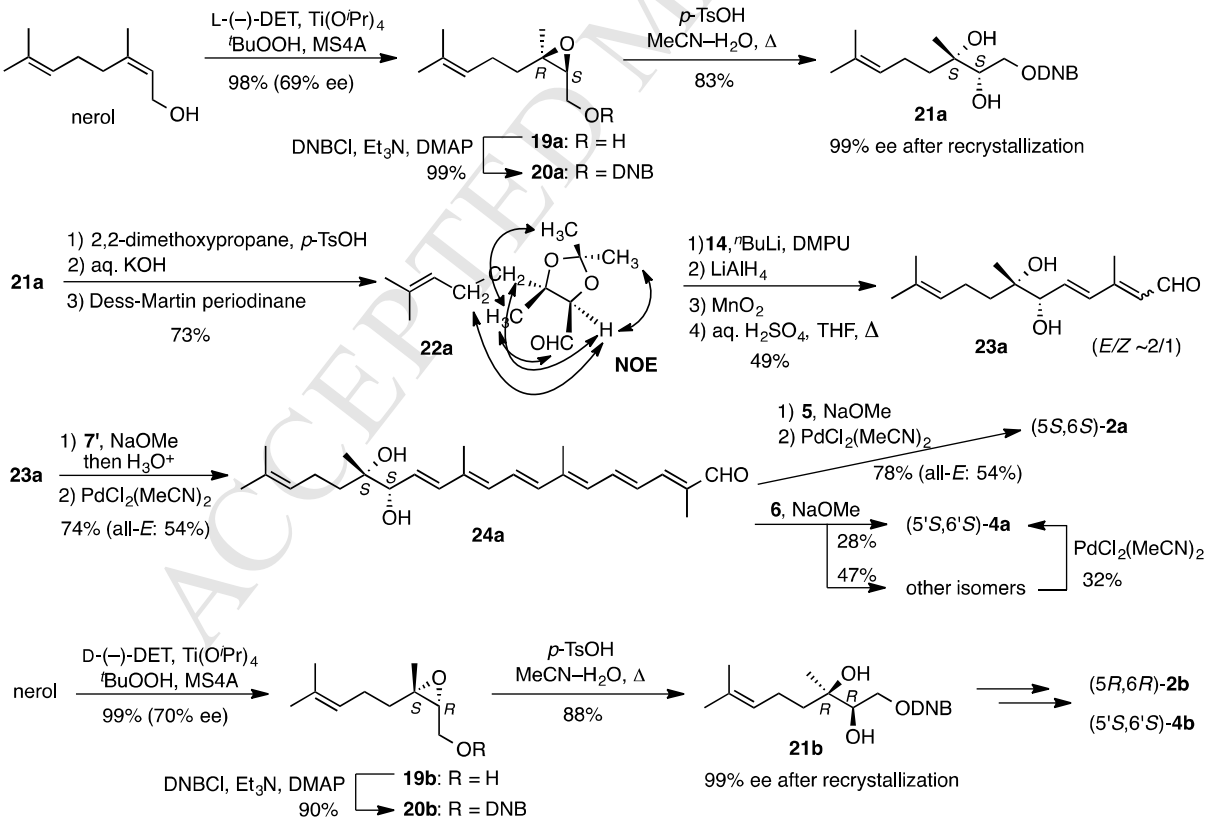
The antipodes (5*S*,6*R*)-**1b** and (5'*S*,6'*S*)-**3b** were synthesized in a similar fashion from (2*R*,3*R*)-epoxygeranyl benzoate **9b**.



Scheme 2. Synthesis of *erythro*-lycopene-5,6-diols (**1a,b**) and *erythro*-γ-carotene-5',6'-diols (**3a,b**).

Next, *threo*(*syn*)-lycopene-5,6-diols (**2a,b**) and *threo*(*syn*)-γ-carotene-5',6'-diols (**4a,b**) were synthesized starting from optically active 2,3-epoxynerols **19a,b**[10,19] as shown in Scheme 3. The reported enantiomeric purities of 2,3-epoxynerols **19a,b** prepared by Sharpless asymmetric epoxidation are lower (62–77% ee)[10,19] than those of 2,3-epoxygeraniols **8a,b** (81–91% ee).[9–11] Although Mori *et al*.[19] reported that enantiomeric purities can be improved by repeated recrystallization of their 3,5-dinitorobenzoates **20a,b** and chromatographic purification of the crude products obtained from the mother liquor, this purification is troublesome. We found that recrystallization of 2,3-dihydroxyneryl 3,5-dinitrobenzoates **21a,b**, prepared by acidic hydrolysis of 2,3-epoxyneryl benzoate **20a,b**, from methanol-water (4:1) directly afford enantiomerically pure crystals (97–99% ee). These enantiomeric excesses were determined by HPLC analysis [CHIRALPAK IA; Daisel, 2-PrOH–hexane (3:7), 30 °C].

In the same procedure as preparation of *erythro*(*anti*)-carotenoids **1a,b** and **3a,b**, 2,3-dihydroxyneryl benzoates **21a,b** were transformed into *threo*(*syn*)-lycopene-5,6-diols (**2a,b**) and *threo*(*syn*)-γ-carotene-5',6'-diols (**4a,b**), whose ^{1}H NMR spectral data were identical with those of natural carotenoid isolated from gac.[5] Their *syn*-configurations were confirmed by NOESY experiments of aldehyde **22a** shown in Scheme 3.



Scheme 3. Synthesis of *threo*-lycopene-5,6-diols (**2a,b**) and *threo*-γ-carotene-5',6'-diols (**4a,b**).

Next, HPLC conditions for identification of each enantiomers **1a,b**–**4a,b** were established by using a column carrying a chiral stationary phase as shown in Figs. 3 and 4. Diasteromers **1a,b** and **2a,b** and also **3a,b** and **4a,b** can be easily separated by usual silica gel HPLC column.[5] Thus combination of two HPLC conditions enables to identify two absolute configurations, being applicable to a natural product,[20] if it is available.

In sumarry, we succeeded in the total synthesis of lycopene-5,6-diol stereoisomers (**1a,b**) and (**2a,b**) and γ-carotene-5',6'-diol stereoisomers (**3a,b**) and (**4a,b**) in a stereospecific manner. Relative stereochemistries of the diol moiety of natural products could be confirmed[5] by comparison of their NMR spectral data with those of synthetic samples. HPLC separation methods for each enantiomers were also establised toward deteremination of the absolute stereochemistries of natural products. These synthetic carotenoids were expected to become useful authentic samples not only for the further studies of metabolisms of lycopene and γ-carotene in various tissues but also for the investigation of their physiological functions.

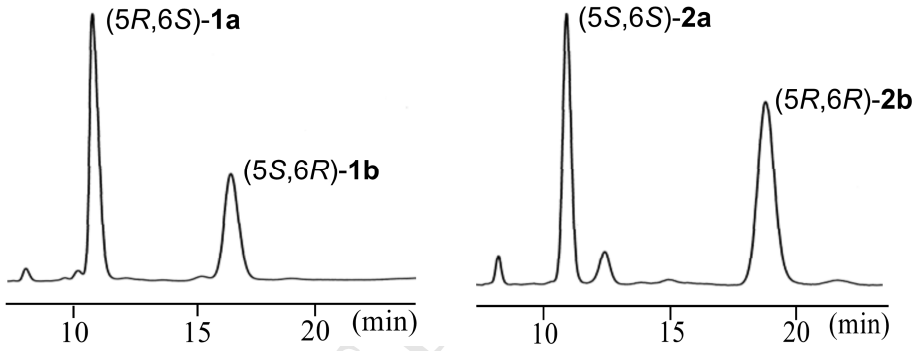


Fig. 3. HPLC elution profiles of lycopene-5,6-diol stereoisomers (**1a,b**) and (**2a,b**). Column: CHIRALPAK AD-H (daicel) 0.46 × 25 cm; elutent: 2-PrOH-hexane (15:85); flow rate: 1.0 mL/min; temperature: 25 °C; detection: 450 nm.

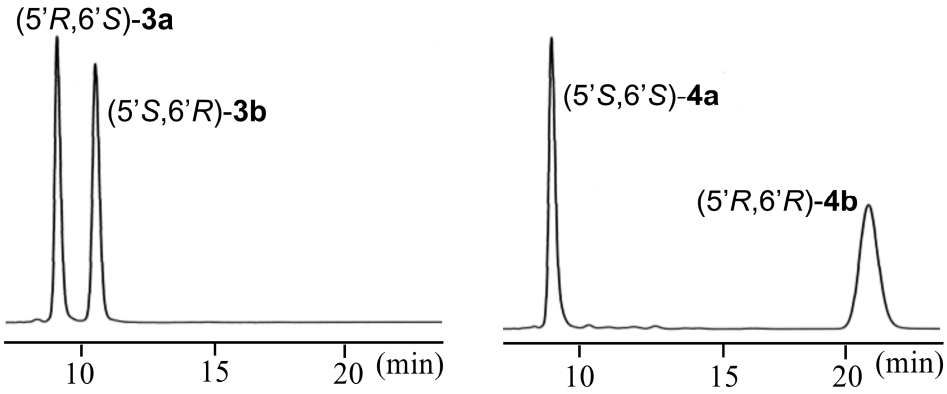


Fig. 4. HPLC elution profiles of γ-carotene-5',6'-diol stereoisomers (**3a,b**) and (**4a,b**). Column: CHIRALPAK AD-H (daicel) 0.46 × 25 cm; elutent: 2-PrOH-hexane (15:85); flow rate: 0.6 mL/min; temperature: 25 °C; detection: 450 nm.

3. Experimental

3.1 General

UV-VIS spectra were recorded on a JASCO V-650 instrument. IR spectra were measured on a Perkin-Elmer spectrum 100 FT-IR spectrometer. ^{1}H and ^{13}C NMR spectra were determined on a Varian Gemini-300 or a VXR-500 superconducting FT-NMR spectrometer. The chemical sifts are expressed in ppm relative to tetramethylsilane ($\delta = 0$) as internal standard for ^{1}H NMR and $CDCl_3$ ($\delta =$ 77.0) for ^{13}C NMR. Mass spectra were taken on a Thermo Fisher Scientific Exactive spectrometer. Optical rotations were measured on a JASCO P-2200 porarometer and CD spectra on a Shimadzu-AVIN 62A DS circular dichroism spectrometer.

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.

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 assighments of C_{15}-ester **16**, C_{15}-aldehydes **17** and **23**, C_{25}-apocarotenals **18** and **24**, and carotenoids **1–4** are given using the carotenoid numbering system.

*3.1.1. (2S,3S)- and (2R,3R)-3-Methyl-3-(4-methylpent-3-en-1-yl)oxiran-2-yl)methyl 3,5-dinitorobenzoate **9a,b**.* (2*S*,3*S*)-Epoxygeraniol **8a** (84% ee) and (2*R*,3*R*)-epoxygeraniol **8b** (88% ee) were prepared according to the known Sharpless asymmetric epoxidation method of geraniol.[9–11] To a stirred solution of (2*S*,3*S*)-**8a** (84% ee; 9.30 g, 54.7 mmol), Et_3N (11.4 mL, 82 mmol) and DMAP (133 mg, 1.1 mmol) in dry CH_2Cl_2 (60 mL) was added 3,5-dinitrobenzoyl chloride (13.2 g, 57.3 mmol) in some portions at 0 °C and the mixture was stirred for a further 30 min. After CH_2Cl_2 was evaporated off, the resulting mixture was diluted with AcOEt and washed with water and then brine. The organic layer was dried and evaporated to give a residue, which was purified by flash CC (AcOEt-hexane, 1:3) to provide the benzoate **9a** (19.33 g, 97%) as a pale yellow solid. Recrystallization from MeOH (90 mL) gave 16.03 g of (2*S*,3*S*)-**9a** (99% ee) as a pale yellow needle. (2*R*,3*R*)-**9b** was also prepared (97%) by the same procedure. The enantiomeric purities of **9a** and **9b** were established by chiral HPLC [CHIRALPAK ID 0.46×25 cm (Daicel), EtOH-hexane (2:8) 1.0 mL/min, 30°C; **9a**: 15.2 min, **9b**: 20.5 min].

(2*S*,3*S*)-**9a**: mp 62–63 °C; $[\alpha]_D^{27}$ –19.9 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) ν 1737 (CO), 1549 and 1346 (NO_2) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.40 (3H, s, CH_3), 1.55 (1H, ddd, *J*=7.5, 9.5, 14 Hz) and 1.74 (1H, ddd, *J*=5.5, 7, 14 Hz) (CH_2), 1.63 and 1.68 (each 3H, br s, *gem*-CH_3), 2.13 (2H, br q, *J*= 7 Hz, CH_2), 3.19 (1H, dd, *J*=3.5, 7.5 Hz, OCH_2CH), 4.40 (1H, dd, *J*=7.5, 12.5 Hz) and 4.75 (1H, dd, *J*=3.5, 12.5 Hz) (OCH_2), 5.10 (1H, tsept, *J*=7, 1.5 Hz, =CH), 9.21 (2H, d, *J*=2 Hz, ArH), 9.25 (1H, t, *J*=2 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.96, 17.64, 23.55, 25.64, 38.15, 59.14, 60.82, 65.93, 122.59, 122.95, 129.53 (×2), 132.44, 133.38, 148.64 (×2), 162.41; HRMS (ESI) *m*/*z* calcd for $C_{17}H_{20}O_7N_2Na$ $[M+Na]^+$ 387.1163, found 387.1161.

(2*R*,3*R*)-**9b**: mp 62–64 °C; $[\alpha]_D^{24}$ +17.8 (*c* 1.00, $CHCl_3$); HRMS (ESI) *m*/*z* calcd for $C_{17}H_{20}O_7N_2Na$ $[M+Na]^+$ 387.1163, found 387.1161.

*3.1.2. Treatment of (2S,3S)-epoxy benzoate **9a** with aqueous perchloic acid in DMF.* An aqueous solution of $HClO_4$ (60%; 1.50 mL) was added slowly to a stirred solution of (2*S*,3*S*)-**9a** (3.64 g, 10 mmol) in DMF (20 mL) at 0 °C. After being stirred at rt for 15 h, the mixture was poured into saturated aq. $NaHCO_3$ and extracted with AcOEt. The extracts were washed with brine, dried and evaporated to give a residue, which was purified by flash CC (MeOH-AcOEt-hexane, 1:35:65 to 2:40:60) to provide (2*S*,3*R*)-diol **10a** (2.63 g, 66%) and (2*S*,3*R*)-formate **11a** (875 mg, 21%) as pale yellow viscous oils, respectively.

(2*S*,3*R*)-**10a**: $[\alpha]_D^{24}$ –11.7 (*c* 0.98, $CHCl_3$); IR ($CHCl_3$) ν 3564 (OH), 1735 (CO), 1549 and 1345 (NO_2) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.33 (3H, s, CH_3), 1.48 and 1.75 (each 1H, m, CH_2), 1.65 and 1.70 (each 3H, br s, *gem*-CH_3), 2.14 (1H, s, OH), 2.14 (2H, m, CH_2), 2.71 (1H, d, *J*=5 Hz, OH), 3.89 (1H, ddd, *J*=2.5, 5.5, 8.5 Hz, C*H*OH), 4.50 (1H, dd, *J*=8.5, 11.5 Hz) and 4.66 (1H, dd, *J*=2.5, 11.5 Hz) (OCH_2), 5.15 (1H, tsept, *J*=7, 1 Hz, =CH), 9.18 (2H, d, *J*=2 Hz, ArH), 9.24 (1H, t, *J*=2 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.72, 21.98, 23.41, 25.68, 37.13, 67.85, 73.83, 75.55, 122.53, 123.72, 129.52 (×2), 132.73, 133.60, 148.62 (×2), 162.90; HRMS (ESI) *m*/*z* calcd for $C_{17}H_{22}O_8N_2Na$ $[M+Na]^+$ 405.1268, found 405.1265.

(2*S*,3*R*)-**11a**: $[\alpha]_D^{25}$ –3.5 (*c* 1.09, $CHCl_3$); IR ($CHCl_3$) ν 3598 and 3492 (OH), 1734 (CO), 1550 and 1345 (NO_2) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.31 (3H, s, CH_3), 1.57–1.72 (2H, m, CH_2), 1.66 and 1.71 (each 3H, br s, *gem*-CH_3), 1.92 (1H, br s, OH), 2.16 (2H, br q, *J*=7.5 Hz, CH_2), 4.53 (1H, dd, *J*=9, 12 Hz) and 4.96 (1H, dd, *J*=2, 12 Hz) (OCH_2), 5.14 (1H, tsept, *J*=7, 1 Hz, =CH), 5.40 (1H, br dd, *J*=2, 9 Hz, C*H*OCHO), 8.21 (1H, s, OCHO), 9.12 (2H, d, *J*=2.5 Hz, ArH), 9.22 (1H, t, *J*=2.5 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.73, 21.91, 23.28, 25.69, 38.40, 65.31, 73.14, 75.05, 122.55, 123.23, 129.51 (×2), 133.16, 133.35, 148.66 (×2), 160.26, 162.39; HRMS (ESI) *m*/*z* calcd for $C_{18}H_{22}O_9N_2Na$ $[M+Na]^+$ 433.1218, found 433.1219 .

*3.1.3. Hydrolysis of epoxy benzoates **9a,b** by use of p-TsOH in acetonitrile.* A solution of (2*S*,3*S*)-**9a** (3.30 g, 9.1 mmol) and *p*-TsOH•H_2O (172 mg, 0.90 mmol) in MeCN (33 mL) and H_2O (3.3 mL) was heated at 50 °C for 1.5 h. After cooling, $NaHCO_3$ (120 mg) was added to this mixture and MeCN was evaporated off. The resulting mixture was diluted with AcOEt and washed with brine. The organic layer was dried and evaporated to give a residue, which was purified by flash CC (AcOEt-hexane, 2:3) to provide (2*S*,3*R*)-**10a** (2.58 g, 74%) as a pale yellow viscous oil. Its spectral data were identical with those described above. (2*R*,3*S*)-**10b** was also prepared (74%) by the same procedure.

(2*R*,3*S*)-**10b**: $[\alpha]_D^{22}$ +7.3 (*c* 1.02, $CHCl_3$); HRMS (ESI) *m*/*z* calcd for $C_{17}H_{22}O_8N_2Na$ $[M+Na]^+$ 405.1268, found 405.1265.

*3.1.4. Treatment of (2S,3R)-dihydroxy benzoate **10a** with methanol in the presence of triethylamine.* To a solution of (2*S*,3*R*)-**10a** (100 mg, 0.26 mmol) in MeOH (5 mL) was added Et_3N (0.5 mL) and the

mixture was stirred at rt for 30 min. The solvent was evaporated off and the resulting residue was purified by flash CC (AcOEt-hexane, 1:1 to MeOH-AcOEt-hexane, 4:50:50) to provide (2*S*,3*R*)-triol **12a** (46 mg, 92%) as a colorless oil. Its ^{1}H and ^{13}C NMR spectral data were identical with those reported.[11] $[\alpha]_D^{23}$ –10.8 (*c* 0.92, $CHCl_3$), lit[11] $[\alpha]_D^{25}$ –6.7 (*c* 1.05, $CHCl_3$).

*3.1.5. Treatment of (2S,3R)-formate **11a** with methanol in the presence of triethylamine.* In the same manner as described above, (2*S*,3*R*)-**11a** (95 mg, 0.23 mmol) was treated with Et_3N (0.1 mL) in MeOH (5 mL) to provide (2*S*,3*R*)-**12a** (42 mg, 95%) as a colorless oil. Its ^{1}H and ^{13}C NMR spectral data were identical with those reported.[11] $[\alpha]_D^{23}$ –10.8 (*c* 0.88, $CHCl_3$).

*3.1.6. (4S,5R)- and (4R,5S)-2,2,5-Trimethyl-5-(4-methylpent-3-en-1-yl)-1,3-dioxolan-4-yl)methyl 3,5-dinitrobenzoate **13a,b***. A solution of (2*S*,3*R*)-**10a** (1.20 g, 3.14 mmol) and *p*-TsOH•H_2O (12 mg, 0.06 mmol) in acetone (8 mL) and 2,2-dimethoxypropane (3 mL) was heated at 60 °C for 30 min. After cooling, the mixture was poured into saturated aq. $NaHCO_3$ 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, 1:4) to provide (4*S*,5*R*)-**13a** (1.26 g, 95%) as a pale yellow solid. (4*R*,5*S*)-**13b** was also prepared (86%) by the same procedure.

(4*S*,5*R*)-**13a**: $[\alpha]_D^{22}$ +4.0 (*c* 1.02, $CHCl_3$); IR ($CHCl_3$) ν 1737 (CO), 1549 and 1345 (NO_2) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.27 and 1.67 (each 1H, m, CH_2), 1.39, 1.43 and 1.49 (each 3H, s, CH_3×3), 1.64 and 1.70 (each 3H, br s, *gem*-CH_3), 2.01–2.31 (2H, m, CH_2), 4.17 (1H, t, *J*=5.5 Hz, OCH_2CH), 4.55 (2H, d, *J*=5.5 Hz, OCH_2), 5.13 (1H, tsept, *J*=7, 1 Hz, =CH), 9.19 (2H, d, *J*=2 Hz, ArH), 9.25 (1H, t, *J*=2 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.59, 21.71, 23.04, 25.66, 27.08, 28.28, 35.18, 65.13, 81.39, 81.61, 108.57, 122.59, 123.80, 129.57 (×2), 132.10, 133.39, 148.63 (×2), 162.43; HRMS (ESI) *m*/*z* calcd for $C_{20}H_{27}O_8N_2$ $[MH]^+$ 423.1762, found 423.1763.

(4*R*,5*S*)-**13b**: $[\alpha]_D^{26}$ –1.1 (*c* 1.03, $CHCl_3$); HRMS (ESI) *m*/*z* calcd for $C_{20}H_{27}O_8N_2$ $[MH]^+$ 423.1762, found 423.1762.

*3.1.7. (4R,5R)- and (4S,5S)-2,2,5-Trimethyl-5-(4-methylpent-3-en-1-yl)-1,3-dioxolane-4-carbaldehyde **14a,b***. To a solution of (4*S*,5*R*)-**13a** (3.40 g, 8.46 mmol) in EtOH (40 mL) was added dropwise 10% aq. KOH (9 mL) and the mixture was stirred for a further 10 min. After EtOH was evaporated off, the resulting mixture was poured into water and extracted with AcOEt. The extracts were washed with brine, dried and evaporated to give a crude alcohol, which without purification was dissolved in CH_2Cl_2 (40 mL). To this solution was added Dess-Martin periodinane (4.17 g, 9.88 mol) in some portions at rt and the mixture was stirred for a further 20 min. After CH_2Cl_2 was evaporated off, the resulting mixture was diluted with Et_2O and filtered through a pad of Celite. The filtrate was evaporated to afford a residue, which was purified by flash CC (AcOEt-hexane, 1:4 to 1:3) to provide (4*R*,5*R*)-**14a** (1.42 g, 78% from **13a**) as a colorless oil. (4*S*,5*S*)-**14b** was also prepared (76% from **13b**) by the same procedure.

(4*R*,5*R*)-**14a**: $[\alpha]_D^{20}$ +100.6 (*c* 1.02, $CHCl_3$); IR ($CHCl_3$) ν 1734 (CO) cm^{-1}; ^{1}H NMR (500 MHz,

$CDCl_3$) δ 1.33 (1H, ddd, *J*=5, 11.5, 13.5 Hz) and 1.59 (1H, m) (CH_2), 1.41 and 1.55 (each 3H, s, *gem*-CH_3), 1.43 (3H, s, CH_3), 1.59 and 1.67 (each 3H, br s, *gem*-CH_3), 1.99–2.15 (2H, m, CH_2), 4.11 (1H, d, *J*=2 Hz, C*H*CHO), 5.06 (1H, tsept, *J*=7.5, 1.5 Hz, =CH), 9.75 (1H, d, *J*=2 Hz, CHO); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.56, 22.03, 24.59, 25.62, 27.05, 28.04, 36.59, 83.85, 87.93, 109.96, 123.59, 132.04, 200.35; HRMS (ESI) *m*/*z* calcd for $C_{13}H_{22}O_3Na$ $[M+Na]^+$ 249.1461, found 249.1462.

(4*S*,5*S*)-**14b**: $[\alpha]_D^{24}$ –103.0 (*c* 0.98, $CHCl_3$); HRMS (ESI) *m*/*z* calcd for $C_{13}H_{22}O_3Na$ $[M+Na]^+$ 249.1461, found 249.1460.

*3.1.8. Preparation of (5R,6S)- and (5S,6R)-C$_{15}$-Dienoate **16a,b**.* To a stirred solution of phosphonate **15** (3.31 g, 12.5 mmol) and *N*,*N*'-dimethylpropyleneurea (DMPU) (3.0 mL, 25 mmol) in dry THF (25 mL) was added dropwise *n*-BuLi (1.63 M in hexane; 7.9 mL, 12.9 mmol) at –20 °C and the mixture was stirred for a further 20 min. A solution of (4*R*,5*R*)-**14a** (1.42 g, 6.28 mmol) in dry THF (7 mL) was then added dropwise to this solution at –20 °C. After being stirred at –20 °C for a further 20 min, the mixture was poured into saturated aq. NH_4Cl 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, 15:85) to afford an isomeric mixture (*E*/*Z* ~1/1) (5*R*,6*S*)-**16a** (1.96 g, 93%) as a colorless oil. (5*S*,6*R*)-**16b** was also prepared (89%) by the same procedure.

(5*R*,6*S*)-**16a**: IR ($CHCl_3$) ν 1704 (CO), 1642 and 1612 (C=C) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 and 1.60 (each 1H, m, 4-H_2), 1.29 (3H, t, *J*=7 Hz, CH_2CH_3), 1.39, 1.40 and 1.48 (each 3H, s, CH_3×3), 1.60 and 1.68 (each 3H, br s, *gem*-CH_3), 2.02 and 2.29 (each 3/2H, d, *J*=1 Hz, 9-CH_3), 1.95–2.24 (2H, m, 3-H_2), 4.17 and 4.18 (each 1H, q, *J*=7 Hz, OCH_2CH_3), 4.32 and 4.36 (each 1/2H, br d, *J*=7.5 Hz, 6-H), 5.09 (1H, br t, *J*=7 Hz, 2-H), 5.73 and 5.82 (each 1/2H, br s, 10-H), 6.03 and 6.05 (each 1/2H, dd, *J*=7.5, 16 Hz, 7-H), 6.39 and 7.84 (each 1/2H, d, *J*=16 Hz, 8-H); HRMS (ESI) *m*/*z* calcd for $C_{20}H_{32}O_4Na$ $[M+Na]^+$ 359.2193, found 359.2191.

(5*S*,6*R*)-**16b**: HRMS (ESI) *m*/*z* calcd for $C_{20}H_{32}O_4Na$ $[M+Na]^+$ 359.2193, found 359.2191.

*3.1.9. Preparation of (5R,6S)- and (5S,6R)-C$_{15}$-Dienal **17a,b**.* A solution of (5*R*,6*S*)-**16a** (1.10 g, 3.27 mmol) in dry Et_2O (7 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (124 mg, 3.26 mmol) in dry Et_2O (20 mL) at 0 °C. After being stirred at 0 °C for 10 min, the excess of $LiAlH_4$ was decomposed by dropwise addition of water. The mixture was filtered through a pad of Celite and the filtrate was dried and evaporated. This was dissolved in Et_2O (20 mL) and hexane (20 mL) and stirred with MnO_2 (7 g) at rt for 1 h. After MnO_2 was filtered off, the filtrate was concentrated to give the crude aldehyde. This was dissolved in THF (20 mL) and H_2SO_4 (3M in water; 4 mL), and the mixture was heated at 80 °C for 2h. After cooling, the mixture was neutralized with saturated aq. $NaHCO_3$ and extracted with AcOEt. The extracts were washed with brine, dried and evaporated to give a residue, which was purified by flash CC (acetone-hexane, 1:2) to provide an isomeric mixture (*E*/*Z* ~2/1) of (5*R*,6*S*)-**17a** (498 mg, 60% from **16a**) as an yellow-brown viscous oil. (5*S*,6*R*)-**17b** was also prepared (60% from **16b**) by the same procedure.

(5*R*,6*S*)-**17a**: IR ($CHCl_3$) ν 3611, 3566 and 3454 (OH), 1665 (CO), 1634 and 1599 (C=C) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.25 (2H) and 1.27 (1H) (each s, 5-CH_3), 1.37 and 1.62 (each 1H, m, 4-H_2), 1.63 and 1.69 (each 3H, br s, *gem*-CH_3), 2.05 (2/3H) and 2.18 (1/3H) (each s, OH), 2.10 (2H, m, 3-H_2), 2.10 (1H) and 2.28 (2H) (each d, *J*=1 Hz, 9-CH_3), 4.12 (1H, m, 6-H), 5.12 (1H, br t, *J*=7.5 Hz, 2-H), 5.91 (1/3H) and 5.98 (2/3H) (each br d, *J*=8 Hz, 10-H), 6.23 (1/3H) and 6.31 (2/3H) (each dd, *J*=8, 15.5 Hz, 7-H), 6.48 (2/3H) and 7.36 (1/3H) (each d, *J*=15.5 Hz, 8-H), 10.13 (2/3H) and 10.20 (1/3H) (each d, *J*=8 Hz, CHO); HRMS (ESI) *m*/*z* calcd for $C_{15}H_{24}O_3Na$ $[M+Na]^+$ 275.1618, found 275.1619.

(5*S*,6*R*)-**17b**: HRMS (ESI) *m*/*z* calcd for $C_{15}H_{24}O_3Na$ $[M+Na]^+$ 275.1618, found 275.1617.

*3.1.10. Preparation of (5R,6S)- and (5S,6R)-C_{25}-Apocarotenal **18a,b**.* Trimethyl orthoformate (4 mL) and an acidic solution (1.0 mL) prepared from *p*-TsOH•H_2O (500 mg) and H_3PO_4 (700 mg) in MeOH (35 mL) were added to a solution of phosphonium salt **7**[8] (4.70 g, 10. 5 mmol) in MeOH (20 mL) and the mixture was stirred at rt for 2 h. The resulting solution of phosphonium salt **7'** was neutralized with NaOMe until just before a red color of an ylide appeared and a solution of (5*R*,6*S*)-**17a** (*E*/*Z* ~2/1: 630 mg, 2.50 mmol) in CH_2Cl_2 (5 mL) and then NaOMe (650 mg, 12.0 mmol) were added to it. After being stirred at rt for 30 min, the mixture was quenched by saturated aq. NH_4Cl and extracted with AcOEt. The extracts were shaken with 3% aq. HCl twice. The organic layer was washed with brine, dried and evaporated to give a residue, which was purified by flash CC (acetone-CH_2Cl_2, 12:88 to MeOH-acetone-CH_2Cl_2, 2:15:85). The resulting isomeric mixture of condensed products was dissolved in THF (2 mL) and MeCN (60 mL), and a solution (20 mL) prepared from $PdCl_2(MeCN)_2$ (26 mg), Et_3N (14 μL) and water (2.4 mL) in MeCN (17.6 mL) was added to it. After being stirred at rt for 2 h, the solvent was evaporated off to give a residue, which was purified by flash CC (MeOH-acetone-CH_2Cl_2, 2:15:85) to afford an isomeric mixture (all-*E*-isomer: 54% from HPLC analysis) of **18a** (751 mg, 78% from **17a**). Preparative HPLC purification [Cosmosil 5SL-II (SiO_2) 2×25 cm; acetone-CH_2Cl_2-hexane, 1:7:3] yielded all-*E*-isomer of (5*R*,6*S*)-**18a** (314 mg, 33% from **17a**) and other isomeric mixture of **18a** (395 mg, 41 % from **17a**) as a red-orange foam, respectively. (5*S*,6*R*)-**18b** was also prepared (all-*E*-isomer: 38% from **17b** after preparative HPLC) by the same procedure.

(5*R*,6*S*)-**18a**: UV-VIS (EtOH) λ 420 nm; IR ($CHCl_3$) ν 3601 and 3562 (OH), 1660 (CO), 1600 and 1551 (C=C) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.23 (3H, s, 5-CH_3), 1.38 (1H, ddd, *J*=5.5, 11, 14 Hz) and 1.63 (1H, m) (4-H_2), 1.62 and 1.69 (each 3H, br s, *gem*-CH_3), 1.89 (3H, br s, 13'-CH_3), 1.95 (3H, br s, 9-CH_3), 2.04 (3H, br s, 13-CH_3), 2.04–2.18 (2H, m, 3-H_2), 2.11 (1H, br s, 5-OH), 2.20 (1H, br d, *J*=4 Hz, 6-OH), 4.03 (1H, dd, *J*=4, 7.5 Hz, 6-H), 5.12 (1H, br t, *J*=6.5 Hz, 2-H), 5.81 (1H, dd, *J*=7.5, 16 Hz, 7-H), 6.21 (1H, br d, *J*=11 Hz, 10-H), 6.32 (1H, br d, *J*=12 Hz, 14-H), 6.39 (1H, d, *J*=16 Hz, 8-H), 6.39 (1H, d, *J*=15.5 Hz, 12-H), 6.70 (1H, dd, *J*=12, 14.5 Hz, 15'-H), 6.75 (1H, dd, *J*=11, 15.5 Hz, 11-H), 6.96 (1H, br d, *J*=12 Hz, 14'-H), 7.03 (1H, dd, *J*=12, 14.5 Hz, 15-H), 9.46 (1H, s, CHO); ^{13}C NMR (125 MHz, $CDCl_3$) δ 9.60 (13'-CH_3), 13.02 (13-CH_3), 13.09 (9-CH_3), 17.66 (1-CH_3), 22.02 (C3), 23.40 (5-CH_3), 25.70 (1-CH_3), 36.55 (C4), 74.84 (C5), 79.60 (C6), 124.40 (C2),

127.09 (C11), 127.41 (C7), 127.69 (C15'), 131.44 (C14), 132.00 (C1), 132.22 (C10), 136.19 (C9), 137.05 (C13'), 137.48 (C15), 137.55 (C8 and C12), 141.39 (C13), 148.82 (C14'), 194.52 (CHO); HRMS (ESI) *m*/*z* calcd for $C_{25}H_{36}O_3Na$ $[M+Na]^+$ 407.2557, found 407.2559.

(5*S*,6*R*)-**18b**: HRMS (ESI) *m*/*z* calcd for $C_{25}H_{36}O_3Na$ $[M+Na]^+$ 407.2557, found 407.2548.

*3.1.11. Preparation of (5R,6S)- and (5S,6R)-erythro-Lycopene-5,6-diol **1a,b**.* To a solution of phosphonium salt **5**[6] (2.30 g, 4.0 mmol) in CH_2Cl_2 (13 ml) was added NaOMe until just before a red color of an ylide appeared and a solution and a solution of (5*R*,6*S*)-**18a** (250 mg, 0.65 mmol) in CH_2Cl_2 (7 mL) and then NaOMe (1M in MeOH; 5.0 mL, 5.0 mmol) were added to it. After being stirred at rt for 40 min, the mixture was quenched by saturated aq. NH_4Cl 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, 35:65 to MeOH-AcOEt-hexane, 3:40:60). The resulting isomeric mixture of condensed products was dissolved in THF (5 mL) and MeCN (40 mL), and a solution (8 mL) prepared from $PdCl_2(MeCN)_2$ (26 mg), Et_3N (14 μL) and water (2.4 mL) in MeCN (17.6 mL) was added to it. After being stirred at rt for 2 h, the solvent was evaporated off to give a residue, which was purified by flash CC (MeOH-AcOEt-hexane, 3:40:60) to afford an isomeric mixture (all-*E*-isomer: 51% from HPLC analysis) of **1a** (259 mg, 70% from **18a**) as a red solid. Crystallization from CH_2Cl_2-Et_2O-hexane afforded all-*E*-isomer of (5*R*,6*S*)-**1a** (78 mg, 21% from **18a**) as a red powder. (5*S*,6*R*)-**1b** was also prepared (all-*E*-isomer: 10% from **18b** after crystallization) by the same procedure. ^{1}H NMR spectra of **1a,b** was identical with a natural specimen.[5]

(5*R*,6*S*)-**1a**: UV-VIS (EtOH) λ 280, 431, 456, 488 nm; CD (6.04×10^{-5} mol/L, EtOH) λ(Δε) 205 (−0.03), 250 (–1.09), 270 (–2.48), 272 (–2.20), 279 (–3.11), 322 (0), 331 (+0.50), 344 (+0.83), 352 (0); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.22 (3H, s, 5-CH_3), 1.38 (1H, ddd, *J*=5.5, 11, 14 Hz) and 1.63 (1H, m) (4-H_2), 1.62 and 1.69 (each 6H, br s, *gem*-CH_3×2), 1.82 (3H, br s, 5'-CH_3), 1.92 (3H, br s, 9-CH_3), 1.97 (9H, br s, 9'-CH_3, 13-CH_3 and 13'-CH_3) 2.03–2.16 (6H, m, 3-H_2, 3'-H_2 and 4'-H_2), 2.06 (1H, s, 5-OH), 2.07 (1H, br d, *J*=3.5 Hz, 6-OH), 4.02 (1H, br dd, *J*=3.5, 7 Hz, 6-H), 5.11 and 5.12 (each 1H, m, 2-H and 2'-H), 5.74 (1H, dd, *J*=7, 16 Hz, 7-H), 5.95 (1H, br d, *J*=11.5 Hz, 6'-H), 6.18 (1H, br d, *J*=11.5 Hz, 10'-H), 6.20 (1H, br d, *J*=11.5 Hz, 10-H), 6.25 (1H, d, *J*=15.5 Hz, 8'-H), 6.25 (1H, overlapped, 14'-H), 6.27 (1H,overlapped, 14-H), 6.35 (1H, d, *J*=15 Hz, 12'-H), 6.38 (2H, d, *J*=15.5 Hz, 8-H and 12-H), 6.50 (1H, dd, *J*=11.5, 15.5 Hz, 7'-H), 6.59 (1H, dd, *J*=11.5, 15 Hz, 11-H), 6.60–6.68 (2H, m, 15-H and 15'-H), 6.65 (1H, dd, *J*=11.5, 15 Hz, 11'-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.80 (13-CH_3 and 13'-CH_3), 12.92 (9'-CH_3), 13.02 (9-CH_3), 16.98 (5'-CH_3), 17.68 and 17.71 (1-CH_3 and 1'-CH_3), 22.07 (C3), 23.44 (5-CH_3), 25.71 and 25.72 (1-CH_3 and 1'-CH_3), 26.71 (C3'), 36.63 (C4), 40.25 (C4'), 74.85 (C5), 79.79 (C6), 123.96 (C2'), 124.49 and 124.51 (C2 and C11), 124.90 (C7'), 125.34 (C11'), 125.73 (C6'), 126.24 (C7), 129.88 and 130.51 (C15 and C15'), 131.50 (C10'), 131.77 and 131.95 (C1 and C1'), 132.50 (C14'), 132.87 (C10), 133.21 (C14), 134.28 (C9), 135.39 (C8'), 136.19 and 136.32 (C13 and C9'), 136.86 (C13'), 137.29 (C12'), 137.95 (C8), 138.57 (C12), 139.59 (C5'); HRMS (ESI) *m*/*z* calcd for $C_{40}H_{58}O_2Na$ $[M+Na]^+$ 593.4329, found 593.4326.

(5*S*,6*R*)-**1b**: CD (5.91×10^{-5} mol/L, EtOH) λ(Δε) 226 (0), 250 (–0.65), 270 (+0.96), 272 (+0.86), 279

(+2.20), 289 (0), 330 (–0.90), 344 (–1.19), 382 (–0.19); HRMS (ESI) *m*/*z* calcd for $C_{40}H_{58}O_2Na$ $[M+Na]^+$ 593.4326, found 593.4319.

3.1.12. Preparation of (5'R,6'S)- and (5'S,'6R)-erythro-γ-Carotene-5',6'-diol ***3a,b***. To a solution of phosphonium salt **6**[7] (820 dg, 2.13 mmol) in CH_2Cl_2 (5 ml) was added NaOMe until just before a red color of an ylide appeared and a solution and a solution of (5*R*,6*S*)-**18a** (165 mg, 0.43 mmol) in CH_2Cl_2 (7 mL) and then NaOMe (1M in MeOH; 2.8 mL, 2.8 mmol) were added to it. After being stirred at rt for 20 min, the mixture was quenched by saturated aq. NH_4Cl 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, 35:65 to MeOH-AcOEt-hexane, 2:40:60) and preparative HPLC [Cosmosil 5SL-II (SiO_2) 2×25 cm; MeOH-Et_2O-hexane, 0.3:35:60] to provide all-*E*-isomer of (5'*R*,6'*S*)-**2a** (314 mg, 31% from **18a**) as a red power and other isomeric mixture of **3a** (145 mg, 59 % from **18a**). This isomeric mixture was dissolved in THF (2 mL) and MeCN (20 mL), and a solution (6 mL) prepared from $PdCl_2(MeCN)_2$ (26 mg), Et_3N (14 μL) and water (2.4 mL) in MeCN (17.6 mL) was added to it. After being stirred at rt for 2.5 h, the solvent was evaporated off to give a residue, which was purified by flash CC and preparative HPLC described above to afford all-*E*-isomer of **3a** (42 mg, 17% from **18a**: combined yield, 48%). (5'*S*,6'*R*)-**3b** was also prepared (all-*E*-isomer: combined yield, 50% from **18b** after preparative HPLC) by the same procedure. ^{1}H NMR spectra of **3a,b** was identical with a natural specimen.[5]

(5'*R*,6'*S*)-**3a**: UV-VIS (EtOH) λ 267, 424, 446, 474 nm; CD (8.16×10^{-5} mol/L, EtOH) λ(Δε) 210 (–1.62), 236 (+0.40), 269 (–2.54), 305 (0), 329 (+0.84), 355 (+0.03); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.03 (6H, s, 1-*gem*-Me), 1.22 (3H, s, 5'-CH_3), 1.38 (1H, ddd, *J*=5.5, 11, 14 Hz, 4'-H), 1.47 (2H, m, 2-H_2), 1.59–1.65 (3H, m, 3-H_2 and 4'-H), 1.62 and 1.68 (each 3H, br s, 1'-*gem*-Me), 1.72 (3H, br s, 5-CH_3), 1.92 (3H, br s, 9'-CH_3), 1.96 (3H) and 1.97 (6H) (each br s, 9-CH_3, 13-CH_3 and 13'-CH_3) 2.02 (2H, br t, *J*=6.5 Hz, 4-H_2), 2.07 (1H, s, 5'-OH), 2.08 (1H, d, *J*=4 Hz, 6'-OH), 2.05–2.16 (2H, m, 3'-H_2), 4.02 (1H, dd, *J*=4, 7.5 Hz, 6'-H), 5.12 (1H, tsept, *J*=7, 1.5 Hz, 2'-H), 5.74 (1H, dd, *J*=7.5, 15 Hz, 7'-H), 6.13 (1H, d, *J*=15.5 Hz, 8-H), 6.15 (1H, br d, *J*=11 Hz, 10-H), 6.18 (1H, br d, *J*=15.5 Hz, 7-H), 6.20 (1H, br d, *J*=11 Hz, 10'-H), 6.25 (1H, br d, *J*=11 Hz, 14-H), 6.27 (1H, br d, *J*=11 Hz, 14'-H), 6.35 (1H, d, *J*=15 Hz, 12-H), 6.38 (2H, d, *J*=15 Hz, 8'-H and 12'-H), 6.59 (1H, dd, *J*=11, 15 Hz, 11'-H), 6.60–6.68 (2H, m, 15-H and 15'-H), 6.66 (1H, dd, *J*=11, 15 Hz, 11-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.78, 12.80 and 12.85 (9-CH_3, 13-CH_3 and 13'-CH_3), 13.02 (9'-CH_3), 17.68 and 25.72 (1'-*gem*-CH_3), 19.29 (C3), 21.77 (5-CH_3), 22.06 (C3'), 23.44 (5'-CH_3), 28.99 (1-*gem*-CH_3), 33.14 (C4), 34.29 (C1), 36.63 (C4'), 39.67 (C2), 74.84 (C5'), 79.79 (C6'), 124.46 and 124.51 (C2' and C11'), 125.25 (C11), 126.23 (C7'), 126.78 (C7), 129.42 (C5), 129.80 and 130.49 (C15 and C15'), 130.81 (C10), 131.99 (C1'), 132.30 (C14), 132.86 (C10'), 133.20 (C14'), 134.25 (C9'), 136.12 and 136.19 (C9 and C13'), 136.84 (C13), 137.17 (C12), 137.75 (C8), 137.93 (C6), 137.95 (C8'), 138.57 (C12'); HRMS (ESI) *m*/*z* calcd for $C_{40}H_{58}O_2Na$ $[M+Na]^+$ 593.4329, found 593.4325.

(5'*S*,6'*R*)-**3b**: CD (8.09×10^{-5} mol/L, EtOH) λ(Δε) 213 (+1.38), 240 (–0.79), 269 (+1.80), 290 (0), 327 (–1.14), 354 (–0.34); HRMS (ESI) *m*/*z* calcd for $C_{40}H_{58}O_2Na$ $[M+Na]^+$ 593.4329, found 593.4332.

*3.1.13. (2S,3R)- and (2R,3S)-3-Methyl-3-(4-methylpent-3-en-1-yl)oxiran-2-yl)methyl 3,5-dinitorobenzoate **20a,b***. (2*S*,3*R*)-Epoxynerol **19a** (69% ee) and (2*R*,3*S*)-epoxynerol **19b** (70% ee) were prepared according to the known Sharpless asymmetric epoxidation method of nerol.[10,19] In the same procedure described for the preparation of compound **9a**, (2*S*,3*R*)-**19a** (69% ee; 4.90 g) and (2*R*,3*S*)-**19b** (70% ee; 4.64 g) were converted into (2*S*,3*R*)-**20a** (10.39 g; 99%) and (2*R*,3*S*)-**20b** (9.88 g; 99%) as a pale yellow solid, respectively. Recrystallization of **20a** (10.39 g) from MeOH (130 mL) afforded 5.87 g (56% yield) of **20a** (56% ee) as a pale yellow needle. Evaporation of the filtrate gave 4.60 g (44% yield) of crude **20a** (92% ee). The enantiomeric purities of **20a** and **20b** were established by chiral HPLC [CHIRALPAK ID 0.46×25 cm (Daicel), EtOH-hexane (2:8) 0.7 mL/min, 30°C; **20a**: 19.9 min, **20b**: 21.8 min]. Thus without recrystallization, **20a** and **20b** were used in the next step.

(2*S*,3*R*)-**20a**: IR ($CHCl_3$) ν 1735 (CO), 1549 and 1346 (NO_2) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.41 (3H, s, CH_3), 1.52–1.79 (2H, m, CH_2), 1.65 and 1.71 (each 3H, br s, *gem*-CH_3), 2.18 (2H, m, CH_2), 3.19 (1H, dd, *J*=3.5, 7.5 Hz, OCH_2CH), 4.36 (1H, dd, *J*=7.5, 12 Hz) and 4.76 (1H, dd, *J*=3.5, 12 Hz) (OCH_2), 5.13 (1H, br t, *J*=7 Hz, =CH), 9.20 (2H, d, *J*=2 Hz, ArH), 9.25 (1H, t, *J*=2 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.64, 21.95, 24.11, 25.66, 33.28, 60.38, 61.12, 65.77, 122.59, 122.83, 129.53 (×2), 132.81, 133.39, 148.64 (×2), 162.43; HRMS (ESI) *m*/*z* calcd for $C_{17}H_{20}O_7N_2Na$ $[M+Na]^+$ 387.1163, found 387.1162.

(2*R*,3*S*)-**20b**: HRMS (ESI) *m*/*z* calcd for $C_{17}H_{20}O_7N_2Na$ $[M+Na]^+$ 387.1163, found 387.1162.

*3.1.14. (2S,3S)- and (2R,3R)-2,3-Dihydroxy-3,7-dimethyloct-6-en-1-yl 3,5-dinitrobenzoate **21a,b***. In the same procedure described for hydrolysis of compound **9a** by use of *p*-TsOH in acetonitrile, (2*S*,3*R*)-**20a** (69% ee; 7.00 g) and (2*R*,3*S*)-**20b** (70% ee; 7.00 g) were converted into (2*S*,3*S*)-**21a** (6.10 g; 83%) and (2*R*,3*R*)-**21b** (6.47 g; 88%) as a pale yellow solid, respectively. Twice-recrystallization of **21a,b** from MeOH-H_2O (4:1) afforded 2.08 g of **21a** (99% ee) and 2.31 g of **21b** (99% ee) as a pale yellow needle, respectively. The enantiomeric purities of **21a** and **21b** were established by chiral HPLC [CHIRALPAK IA 0.46×25 cm (Daicel), 2-PrOH-hexane (3.7) 1.0 mL/min, 30°C; **21a**: 16.3 min, **21b**: 19.1 min].

(2*S*,3*S*)-**21a**: mp 117–118 °C; $[\alpha]_D^{20}$ –18.2 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) ν 3571 and 3453 (OH), 1735 (CO), 1549 and 1345 (NO_2) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.27 (3H, s, CH_3), 1.57–1.74 (2H, m, CH_2), 1.65 and 1.70 (each 3H, br s, *gem*-CH_3), 2.14 (2H, br q, *J*=7.5 Hz, CH_2), 2.18 (1H, s, OH), 2.77 (1H, d, *J*=5 Hz, OH), 3.92 (1H, ddd, *J*=2.5, 5, 8.5 Hz, C*H*OH), 4.48 (1H, dd, *J*=8.5, 11.5 Hz) and 4.76 (1H, dd, *J*=2.5, 11.5 Hz)(OCH_2), 5.14 (1H, br t, *J*=7 Hz, =CH), 9.19 (2H, d, *J*=2 Hz, ArH), 9.24 (1H, t, *J*=2 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.71, 21.89, 22.10, 25.68, 38.87, 67.78, 73.76, 74.64, 122.53, 123.62, 129.52 (×2), 132.69, 133.58, 148.63 (×2), 162.84; HRMS (ESI) *m*/*z* calcd for $C_{17}H_{22}O_8N_2Na$ $[M+Na]^+$ 405.1268, found 405.1267.

(2*R*,3*R*)-**21b**: mp 115–117 °C; $[\alpha]_D^{21}$ +16.2 (*c* 0.93, $CHCl_3$); HRMS (ESI) *m*/*z* calcd for $C_{17}H_{22}O_8N_2Na$ $[M+Na]^+$ 405.1268, found 405.1267.

*3.1.15. Preparation of (5S,6S)- and (5R,6R)-threo-lycopene-5,6-diol **2a,b**, and (5'S,6'S)- and (5'R,'6R)-erythro-γ-carotene-5',6'-diol **4a,b**.* In the same procedure described for the preparation of (5*R*,6*S*)-*erythro*-lycopene-5,6-diol **1a** and (5'*R*,6'*S*)-*erythro*-γ-carotene-5',6'-diol **3a**, *threo*-lycopene-5,6-diols **2a**,**b** and *threo*-γ-carotene-5',6'-diols **4a**,**b** were prepared from (2*S*,3*S*)-**21a** and (2*R*,3*R*)-**21b** via C_{10}-aldehydes **22a,b**, C_{15}-aldehydes **23a,b** and C_{25}-apocarotenals **24a,b**.

(4*R*,5*S*)-**22a** (74% form **21a**): $[\alpha]_D^{27}$ +55.4 (*c* 1.24, $CHCl_3$); IR ($CHCl_3$) ν 1735 (CO) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.18 (3H, s, CH_3), 1.39 and 1.55 (each 3H, s, *gem*-CH_3), 1.61 and 1.68 (each 3H, br s, *gem*-CH_3), 1.66–1.71 (2H, m, CH_2), 2.04–2.17 (2H, m, CH_2), 4.14 (1H, d, *J*=2 Hz, C*H*CHO), 5.10 (1H, tsept, *J*=1.5, 7.5 Hz, =CH), 9.71 (1H, d, *J*=2 Hz, CHO); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.64, 22.31, 22.33, 25.63, 27.15, 28.47, 40.36, 83.67, 85.82, 110.05, 123.52, 132.18, 200.73; HRMS (ESI) *m*/*z* calcd for $C_{13}H_{22}O_3Na$ $[M+Na]^+$ 249.1461, found 249.1461.

(4*S*,5*R*)-**22b** (73% form **21b**): $[\alpha]_D^{23}$ –55.2 (*c* 1.00, $CHCl_3$); HRMS (ESI) *m*/*z* calcd for $C_{13}H_{22}O_3Na$ $[M+Na]^+$ 249.1461, found 249.1461.

(5*S*,6*S*)-**23a** (49% from **22a**): IR ($CHCl_3$) ν 3606 and 3463 (OH), 1664 (CO), 1634 and 1600 (C=C) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.14 (2H) and 1.15 (1H) (each s, 5-CH_3), 1.54–1.62 (2H, m, 4-H_2), 1.64 and 1.70 (each 3H, br s, *gem*-CH_3), 2.05 (1/3H) and 2.07 (2/3H) (each s, OH), 2.09 (1H) and 2.28 (2H) (each d, *J*=1 Hz, 9-CH_3), 2.13 (2H, m, 3-H_2), 2.43 (2/3H) and 2.48 (1/3H) (each d, *J*=3.5 Hz, OH), 4.12 (1H, m, 6-H), 5.14 (1H, br t, *J*=7.5 Hz, 2-H), 5.91 (1/3H) and 5.98 (2/3H) (each br d, *J*=8 Hz, 10-H), 6.19 (1/3H) and 6.27 (2/3H) (each dd, *J*=6.5, 15.5 Hz, 7-H), 6.47 (2/3H) and 7.36 (1/3H) (each d, *J*=15.5 Hz, 8-H), 10.13 (2/3H) and 10.20 (1/3H) (each d, *J*=8 Hz, CHO); HRMS (ESI) *m*/*z* calcd for $C_{15}H_{24}O_3Na$ $[M+Na]^+$ 275.1618, found 275.1617.

(5*R*,6*R*)-**23b** (53% from **22b**): HRMS (ESI) *m*/*z* calcd for $C_{15}H_{24}O_3Na$ $[M+Na]^+$ 275.1618, found 275.1617.

(5*S*,6*S*)-**24a** (all-*E*-isomer: 36% from **23a** after preparative HPLC): UV-VIS (EtOH) λ 418 nm; IR ($CHCl_3$) ν 3604, 3567 and 3478 (OH), 1661 (CO), 1611, 1600 and 1551 (C=C) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.14 (3H, s, 5-CH_3), 1.54 (2H, t, *J*=8 Hz, 4-H_2), 1.63 and 1.69 (each 3H, br s, *gem*-CH_3), 1.89 (3H, br s, 13'-CH_3), 1.95 (3H, br s, 9-CH_3), 2.04 (3H, br s, 13-CH_3), 2.12 (2H, br q, *J*=8 Hz, 3-H_2), 2.12 (1H, br s, 5-OH), 2.26 (1H, br d, *J*=2.5 Hz, 6-OH), 4.05 (1H, dd, *J*=2.5, 7.5 Hz, 6-H), 5.13 (1H, tsept, *J*=7.5, 1.5 Hz, 2-H), 5.77 (1H, dd, *J*=7.5, 15.5 Hz, 7-H), 6.21 (1H, br d, *J*=11 Hz, 10-H), 6.32 (1H, br d, *J*=12 Hz, 14-H), 6.39 (1H, d, *J*=15.5 Hz, 8-H), 6.40 (1H, d, *J*=15 Hz, 12-H), 6.70 (1H, dd, *J*=11.5, 14.5 Hz, 15'-H), 6.74 (1H, dd, *J*=11, 15 Hz, 11-H), 6.96 (1H, br d, *J*=11.5 Hz, 14'-H), 7.02 (1H, dd, *J*=11.5, 14.5 Hz, 15-H), 9.45 (1H, s, CHO); ^{13}C NMR (125 MHz, $CDCl_3$) δ 9.62 (13'-CH_3), 13.05 and 13.10 (9-CH_3 and 13-CH_3), 17.70 (1-CH_3), 21.43 (5-CH_3), 22.12 (C3), 25.72 (1-CH_3), 38.81 (C4), 75.03 (C5), 78.71 (C6), 124.30 (C2), 127.12 (C11), 127.47 (C7), 127.74 (C15'), 131.48 (C14), 132.07 (C1), 132.29 (C10), 136.22 (C9), 137.11 (C13'), 137.57 and 137.61 (C12 and C15), 137.73 (C8), 141.41 (C13), 148.82 (C14'), 194.53 (CHO); HRMS (ESI) *m*/*z* calcd for $C_{25}H_{36}O_3Na$ $[M+Na]^+$ 407.2557, found 407.2557.

(5*R*,6*R*)-**24b** (all-*E*-isomer: 20% from **23b** after preparative HPLC): HRMS (ESI) *m*/*z* calcd for $C_{25}H_{36}O_3Na$ $[M+Na]^+$ 407.2557, found 407.2556.

(5*S*,6*S*)-**2a** (78% from **24a** for isomeric mixture, all-*E*-isomer: 24% from **24a** after crystallization): UV-VIS (EtOH) λ 280, 430, 455, 486 nm; CD (5.80×10^{-5} mol/L, EtOH) λ(Δε) 240 (−0.42), 271 (–2.80), 280 (–4.72), 318 (0), 331 (+0.70), 344 (+1.31), 358 (0); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.14 (3H, s, 5-CH_3), 1.53 (2H, t, *J*=8 Hz, 4-H_2), 1.62 (3H), 1.63 (3H) and 1.69 (6H) (each br s, *gem*-CH_3×2), 1.82 (3H, br s, 5'-CH_3), 1.92 (3H, br s, 9-CH_3), 1.97 (9H, br s, 13-CH_3, 9'-CH_3 and 13'-CH_3) 2.08 (1H, s, 5-OH), 2.08–2.14 (6H, m, 3-H_2, 3'-H_2 and 4'-H_2), 2.12 (1H, br d, *J*=3 Hz, 6-OH), 4.04 (1H, dd, *J*=3, 8 Hz, 6-H), 5.11 and 5.13 (each 1H, m, 2-H and 2'-H), 5.70 (1H, dd, *J*=8, 15.5 Hz, 7-H), 5.95 (1H, br d, *J*=11.5 Hz, 6'-H), 6.18 (1H, br d, *J*=11.5 Hz, 10'-H), 6.20 (1H, br d, *J*=11.5 Hz, 10-H), 6.25 (1H, d, *J*=15 Hz, 8'-H), 6.25 (1H, overlapped, 14'-H), 6.27 (1H, overlapped, 14-H), 6.35 (1H, d, *J*=15 Hz, 12'-H), 6.38 (2H, d, *J*=15.5 Hz, 8-H and 12-H), 6.50 (1H, dd, *J*=11.5, 15 Hz, 7'-H), 6.59 (1H, dd, *J*=11.5, 15 Hz, 11-H), 6.60–6.68 (2H, m, 15-H and 15'-H), 6.65 (1H, dd, *J*=11.5, 15 Hz, 11'-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.80, 12.82, 12.92 and 12.99 (9-CH_3, 9'-CH_3, 13-CH_3 and 13'-CH_3), 16.98 (5'-CH_3), 17.69 and 17.14 (1-CH_3 and 1'-CH_3), 21.43 (5-CH_3), 22.12 (C3), 25.71 (1-CH_3 and 1'-CH_3), 26.70 (C3'), 38.80 (C4), 40.25 (C4'), 75.01 (C5), 78.86 (C6), 123.96 (C2'), 124.35 (C2), 124.48 (C11), 124.89 (C7'), 125.34 (C11'), 125.72 (C6'), 126.26 (C7), 129.87 and 130.51 (C15 and C15'), 131.50 (C10'), 131.77 and 132.00 (C1 and C1'), 132.50 (C14'), 132.89 (C10), 133.21 (C14), 134.27 (C9), 135.38 (C8'), 136.18 and 136.32 (C9' and C13), 136.86 (C13'), 137.29 (C12'), 138.15 (C8), 138.58 (C12), 139.59 (C5'); HRMS (ESI) *m*/*z* calcd for $C_{40}H_{58}O_2Na$ $[M+Na]^+$ 593.4329, found 593.4329.

(5*R*,6*R*)-**2b** (56% from **24b** for isomeric mixture, all-*E*-isomer: 5% from **24b** after crystallization): CD (5.88×10^{-5} mol/L, EtOH) λ(Δε) 213 (0), 242 (–0.36), 270 (+1.68), 272 (+1.54), 279 (+3.18), 293 (0), 329 (–1.20), 344 (–1.73), 387 (–0.17); HRMS (ESI) *m*/*z* calcd for $C_{40}H_{58}O_2Na$ $[M+Na]^+$ 593.4329, found 593.4329.

(5*S*,6*S*)-**4a** (96% from **24a** for isomeric mixture, all-*E*-isomer: 28% from **24a** after preparative HPLC): UV-VIS (EtOH) λ 267, 423, 446, 474 nm; CD (9.48×10^{-5} mol/L, EtOH) λ(Δε) 215 (–1.85), 227 (0), 236 (+0.76), 247 (0), 273 (–3.06), 301 (0), 331 (+0.93), 359 (0); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.03 (6H, s, 1-*gem*-Me), 1.14 (3H, s, 5'-CH_3), 1.53 (2H, t, *J*=7.5 Hz, 4'-H_2), 1.62 (2H, m, 3-H_2), 1.63 and 1.69 (each 3H, br s, 1'-*gem*-CH_3), 1.72 (3H, br s, 5-CH_3), 1.92 (3H, br s, 9'-CH_3), 1.97 (3H) and 1.98 (6H) (each br s, 9-CH_3, 13-CH_3 and 13'-CH_3) 2.02 (2H, br t, *J*=6.5 Hz, 4-H_2), 2.09 (1H, s, 5'-OH), 2.12 (2H, br q, *J*=7.5 Hz, 3'-H_2), 2.14 (1H, br d, *J*=3 Hz, 6'-OH), 4.04 (1H, dd, *J*=3, 7.5 Hz, 6'-H), 5.13 (1H, br t, *J*=7.5 Hz, 2'-H), 5.70 (1H, dd, *J*=7.5, 15.5 Hz, 7'-H), 6.13 (1H, d, *J*=15.5 Hz, 8-H), 6.15 (1H, br d, *J*=11.5 Hz, 10-H), 6.18 (1H, br d, *J*=15.5 Hz, 7-H), 6.20 (1H, br d, *J*=11.5 Hz, 10'-H), 6.25 (1H, overlapped, 14-H), 6.27 (1H, overlapped, 14'-H), 6.35 (1H, d, *J*=15 Hz, 12-H), 6.38 (2H, d, *J*=15 Hz, 8'-H and 12'-H), 6.59 (1H, dd, *J*=11.5, 15 Hz, 11'-H), 6.60–6.68 (2H, m, 15-H and 15'-H), 6.66 (1H, dd, *J*=11, 15 Hz, 11-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.78, 12.80, 12.85 and 12.99 (9-CH_3, 9'-CH_3, 13-CH_3 and 13'-CH_3), 17.69 and 25.72 (1'-*gem*-CH_3), 19.28 (C3), 21.43 (5'-CH_3), 21.77 (5-CH_3), 22.12 (C3'), 28.99 (1-*gem*-CH_3), 33.14 (C4), 34.29 (C1), 38.81 (C4'), 39.67 (C2), 75.00 (C5'), 78.86 (C6'), 124.35 and 124.45 (C2' and C11'), 125.25 (C11), 126.26 (C7'), 126.78 (C7), 129.42 (C5), 129.80 and 130.49 (C15 and C15'), 130.81 (C10), 131.99 (C1'), 132.30 (C14),

132.89 (C10'), 133.20 (C14'), 134.26 (C9'), 136.12 and 136.19 (C9 and C13'), 136.84 (C13), 137.17 (C12), 137.75 (C8), 137.92 (C6), 138.14 (C8'), 138.58 (C12'); HRMS (ESI) *m*/*z* calcd for $C_{40}H_{58}O_2Na$ $[M+Na]^+$ 593.4329, found 593.4326.

(5*R*,6*R*)-**4b** (82% from **24b** for isomeric mixture, all-*E*-isomer: 17% from **24b** after preparative HPLC): CD (8.72×10^{-5} mol/L, EtOH) λ(Δε) 212 (+0.75), 224 (0), 240 (–0.61), 253 (0), 269 (+1.17), 290 (0), 327 (–0.67), 365 (0); HRMS (ESI) *m*/*z* calcd for $C_{40}H_{58}O_2Na$ $[M+Na]^+$ 593.4329, found 593.4328.

References and notes

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unsuccessful due to its decomposition during a series of acquisition some spectral data. The fact that carotenoids synthesized here are relatively stable by keeping in a freezer for several months has convinced us to determine the absolute configurations of natural specimens if it is obtained and kept in an appropriate way.