Carotenoids and Related Polyenes, Part 12[1)] First Total Synthesis and Absolute Configuration of 3′-Deoxycapsanthin and 3,4-Didehydroxy-3′-deoxycapsanthin

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The synthesis of 3′-deoxycapsanthin (1) and 3,4-didehydroxy-3′-deoxycapsanthin (2), carotenoids of paprika, has been achieved by employing Lewis acid-promoted regio- and stereoselective rearrangement of the C_{15}-epoxy dienal 5a. The absolute stereochemistry of the newly formed C-5 chiral center of rearrangement product 6a was determined to be (*R*) from its alternative synthesis derived from (+)-(*R*)-camphonanic acid (11).

Key words 3′-deoxycapsanthin; 3,4-didehydroxy-3′-deoxycapsanthin; tetrasubstituted epoxide; regioselective rearrangement; stereoselective rearrangement; absolute configuration

3′-Deoxycapsanthin (**1**) and 3,4-didehydroxy-3′-capsanthin (**2**) (Fig. 1) were recently isolated[2)] from ripe fruits of paprika (*Capsicum annuum*) together with the major pigments capsanthin (**3**) and capsorubin (**4**), which have anticancer[3)] and anti-oxidative properties.[4,5)] These carotenoids, having a κ-end group, are considered[6,7)] to be formed in nature from 5,6-epoxy carotenoids through ring opening of the epoxy moiety. The structures of **1** and **2** were determined[2)] by extensive analysis using modern NMR techniques, and their absolute configurations were assigned on the basis of biosynthetic considerations[6,7)] and by comparing their circular dichroism (CD) data with those of capsanthin (**3**) (Fig. 1).

Previously, we reported[8,9)] the biomimetic type total synthesis of capsanthin (**3**) and capsorubin (**4**) *via* regioselective cleavage of the oxirane ring at the C-5 position,[10)] and the subsequent regio- and stereoselective ring contraction of the C_{15}-3-silyloxy-5,6-epoxy dienal **5b** (Chart 1). Continuing our work on the total synthesis of carotenoids,[1)] we present here the first total synthesis of 3′-deoxycapsanthin (**1**) and 3,4-didehydroxy-3′-deoxycapsanthin (**2**) through the C_{15}-cyclopentyl ketone **6a** (Chart 1), prepared by rearrangement of the optically active C_{15}-5,6-epoxy dienal **5a**.

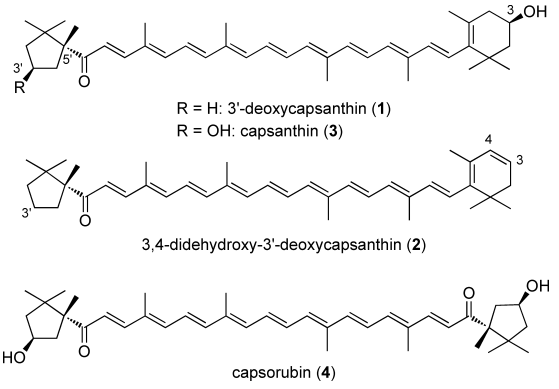

Fig. 1. Structures of Carotenoids

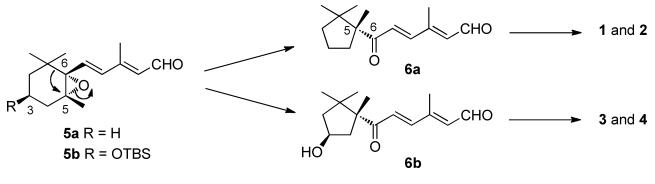

Chart 1

Results and Discussion

The optically active C_{15}-epoxy dienal **5a** was prepared (Chart 2) from the known[11)] epoxy aldehyde **9**, which was synthesized *via* Sharpless asymmetric epoxidation of the allylic alcohol **7** derived[12)] from commercially available β-ionone. Emmons–Horner reaction of the aldehyde **9** with the phosphonate **15** in the presence of *n*-butyllithium and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) gave the all-*E* dienoate **10** (72%) and its 9*Z* isomer (13%), which could be readily separated by flash column chromatography (CC). Reduction of the ester **10** with $LiAlH_4$ followed by MnO_2 oxidation gave the C_{15}-epoxy dienal **5a** in 95% yield.

Treatment of **5a** with $SnCl_4$ yielded the regioselectively rearranged cyclopentyl ketone **6a** in 76% yield. HPLC analysis using a chiral column (CHIRALPAK AY-H; Daicel) revealed that the enantiomeric excess (ee) of the cyclopentyl ketone **6a** (84% ee) remained almost unchanged during the rearrangement of C_{15}-epoxy dienal **5a** (94% ee). From the previous results,[8,9)] the absolute stereochemistry of the newly formed C-5 chiral center in rearrangement product **6a** was expected to be (*R*); however, its configuration was determined by an alternative synthesis from (+)-(*R*)-camphonanic acid (**11**)[13)] (Chart 2).

Esterification of the acid **11** with $TMSCHN_2$[14)] followed by reduction with $LiAlH_4$ gave the corresponding alcohol **12**[15)] (88%). Subsequently, alcohol **12** was oxidized using Dess–Martin periodinane (DMP) to provide the extremely volatile aldehyde **13**[15)] in 57% yield. This aldehyde was subsequently coupled with vinyl lithium, prepared from the vinyl iodide **16**[16)] (*E*/*Z* *ca.* 7/3) and *tert*-butyllithium, to provide the alcohol **14** in 41% yield. Upon deprotection of the *tert*-butyldimethylsilyl (TBS) group in **14** with tetrabutylammonium fluoride (TBAF) and subsequent DMP oxidation, the all-*E* (*R*)-cyclopentyl ketoaldehyde **6a** (46%; 89% ee determined by chiral HPLC) was obtained accompanied by its 9*Z* isomer (21%). The optical rotation, the retention time on chiral HPLC, and the spectral data of all-*E* (*R*)-cylpentyl ketoaldehyde **6a** were identical to those of the product prepared from epoxy dienal **5a**.

This ketoaldehyde **6a** was transformed into 3′-deoxycap-

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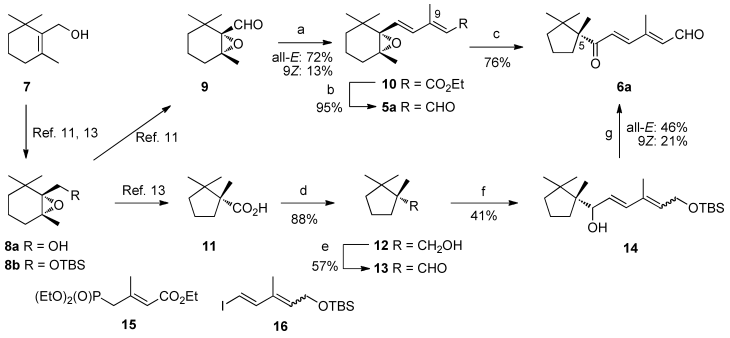
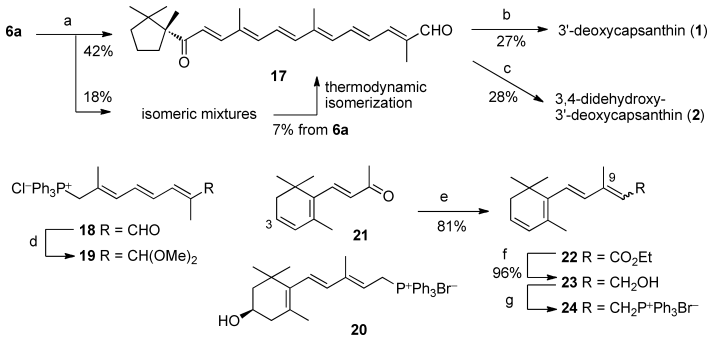


Reagents and conditions: (a) **15**, ^{n}BuLi, DMPU, THF; (b) $LiAlH_4$, Et_2O then MnO_2, EtO_2–hexane; (c) $SnCl_4$, CH_2Cl_2; (d) $TMSCHN_2$, MeOH–benzene then $LiAlH_4$, Et_2O; (e) DMP, CH_2Cl_2; (f) **16**, ^{t}BuLi, Et_2O; (g) TBAF, THF then DMP, CH_2Cl_2.

Chart 2



Reagents and Conditions: (a) **19**, NaOMe, MeOH then Dowex (H^+); (b) **20**, NaOMe, MeOH; (c) **24**, NaOMe, MeOH; (d) $CH(OMe)_3$, H^+, MeOH; (e) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, 50 °C; (f) $LiAlH_4$, Et_2O; (g) $PPh_3 \cdot HBr$, MeOH.

Chart 3

santhin (**1**) and 3,4-didehydroxy-3′-deoxycapsanthin (**2**) through apocarotenal **17** (Chart 3). Wittig condensation of the C_{15}-aldehyde **6a** with the C_{10}-phosphonium salt **19**[17] in the presence of NaOMe as a base, followed by one-pot treatment with ion exchange resin (Dowex 50W-X8, H^+), provided an isomeric mixture of C_{25}-apocarotenals. Preparative HPLC (PHPLC) provided the all-*E* isomer **17** (42%) and an isomeric mixture (18%), which thermodynamically isomerized while standing in ethereal solution at room temperature (rt) for 1 d to yield the desired all-*E* isomer **17** (7% from **6a**). The stereochemistry of **17** was determined by comparison of its ^{1}H-NMR data with previously prepared[8,9] 3-hydroxycyclopentyl apocarotenal.

Wittig reaction of the C_{25}-apocarotenal **17** with the C_{15}-phosphonium salt **20**[8,9] afforded a mixture of condensation products, which were separated by PHPLC to provide all-*E* 3′-deoxycapsanthin (**1**) (27%) and an isomeric mixture (20%). The latter was also transformed (6% from **17**) into the desired all-*E* isomer by thermodynamic isomerization. The spectral data of the synthetic product **1** were in good agreement with those of the reported[2] natural product.

Next, the C_{15}-Wittig salt **24** was prepared for the synthesis of 3,4-didehydroxy-3′-deoxycapsanthin (**2**). Emmons–Horner reaction of 3,4-didehyro-β-ionone (**21**), prepared[18] from commercially available α-ionone, with triethyl phosphonoacetate in the presence of NaH provided the ester **22** (81%) as an isomeric mixture (9*E*/*Z* *ca.* 85/15), which without separation, was reduced with $LiAlH_4$ to afford the alcohol **23** in 96% yield. This was followed by treatment with $PPh_3 \cdot HBr$ to provide the Wittig salt **24**, which without purification was condensed with the apocarotenal **17**. PHPLC purification of the condensation products afforded all-*E* 3,4-didehydroxy-3′-deoxycapsanthin (**2**) (28%) accompanied by an isomeric mixture. Spectral data of the synthetic product **2** were in good agreement with those of the reported[2] natural product.

In conclusion, considering of the biosynthesis of the κ-end group in carotenoids, we applied the regio- and stereoselective rearrangement of 5,6-epoxy dienal **5a** with $SnCl_4$ to accomplish the first total synthesis of optically active 3′-deoxycapsanthin (**1**) and 3,4-didehydroxy-3′-capsanthin (**2**). Moreover, we assigned the absolute configuration of the κ-end group in **1** and **2** on the basis of their enantiospecific total synthesis.

Experimental

General UV spectra were recorded on a JASCO V-650 instrument. IR spectra were measure on a Perkin Elmer FT-IR spectrometer, model Paragon 1000. ^{1}H- and ^{13}C-NMR spectra were determined on a Varian Mercury-300 or a Varian VXR-500 superconducting FT-NMR spectrometer, with deuteriochloroform solutions (tetramethylsilane as the internal reference). *J*-Values are given in Hz. Mass spectra were obtained on a Hitachi M-4100 or Orbitrap Exactive spectrometer. Optical rotations were measured on a JASCO P-2200 polarimeter ($[\alpha]_D$ values are in units of 10^{-1} deg cm^2 g^{-1}) and CD spectra on a Shimadzu-AVIN 62A DS circular dichroism spectrometer. Flash CC was performed on silica gel (Kanto Chemical No. 37563-79). PHPLC 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. Ether refers to diethyl ether, and hexane to *n*-hexane. NMR assignments are given using the carotenoids numbering system.

Ethyl (2*E*/*Z*,4*E*)-3-Methyl-5-[(1*S*,6*R*)-2,2,6-trimethyl-7-oxabicyclo-[4.1.0]hept-1-yl]penta-2,4-dienoate (10) To a solution of triethyl 3-methyl-4-phosphonocrotonate (**15**) (1.90 g, 7.2 mmol) and DMPU (1.7 ml, 14.4 mmol) in dry tetrahydrofuran (THF) (20 ml) was added *n*BuLi (1.60 M in hexane; 4.5 ml, 7.2 mmol) at 0 °C. After being stirred at 0 °C for 30 min, a solution of the epoxy aldehyde **9**[11] (930 mg, 5.5 mmol) in dry THF (12 ml) was added to the reaction mixture at 0 °C and stirring was continued for 40 min. After being quenched with saturated aq. NH_4Cl, the mixture was extracted with ether. The extracts were washed with brine, dried and evaporated to give the residue, which was purified by flash CC (ether–hexane, 1 : 9) to provide the all-*E* epoxy ester **10** (1.11 g, 72%) and its 9*Z* isomer (201 mg, 13%) as pale yellow oils, respectively. Their ^{1}H-NMR, IR and UV spectra were identical with those of previous prepared[9] racemic compounds.

All-*E* Isomer: $[\alpha]_D^{26}$ −41.6 (*c*=1.02, EtOH) {lit.[19]: $[\alpha]_D$ −44.5 (*c*=0.74, EtOH)}. High resolution-electron ionization (HR-EI)-MS *m*/*z*: 278.1900 (M^+) (Calcd for $C_{17}H_{26}O_3$: 278.1881).

9*Z* Isomer: $[\alpha]_D^{27}$ +20.5 (*c*=0.63, EtOH) {lit.[19]: $[\alpha]_D$ +24 (*c*=0.482, EtOH)}. HR-EI-MS *m*/*z*: 278.1891 (M^+) (Calcd for $C_{17}H_{26}O_3$: 278.1881).

(2*E*,4*E*)-3-Methyl-5-[(1*S*,6*R*)-2,2,6-trimethyl-7-oxabicyclo[4.1.0]hept-1-yl]penta-2,4-dienal (5a) A solution of the ester **10** (1.55 g, 5.6 mmol) in dry ether (30 ml) was added dropwise to a stirred suspension of $LiAlH_4$ (220 mg, 5.8 mmol) in dry ether at 0 °C. After being stirred at 0 °C for 25 min, the excess of $LiAlH_4$ was decomposed by dropwise addition of water and the mixture was extracted with ether. The extracts were dried and evaporated to give a residue, which without purification, was dissolved in ether–hexane (*ca.* 1 : 4) and shaken with MnO_2 (10 g) at rt for 3 h. The mixture was filtered through Celite. Evaporation of the filtrate followed by purification by flash CC (EtOAc–hexane, 2 : 8) to provide the epoxy dienal **5a** (1.24 g, 95%) as a pale yellow oil. Its ^{1}H-NMR, IR and UV spectra were identical with those of previous prepared[9] racemic compounds. Enatiomeric excess (94%) was determined by HPLC [CHIRALPAK AY-H (Daicel) 0.46×25 cm; 2-PrOH–hexane, 1 : 9; 1.0 ml/min]. $[\alpha]_D^{25}$ −52.3 (*c*=0.97, $CHCl_3$) {lit.[19]: $[\alpha]_D$ −52 (*c*=0.842, $CHCl_3$)}. HR-EI-MS *m*/*z*: 234.1636 (M^+) (Calcd for $C_{15}H_{22}O_2$: 234.1620).

(2*E*,4*E*)-3-Methyl-6-oxo-6-[(*R*)-1,2,2-trimethylcyclopentyl]hexa-2,4-dienal (6a) To a solution of the epoxy dienal **5a** (448 mg, 1.9 mmol) in dry CH_2Cl_2 (12 ml) was added $SnCl_4$ (1 M in CH_2Cl_2; 4.2 ml, 4.2 mmol) at 0 °C. The mixture was stirred at 0 °C for 20 min and then poured into saturated aq. $NaHCO_3$ and extracted with ether. The extracts were washed with brine and dried. Evaporation of the solvent gave a residue, which was purified by flash CC (EtOAc–hexane, 2 : 8) to afford the cyclopentyl ketoaldehyde **6a** (341 mg, 76%) as a pale yellow solid. Its ^{1}H-NMR, IR and UV spectra were identical with those of previous prepared[9] racemic compounds. Enatiomeric excess (84%) was determined by HPLC [CHIRALPAK AY-H (Daicel) 0.46×25 cm; 2-PrOH–hexane, 3 : 7; 1.0 ml/min]. $[\alpha]_D^{25}$ −5.2 (*c*=0.99, EtOH). HR-EI-MS *m*/*z*: 234.1619 (M^+) (Calcd for $C_{15}H_{22}O_2$: 234.1620).

[(*R*)-1,2,2-Trimethylcyclopentyl]methanol (12) To a solution of (+)-(*R*)-camphonanic acid (**11**)[13] (2.72 g, 14.8 mmol) in MeOH–benzene (*ca.* 1 : 4; 164 ml) was added $TMSCHN_2$ (2 M in hexane; 11.4 ml, 22.8 mmol). After being stirred at rt for 30 min, solvent was evaporated off to give the corresponding methyl ester, which without purification, was dissolved in dry ether (15 ml) and this solution was added dropwise to a stirred suspension of $LiAlH_4$ (660 mg, 17.4 mmol) in dry ether at 0 °C. After being stirred at rt for 25 min, the excess of $LiAlH_4$ was decomposed by dropwise addition of water and the mixture was extracted with ether. The extracts were dried and evaporated to give a residue, which was purified by flash CC (ether–hexane, 3 : 7) to afford the alcohol **12** (2.21 g, 89% from **11**) as a colorless amorphous solid. Its ^{1}H-NMR data were identical with those reported.[15] HR-electrospray ionization (ESI)-MS *m*/*z*: 165.1251 $[M+H]^+$ (Calcd for $C_9H_{18}ONa$: 165.1250).

(*R*)-1,2,2-Trimethylcyclopentanecarbaldehyde (13) To a solution of alcohol **12** (1.80 g, 12.7 mmol) in CH_2Cl_2 (60 ml) was added DMP (7.52 g, 17.7 mmol) at 0 °C. After being stirred at rt for 1 h, the mixture was filtered through Celite. Evaporation of the filtrate followed by purification by flash CC (ether–hexane, 15 : 85) provided the aldehyde **13** (1.01 g, 57%) as a colorless amorphous solid (unstable and extremely volatile). Its ^{1}H-NMR data were identical with those reported.[15] $[\alpha]_D^{23}$ +9.8 (*c*=0.50, $CHCl_3$) {lit.[15]: $[\alpha]_D^{35}$ +11.7 (*c*=0.52, $CHCl_3$)}.

(2*E*,4*E*/*Z*)-6-(*tert*-Butyldimethylsilyloxy)-4-methyl-1-[(*R*)-1,2,2-trimethylcyclopentyl]hexa-1,4-dien-1-ol (14) To a solution of the vinyl iodide **16**[16] (4.70 g, 13.9 mmol) in dry ether (40 ml) was added *t*BuLi (1.55 M in pentane; 9.8 ml, 15.3 mmol) at −78 °C. After being stirred for 20 min, a solution of the aldehyde **13** (950 mg, 6.8 mmol) in dry ether (10 ml) was added and stirring was continued for 40 min at −78 °C. After being quenched with saturated aq. NH_4Cl, the mixture was extracted with ether. The extracts were washed with brine, dried and evaporated to give the residue, which was purified by flash CC (ether–hexane, 1 : 9) to provide the adduct **14** (972 mg, 40%; 9*E*/*Z* *ca.* 7/3) as a pale yellow oil. ^{1}H-NMR (300 MHz) δ (corresponding to 9*E* isomer): 0.07 (6H, s, $SiCH_3$×2), 0.90 (9H, *t*Bu), 0.89, 1.03 and 1.07 (each 3H, s, *gem*-CH_3, 5-CH_3), 1.27—1.43 (2H, m) and 1.55—1.67 (4H, m) (2-H_2, 3-H_2, 4-H_2), 1.73 (3H, d, *J*=1 Hz, 9-CH_3), 4.23 (1H, m, 6-H), 4.31 (2H, d, *J*=6.5 Hz, 11-H_2), 5.56 (1H, br t, *J*=6.5 Hz, 10-H), 5.70 (1H, dd, *J*=16, 6.5 Hz, 7-H), 6.20 (1H, d, *J*=16 Hz, 8-H). IR ($CHCl_3$) cm^{-1}: 3605 and 3502 (OH). HR-ESI-MS *m*/*z*: 353.2878 $[M+H]^+$ (Calcd for $C_{21}H_{41}O_2Si$: 353.2870).

Preparation of Compound 6a from Compound 14 To a solution of compound **14** (814 mg, 2.3 mmol; 9*E*/*Z* *ca.* 7/3) in dry THF (8 ml) was added TBAF (1.0 M in THF; 2.5 ml, 2.5 mmol) at rt. After stirring for 45 min, solvent was evaporated off and the resulted residue was purified by flash CC (acetone–hexane, 3 : 7) to provide the corresponding diol (519 mg, 94%). To a solution of this diol in CH_2Cl_2 (25 ml) was added DMP (2.14 g, 5.0 mmol) at 0 °C and the mixture was stirred at rt for 45 min. The mixture was filtered through Celite and the filtrate was evaporated. The resulted residue was purified by flash CC (ether–hexane, 4 : 6) to provide the all-*E* cyclopenyl ketoaldehyde **6a** (248 mg, 46% from **14**) as a pale yellow solid and its 9*Z* isomer (111 mg, 21% from **14**) as a pale yellow oil.

All-*E* Isomer: ^{1}H-NMR and IR spectra were identical with those of **6a** prepared from compound **5a**. Enatiomeric excess (89%) was determined by HPLC [CHIRALPAK AY-H (Daicel) 0.46×25 cm; 2-PrOH–hexane, 3 : 7; 1.0 ml/min]. $[\alpha]_D^{22}$ −7.7 (*c*=0.75, EtOH). HR-ESI-MS *m*/*z*: 235.1689 $[M+H]^+$ (Calcd for $C_{15}H_{23}O_2$: 235.1692).

9*Z* Isomer: $[\alpha]_D^{22}$ −13.2 (*c*=0.45, EtOH). ^{1}H-NMR (300 MHz) δ: 0.87, 1.11 and 1.20 (each 3H, s, *gem*-CH_3, 5-CH_3), 1.48—1.77 (5H, m, 2-H_2, 3-H_2, 4-H), 2.13 (3H, d, *J*=1 Hz, 9-CH_3), 2.48 (1H, m, 4-H), 6.09 (1H, dd-like, *J*=8, 1 Hz, 10-H), 6.79 (1H, d, *J*=15.5 Hz, 7-H), 8.09 (1H, *J*=15.5 Hz, 8-H), 10.30 (1H, d, *J*=8 Hz, CHO). IR ($CHCl_3$) cm^{-1}: 1671 (conj. CO and conj. CHO), 1608 and 1580 (C=C). HR-ESI-MS *m*/*z*: 235.1687 $[M+H]^+$ (Calcd for $C_{15}H_{23}O_2$: 235.1692).

(2*E*,4*E*,6*E*,8*E*,10*E*,12*E*)-2,7,11-Trimethyl-[(*R*)-1,2,2-trimethylcyclopentyl]-14-oxotetradeca-2,4,6,8,10,12-hexaenal (17) An acidic solution (4.0 ml) prepared from toluene-*p*-sulfonic acid (500 mg) and H_3PO_4 (725 mg) in MeOH (38 ml) and methyl orthoformate (4.0 ml) was added to a solution of the phosphonium chloride **18**[17] (3.14 g, 7.0 mmol) in MeOH (40 ml). The reaction mixture was stirred at rt for 3 h and neutralized with NaOMe (1.0 M in MeOH) until just before the red color of an ylide appeared to give a solution of the Wittig salt **19**. To this solution was added a solution of the aldehyde **6a** (411 mg, 1.8 mmol) in MeOH (10 ml) and NaOMe (1.0 M in MeOH; 8 ml, 8 mmol) at rt. After stirring at rt for 1 h, Dowex 50W-X8 (H^+) (22 g) was added to the reaction mixture and this was stirred at rt for 20 min. After Dowex was filtered off, the filtrate was evaporated. The resulting residue was purified by flash CC (EtOAc–hexane–CH_2Cl_2, 0.3 : 5 : 5) and then PHPLC [LiChrosorb Si 60 (7 μm) 2×25 cm; EtOAc–hexane, 13 : 87] to provide all-*E* apocarotenal **17** (273 mg, 42%) and other isomeric mixture (114 mg, 18%). A solution of this isomeric mixture in ether (10 ml) was left in the dark at rt overnight and the resulting mixture was purified again by PHPLC to provide all-*E* apocarotenal **17** (46 mg, 7% from **6a**). ^{1}H-NMR (500 MHz) δ: 0.85, 1.11 and 1.18 (each 3H, s, *gem*-CH_3, 5-CH_3), 1.46—1.54 (2H, m) and 1.65—1.74 (3H, m) (2-H_2, 3-H_2, 4-H), 1.89 (3H, s, 13′-CH_3), 1.98 (3H, s, 9-CH_3), 2.05 (3H, s, 13-CH_3), 2.48—2.54 (1H, m, 4-H), 6.39 (1H, br d, *J*=12 Hz, 14-H), 6.53 (2H, d, *J*=15 Hz, 7-H, 12-H), 6.55 (1H, br d, *J*=11.5 Hz, 10-H), 6.74 (1H, dd, *J*=14, 11.5 Hz, 15-H), 6.76 (1H, dd, *J*=15, 11.5 Hz, 11-H), 6.96 (1H, br d, *J*=11 Hz, 14′-H), 7.02 (1H, dd, *J*=14, 11.5 Hz, 15-H), 7.32 (1H, d, *J*=15 Hz, 8-H). ^{13}C-NMR (125 MHz) δ: 9.67 (13′-CH_3), 12.96 and 13.06 (9-CH_3, 13-CH_3), 19.64 (C3), 20.85 (5-CH_3), 24.59 and 25.60 (*gem*-CH_3), 34.43 (C4), 40.48 (C2), 44.00 (C1), 58.93 (C5), 122.36 (C7), 126.58 (C11), 128.68 (C15′), 133.13 (C14), 135.52 (C9), 137.17 (C15), 137.67 (C13′), 139.44 (C10), 140.59 (C12), 140.91 (C13), 145.97 (C8), 148.42 (C14′), 194.47 (CHO), 203.80 (C6). UV λ_{max} (EtOH) nm: 248, 316, 420, 442. IR ($CHCl_3$) cm^{-1}: 1663 (conj. CO and conj. CHO), 1607 and 1572 (C=C). HR-EI-MS *m*/*z*: 366.2561 (M^+) (Calcd for $C_{25}H_{34}O_2$: 366.2557).

Ethyl (2*E*/*Z*,4*E*)-3-Methyl-5-(2,6,6-trimethylcyclohexa-1,3-dienyl)-penta-2,4-dienoate (22) A solution of the triethyl phosphonoacetate (14.16 g, 63.2 mmol) in dry THF (40 ml) was added dropwise to a stirred suspension of NaH (60% oil dispersion; 2.69 g, 67.4 mmol) in dry THF (15 ml) at 0 °C. After being stirred at 0 °C for 20 min, a solution of the 3,4-didehydro-β-ionone (**21**)[18] (4.00 g, 21.1 mmol) in dry THF (10 ml) was added to it. The reaction mixture was then warmed to 50 °C and stirring was

continued at the same temperature for 3 h. After being quenched by addition of saturated aq. NH_4Cl, the mixture was extracted with ether. The extracts were washed with brine, dried and evaporated to give a residue, which was purified by flash CC (ether–hexane, 7 : 93) to afford the ester **22** (4.46 g, 81%; 9*E*/*Z ca.* 85 : 15), a part of which was separated by PHPLC [LiChrosorb Si 60 (7 μm) 2×25 cm; ether–hexane, 1.5 : 98.5] to provide each pure isomer as a pale yellow oil.

All-*E* Isomer: ^{1}H-NMR (300 MHz) δ: 1.03 (6H, s, *gem*-CH_3), 1.29 (3H, t, J=7 Hz, $CO_2CH_2C\underline{H}_3$), 1.85 (3H, br s, 5-CH_3), 2.09 (2H, dd, J=4, 1.5 Hz, 2-H_2), 2.35 (3H, d, J=1 Hz, 9-CH_3), 4.18 (2H, q, J=7 Hz, $CO_2C\underline{H}_2H_3$), 5.77 (1H, br s, 10-H), 5.78 (1H, dt, J=9.5, 4 Hz, 3-H), 5.85 (1H, dt, J=9.5, 1.5 Hz, 4-H), 6.22 (1H, d, J=16 Hz, 8-H), 6.56 (1H, br d, J=16 Hz, 7-H). UV λ_{max} (EtOH) nm: 259, 344. IR ($CHCl_3$) cm^{-1}: 1700 (conj. COO), 1608 (C=C). HR-ESI-MS *m*/*z*: 261.1848 $[M+H]^+$ (Calcd for $C_{17}H_{25}O_2$: 261.1849).

9*Z* Isomer: ^{1}H-NMR (300 MHz) δ: 1.08 (6H, s, *gem*-CH_3), 1.28 (3H, t, J=7 Hz, $CO_2CH_2C\underline{H}_3$), 1.93 (3H, br s, 5-CH_3), 2.06 (3H, d, J=1 Hz, 9-CH_3), 2.09 (2H, dd, J=4, 1.5 Hz, 2-H_2), 4.16 (2H, q, J=7 Hz, $CO_2C\underline{H}_2H_3$), 5.66 (1H, br s, 10-H), 5.78 (1H, dt, J=9.5, 4 Hz, 3-H), 5.87 (1H, dt, J=9.5, 1.5 Hz, 4-H), 6.59 (1H, br d, J=16.5 Hz, 7-H), 6.78 (1H, d, J=16.5 Hz, 7-H). UV λ_{max} (EtOH) nm: 259, 352. IR ($CHCl_3$) cm^{-1}: 1695 (conj. COO), 1608 (C=C). HR-ESI-MS *m*/*z*: 261.1848 $[M+H]^+$ (Calcd for $C_{17}H_{25}O_2$: 261.1849).

(2*E*/*Z*,4*E*)-3-Methyl-5-(2,6,6-trimethylcyclohexa-1,3-dienyl)penta-2,4-dien-1-ol (23) A solution of the ester **22** (1.07 g, 4.1 mmol; 9*E*/*Z ca.* 85 : 15) in dry ether (10 ml) was added dropwise to a stirred suspension of $LiAlH_4$ (163 mg, 4.3 mmol) in dry ether at 0 °C. After being stirred at 0 °C for 15 min, the excess of $LiAlH_4$ was decomposed by dropwise addition of water and the mixture was extracted with ether. The extracts were dried and evaporated to give a residue, which was purified by flash CC (hexane–acetone, 8 : 2) to give the alcohol **23** (868 mg, 96%; 9*E*/*Z ca.* 4 : 1) as a pale yellow oil. ^{1}H-NMR (300 MHz) δ (corresponding to 9*E* isomer): 1.01 (each 6H, s, *gem*-CH_3), 1.29 (1H, br t, J=6 Hz, OH), 1.84 and 1.87 (each 3H, br s, 5-CH_3, 9-CH_3), 2.08 (2H, dd, J=4.5, 2 Hz, 2-H_2), 4.32 (2H, br t-like, J=6 Hz, $C\underline{H}_2OH$), 5.66 (1H, tq, J=7, 1 Hz, 10-H), 5.72 (1H, dt, J=10, 4.5 Hz, 3-H), 5.85 (1H, dt, J=10, 2 Hz, 4-H), 6.12 (1H, br d, J=16 Hz, 7-H), 6.19 (1H, d, J=16 Hz, 8-H). IR ($CHCl_3$) cm^{-1}: 3910 and 3449 (OH), 1626 (C=C). HR-EI-MS *m*/*z*: 218.1674 (M^+) (Calcd for $C_{15}H_{22}O$: 218.1669).

Preparation of the Wittig Salt (24) A solution of alcohol **23** (868 mg, 4.0 mmol) and triphenylphosphine hydrobromide (1.37 g, 4.0 mmol) in MeOH (35 ml) was stirred at rt for 48 h. Evaporation of the methanol gave a residue, which was washed with ether to provide the crude phosphonium salt **24**, which without purification, was used in next step.

3′-Deoxycapsanthin (1) To a solution of the phosphonium salt **20**[8,9] (1.14 g, 2.0 mmol) and the all-*E* apocarotenal **17** (83 mg, 0.23 mmol) in MeOH (15 ml) was added NaOMe (1.0 M in MeOH; 3.0 ml, 3.0 mmol) at rt. After being stirred at rt for 3.5 h, Dowex 50 W-X8 (H^+) (5 g) was added to the reaction mixture and this was stirred at rt for 5 min. After Dowex was filtered off, the filtrate was evaporated. The resulting residue was purified by flash CC (hexane–CH_2Cl_2–acetone, 6.5 : 3.25 : 0.5) and then PHPLC (COSMOSIL 5C18-MS-II 2×25 cm; MeOH–EtOH, 3 : 1) to provide 3′-deoxycapsanthin (**1**) (27 mg, 21%) as a red solid and isomeric mixture (25 mg). A solution of this isomeric mixture in acetone (10 ml) was left in the dark at rt for 4 d and the resulting mixture was purified again by PHPLC to provide **1** (8 mg, 6% from **17**). The spectral data of synthetic **1** were in good agreement with those of the reported[2] natural product. ^{1}H-NMR (500 MHz) δ: 0.85 and 1.11 (each 3H, s, 1′-*gem*-CH_3), 1.08 (6H, s, 1-*gem*-CH_3), 1.18 (3H, s, 5′-CH_3), 1.48 (1H, t, J=12 Hz, 2H_β), 1.50 (1H, m, 4′-H_β), 1.66—1.74 (3H, m, 2′-H_β, 3′-H_2), 1.74 (3H, s, 5-CH_3), 1.77 (1H, ddd, J=12, 3.5, 2 Hz, 2-H_α), 1.96 (9′-CH_3), 1.97 (6H, s, 9-CH_3, 13′-CH_3), 1.99 (3H, s, 13-CH_3), 2.05 (1H, br dd, J=16.5, 9.5 Hz, 4-H_β), 2.39 (1H, ddd, J=16.5, 5, 1 Hz, 4-H_α), 2.52 (1H, m, 4′-H_α), 4.00 (1H, m, 3-H), 6.11 (1H, br d, J=16 Hz, 7-H), 6.14 (1H, d, J=16 Hz, 8-H), 6.16 (1H, d, J=11.5 Hz, 10-H), 6.26 (1H, br d, J=11.5 Hz, 14-H), 6.35 (1H, br d, J=11.5 Hz, 14′-H), 6.36 (1H, J=15.5 Hz, 12-H), 6.48 (1H, d, J=15 Hz, 7′-H), 6.51 (1H, d, J=14.5 Hz, 12′-H), 6.55 (1H, br d, J=11.5 Hz, 10′-H), 6.61 (1H, dd, J=14.5, 11.5 Hz, 11′-H), 6.62 (1H, dd, J=14, 11.5, 15′-H), 6.67 (1H, dd, J=15.5, 11.5 Hz, 11-H), 6.70, (1H, dd, J=14, 11.5 Hz, 15-H), 7.32 (1H, d, J=15 Hz, 8′-H). ^{13}C-NMR (125 MHz) δ: 12.75, 12.79, 12.87 and 12.89 (9-CH_3, 13-CH_3, 9′-CH_3, 13′-CH_3), 19.63 (C3′), 20.87 (5′-CH_3), 21.63 (5-CH_3), 24.59 and 25.62 (1′-*gem*-CH_3), 28. and 30.27 (1-*gem*-CH_3), 34.43 (C4′), 37.14 (C1), 40.49 (C2′), 42.57 (C4), 43.98 (C1′), 48.44 (C2), 58.88 (C5′), 65.10 (C3), 121.41 (C7′), 124.18 (C11′), 125.47 (C11), 125.83 (C7), 126.25 (C5), 129.74 (C15′), 131.24 (C10), 131.53 (C15), 132.40 (C14), 133.80 (C9′), 135.08 (C14′), 135.96 and 136.09 (C9, C13′), 137.41 (C12), 137.52 and 137.75 (C6, C13), 138.46 (C8), 140.33 (C10′), 141.70 (C12′), 146.40 (C8′), 203.82 (C6′). CD (Et_2O) nm ($\Delta\varepsilon$): 208 (0), 223 (−4.6), 235 (0), 253 (+4.8), 266 (0), 285 (−7.0), 294 (−7.9), 322 (0), 352 (+1.7), 372 (0), 397 (−0.5). UV–vis λ_{max} (Et_2O) nm: 284, 442, 467, 489. UV–vis λ_{max} (EtOH) nm: 228, 288, 474. IR ($CHCl_3$) cm^{-1}: 3466 (OH), 1657 (conj. CO), 1572, 1551 and 1515 (C=C). HR-EI-MS *m*/*z*: 568.4294 (M^+) (Calcd for $C_{40}H_{56}O_2$: 568.4277).

3,4-Didehydroxy-3′-deoxycapsanthin (2) To a solution of the phosphonium salt **24** (2.60 g, 4.8 mmol) and the all-*E* apocarotenal **17** (182 mg, 0.49 mmol) in MeOH (20 ml) was added NaOMe (1 M in MeOH; 6.0 ml, 6.0 mmol) at rt. After being stirred at rt for 1.5 h, Dowex 50 W-X8 (H^+) (10 g) was added to the reaction mixture and this was stirred at rt for 5 min. After Dowex was filtered off, the filtrate was evaporated. The resulting residue was purified by flash CC (hexane–CH_2Cl_2–acetone, 6.5 : 3.25 : 0.25) and then PHPLC (LiChrosorb Si 60 (7 μm) 2×25 cm; hexane–Et_2O, 95 : 5) to provide 3,4-didehydroxy-3′-deoxycapsanthin (**2**) (77 mg, 28%) as a red solid. The spectral data of synthetic **2** were in good agreement with those of the reported[2] natural product. ^{1}H-NMR (500 MHz) δ: 0.85 and 1.10 (each 3H, s, 1′-*gem*-CH_3), 1.04 (6H, s, 1-*gem*-CH_3), 1.18 (3H, s, 5′-CH_3), 1.46—1.58 (2H, m, 2′-H, 4′-H), 1.88 (3H, s, 5-CH_3), 1.96 (3H, s, 9′-CH_3), 1.98 (3H, s, 13′-CH_3), 1.99 (6H, s, 9-CH_3, 13-CH_3), 2.08 (2H, dd, J=4.5, 1.5 Hz, 2-H_2), 2.52 (1H, m, 4′-H), 5.73 (1H, dd, J=9.5, 4.5 Hz, 3-H), 5.85 (1H, dt, J=9.5, 1.5 Hz, 4-H), 6.20 (1H, br d, J=11 Hz, 10-H), 6.20 (1H, br d, J=15.5 Hz, 7-H), 6.26 (1H, br d, J=11 Hz, 14-H), 6.30 (1H, d, J=15.5 Hz, 8-H), 6.35 (1H, br d, J=11 Hz, 14′-H), 6.37 (1H, d, J=15 Hz, 12-H), 6.48 (1H, d, J=15 Hz, 7′-H), 6.52 (1H, d, J=15 Hz, 12′-H), 6.55 (1H, br d, J=11 Hz, 10′-H), 6.61 (1H, dd, J=15, 11 Hz, 11′-H), 6.62 (1H, dd, J=14.5, 11.0 Hz, 15′-H), 6.69 (1H, dd, J=15, 11 Hz, 11-H), 6.70 (1H, dd, J=14.5, 11 Hz, 15-H), 7.32 (1H, d, J=15 Hz, 8′-H). ^{13}C-NMR (125 MHz) δ: 12.69, 12.75, 12.87 and 12.89 (9-CH_3, 13-CH_3, 9′-CH_3, 13′-CH_3), 19.64 (C3′), 20.36 (5-CH_3), 20.89 (5′-CH_3), 24.60 and 25.63 (1′-*gem*-CH_3), 26.81 (1-*gem*-CH_3), 34.00 (C1), 34.45 (C4′), 39.94 (C2), 40.51 (C2′), 43.98 (C1′), 58.89 (C5′), 121.41 (C7′), 124.16 (C11′), 124.95 (C3), 125.62 (C11), 125.76 (C7), 126.79 (C5), 129.72 (C15′), 130.00 (C4), 131.44 (C10), 131.58 (C15), 132.41 (C14), 133.79 (C9′), 135.12 (C14′), 135.94 (C13′), 136.35 (C9), 137.21 (C8), 137.38 (C12), 137.60 (C13), 138.68 (C6), 140.34 (C10′), 141.72 (C12′), 146.40 (C8′), 203.80 (C6′). CD (Et_2O) nm ($\Delta\varepsilon$): 247 (0), 270 (−0.7), 279 (0), 399 (+1.4), 312 (+1.7), 323 (0), 363 (−1.5), 400 (−0.3). UV–vis λ_{max} (Et_2O) nm: 313, 475. IR (KBr) cm^{-1}: 1664 (conj. CO), 1551 and 1561 (C=C). HR-EI-MS *m*/*z*: 550.4189 (M^+) (Calcd for $C_{40}H_{54}O$: 550.4172).

References and Notes

1) For Part 11, see Yamano Y., Ito M., Wada A., *Org. Biomol. Chem.*, **6**, 3421—3427 (2008).
2) Maoka T., Akimoto N., Fujiwara Y., Hashimoto K., *J. Nat. Prod.*, **67**, 115—117 (2004).
3) Maoka T., Mochida K., Kozuka M., Ito Y., Fujiwara Y., Hashimoto K., Enjo F., Ogata M., Nobukuni Y., Tokuda H., Nishino H., *Cancer Lett.*, **172**, 103—109 (2001).
4) Matsufuji H., Nakamura H., Chino M., Takeda M., *J. Agric. Food Chem.*, **46**, 3468—3472 (1998).
5) Maoka T., Goto Y., Isobe K., Fujiwara Y., Hashimoto K., Mochida K., *J. Oleo. Sci.*, **50**, 663—665 (2001).
6) Hornero-Méndez D., de Guevara R. G.-L., Mínguez-Mosquera M. I., *J. Agric. Food Chem.*, **48**, 3857—3864 (2000).
7) Deli J., Molnár P., Matus Z., Tóth G., *J. Agric. Food Chem.*, **49**, 1517—1524 (2001).
8) Yamano Y., Ito M., *Chem. Pharm. Bull.*, **49**, 1662—1663 (2001).
9) Yamano Y., Ito M., *Org. Biomol. Chem.*, **5**, 3207—3212 (2007).
10) The numbering system for carotenoids is used.
11) Vaz B., Domínguez M., Alvarez R., de Lera A. R., *Chem. Eur. J.*, **13**, 1273—1290 (2007).
12) Crombie B. S., Smith C., Varnavas C. Z., Wallace T. W., *J. Chem. Soc., Perkin Trans. 1*, **2001**, 206—215 (2001).
13) Abad A., Agulló C, Arnó M., Cuñat A. C., Zaragozá R. J., *Synlett*, **1993**, 895—896 (1993).
14) Hashimoto N., Aoyama T., Shioiri T., *Chem. Pharm. Bull.*, **29**, 1475—1478 (1981).
15) Nayek A., Drew M. G. B., Ghosh S., *Tetrahedron*, **59**, 5175—5181 (2003).
16) de Lera R. A., Torrado A., Iglesias B., López S., *Tetrahedron Lett.*, **33**, 6205—6208 (1992).
17) Bernhard K., Kienzle F., Mayer H., Müller R. K., *Helv. Chim. Acta*, **63**, 1473—1490 (1980).
18) Serra S., Fuganti C., Brenna E., *Helv. Chim. Acta*, **89**, 1110—1122 (2006).
19) Acemoglu M., Eugster C. H., *Helv. Chim. Acta*, **67**, 184—190 (1984).