Total synthesis of cucurbitaxanthin A, cycloviolaxanthin and capsanthin 3,6-epoxide by applying a regioselective ring opening of tetrasubstituted epoxides†‡

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The synthesis of 3,6-epoxy carotenoids cucurbitaxanthin A **1**, cycloviolaxanthin **2** and capsanthin 3,6-epoxide **3**, was accomplished *via* the C_{15}-3,6-epoxides **20e** and **20f**, prepared by the regioselective ring opening of the 3-hydroxy-5,6-epoxides **10e** and **10f**.

Introduction

Cucurbitaxanthin A **1**, cycloviolaxanthin **2** and capsanthin 3,6-epoxide **3** (Fig. 1), bearing 3,6-epoxy-end groups, were isolated[2] from red paprika *Capsicum annuum* together with the major pigments capsanthin **4** and capsorubin **5** possessing a κ-end group. Cucurbitaxanthin A **1** was also isolated[3] from the pumpkin *Curcurbita maxima* as a major pigment. These carotenoids are considered[2c,4] to be formed in nature from 5,6-epoxy carotenoids through ring opening of the epoxy moiety. Previously, we reported[1,5] the biomimetic type total synthesis of capsanthin **4** and capsorubin **5** *via* regioselective cleavage of the oxirane ring at the C-5[6] position (route *b*) and the subsequent stereoselective ring contraction of the C_{15}-3-silyloxy-5,6-epoxy dienal as shown in Scheme 1.

In a previous communication,[7] we investigated the ring opening of various 5,6-epoxides having a hydroxy group at C-3 and achieved the first total synthesis of cucurbitaxanthin A **1** applying a biomimetic type ring opening (Scheme 1, route *a*) of the C_{15}-3-hydroxy-5,6-epoxy dienoate and dienonitrile. Recently, we have also synthesized cycloviolaxanthin **2** and capsanthin 3,6-epoxide **3** using the common intermediate. Here, we describe a full account of these experiments.

Results and discussion

From previous results,[1,5] in the reaction of 5,6-epoxides **6a–d** (Scheme 2) with Lewis acid, we found that the direction of the oxirane ring cleavage depended upon both the length of the conjugated double bond system and the electron-withdrawing ability of the substituents adjacent to the double bond. The epoxides **6a** and **6b**, carrying strong electron-withdrawing groups (EWG), predominantly provided the cyclopentyl ketones **8a** and **8b**, respectively, *via* cleavage of the oxirane ring at the C-5 position (route *b*), whereas the 5,6-epoxides **6c** and **6d** provided the 5,8-epoxides **7c** and **7d**, respectively, *via* opening of the C-6–oxygen bond of the oxirane ring (route *a*). Therefore the carotenoids **4** and **5** were synthesized[1,5] by applying the ring opening of the C_{15}-epoxy dienal with a silyloxy group at C-3, as shown in Scheme 1.

An attempt[8] to synthesize cycloviolaxanthin **2** was carried out by Eugster and Gmünder's group according to the procedure[9] developed for the synthesis of the C_{13}-nor-carotenoid **9** (method A in Scheme 3). We considered that the biomimetic type ring opening of the 5,6-epoxide **10** possessing a hydroxy group at C-3 (method B) would be a straightforward method of constructing the 3,6-epoxy moieties of carotenoids **1–3**. Therefore, we investigated the ring opening of epoxides **10a–f** (Scheme 4), toward the synthesis of the 3,6-epoxy carotenoids **1–3**.

The epoxides **10a–f** were prepared as shown in Scheme 5. The epoxide **10c** was recently synthesized[10] *via* the asymmetric reduction of the acetylenic ketone **11**. The epoxy dienal **10b** and the epoxy dienoate **10e** were obtained by desilylation (**10b**:[11] 75%, **10e**: 98%) of the corresponding *tert*-butyldimethylsilyl (TBS) ethers **13** and **14**, which were previously prepared[1] from the known[12] optically active C_{10}-epoxy aldehyde **12**. Reduction of the ester **13** with $LiAlH_4$, followed by acetylation, yielded the acetate **15** (84%), which was desilylated (84%) to give compound **10d**. The epoxy enone **10a** was prepared by the condensation (90%) of epoxy aldehyde **12** with triphenylphosphanylidene-2-propanone, followed by desilylation (89%). Emmons–Horner reaction of the aldehyde **12** with the phosphonate **17**[13] provided the dienonitrile **18** (80%) and its 9*Z* isomer (15%). The former was deprotected (91%) to give the compound **10f**.

Treatment of the epoxy enone **10a** and the epoxy dienal **10b** with $SnCl_4$ (2 equiv.) or tris(4-bromophenyl)aminium hexachloroantimonate **19**[14] (0.1 equiv.) resulted in the formation of a complicated mixture including the cyclopentyl ketones **22a** and **22b** (Scheme 4, entries 1–3 in the Table 1). It is considered that the desired cleavage of the C-6–oxygen bond of the oxirane ring would be suppressed by destabilization of the cation at C-6 due to the electron-withdrawing carbonyl groups conjugated to their double bonds. On the contrary, epoxides **10c** and **10d**, whose side chains at C-6 have negligible electron-withdrawing natures, gave slight amounts of the desired 3,6-epoxides **20c** and **20d** (entries 5, 6), formed by ring opening at C-6 and subsequent ring closing by the C-3-hydroxy group. However, preferential migration of the 7,8-double bond to the 6,7-position provided the 5,8-epoxides **21c**

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‡ Electronic supplementary information (ESI) available: Synthesis and characterization data for compounds **15**, **16**, **18**, **10a–f**, **20c**, **20d**, **21c–d** and **22a–c**. See DOI: 10.1039/b807482h

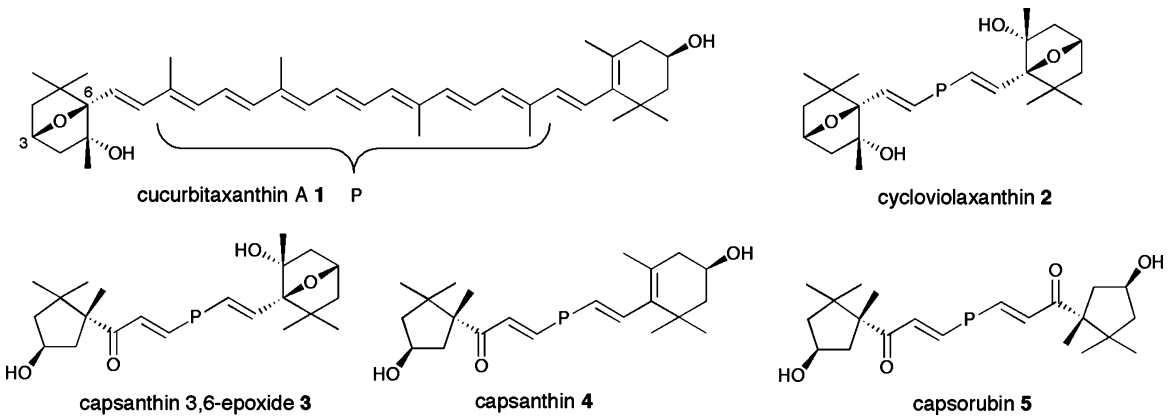
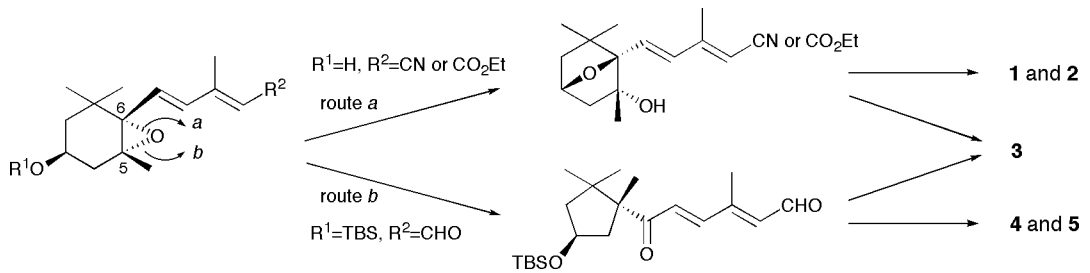
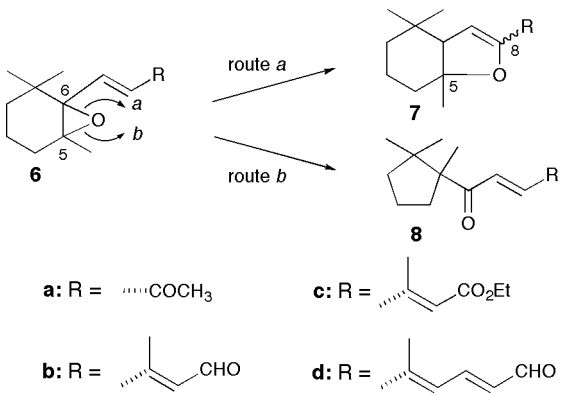


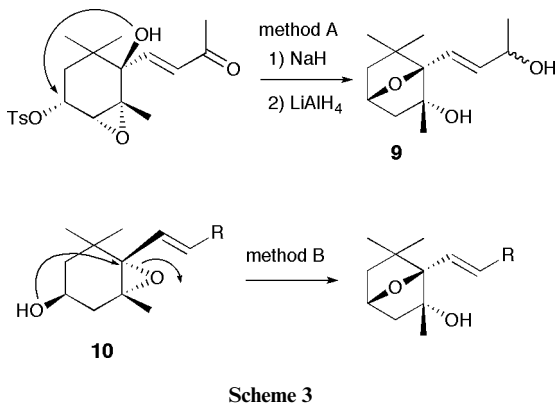
Fig. 1



Scheme 1



Scheme 2



Scheme 3

and **21d** as the major products. The epoxy dienoate **10e** having a weak EWG preferentially afforded the 3,6-epoxide **20e** together with the 5,8-epoxide **21e** by treatment with the aminium salt **19** (entry 8). The epoxy dienonitrile **10f**, in which the electron-withdrawing nature of the substituent at C-6 is comparable with that of the ester **10e**, was then treated with aminium salt **19** to give predominantly the 3,6-epoxide **20f** . To improve the yield of **20f**, 4 Å molecular sieves (MS) were added to eliminate moisture, which would accelerate the formation of polar byproducts in the reaction mixture. As a result, a satisfactory yield of **20f** (78%) was obtained (entry 10). These findings indicate that the formation of the 3,6-epoxides would require both ease of ring opening at C-6 and tolerance to migration of the 7,8-double bond.

^{1}H NMR data of the compound **20c** were identical with those reported.[16] The structures of the other 3,6-epoxides were confirmed by the comparison of their ^{1}H NMR data with those of compound **20c**. In these 3,6-epoxides, the protons at C-3 were observed as triplets ($J \sim 6$ Hz) coupled with only the exo-protons at C-2 and C-4, which were coupled with each other ($J \sim 2$ Hz) based on the W-shape arrangement as shown in Fig. 2. In addition, the observation of three-bond coupling between H-3 (δ 4.40 ppm) and C-6 (δ 91.46 ppm) in the heteronuclear multiple-bond correlation (HMBC) spectrum of compound **20e** supported its 3,6-bridged structure.

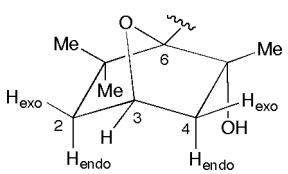
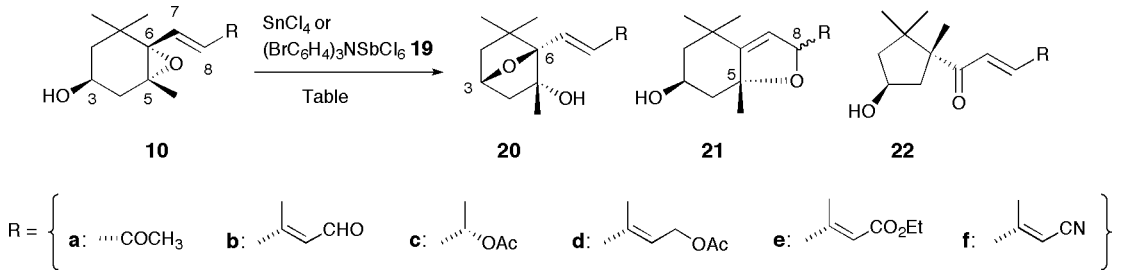
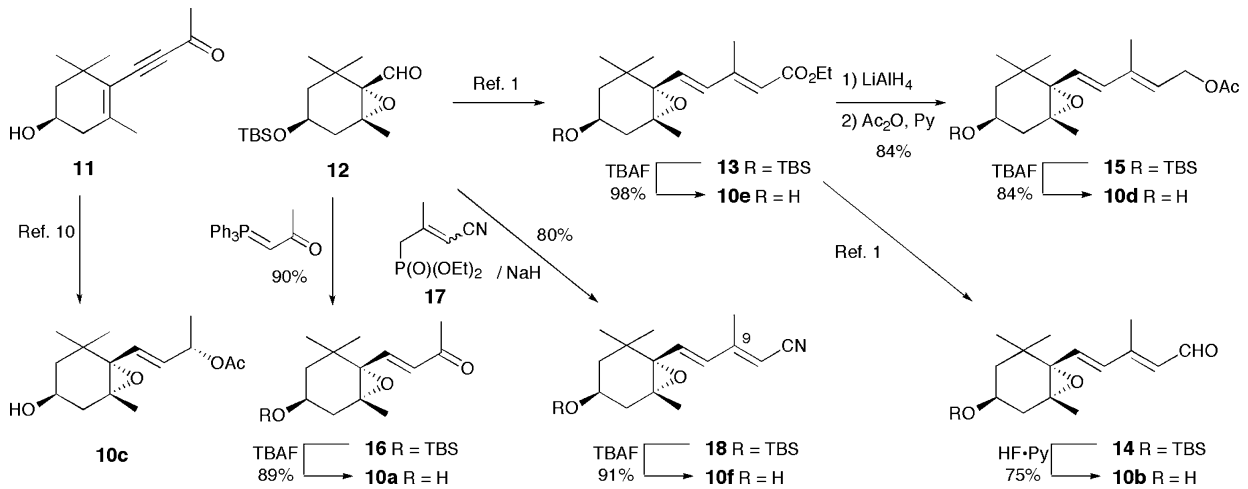


Fig. 2



Scheme 4



Scheme 5

Table 1 Ring opening of 3-hydroxy epoxides **10a–f**

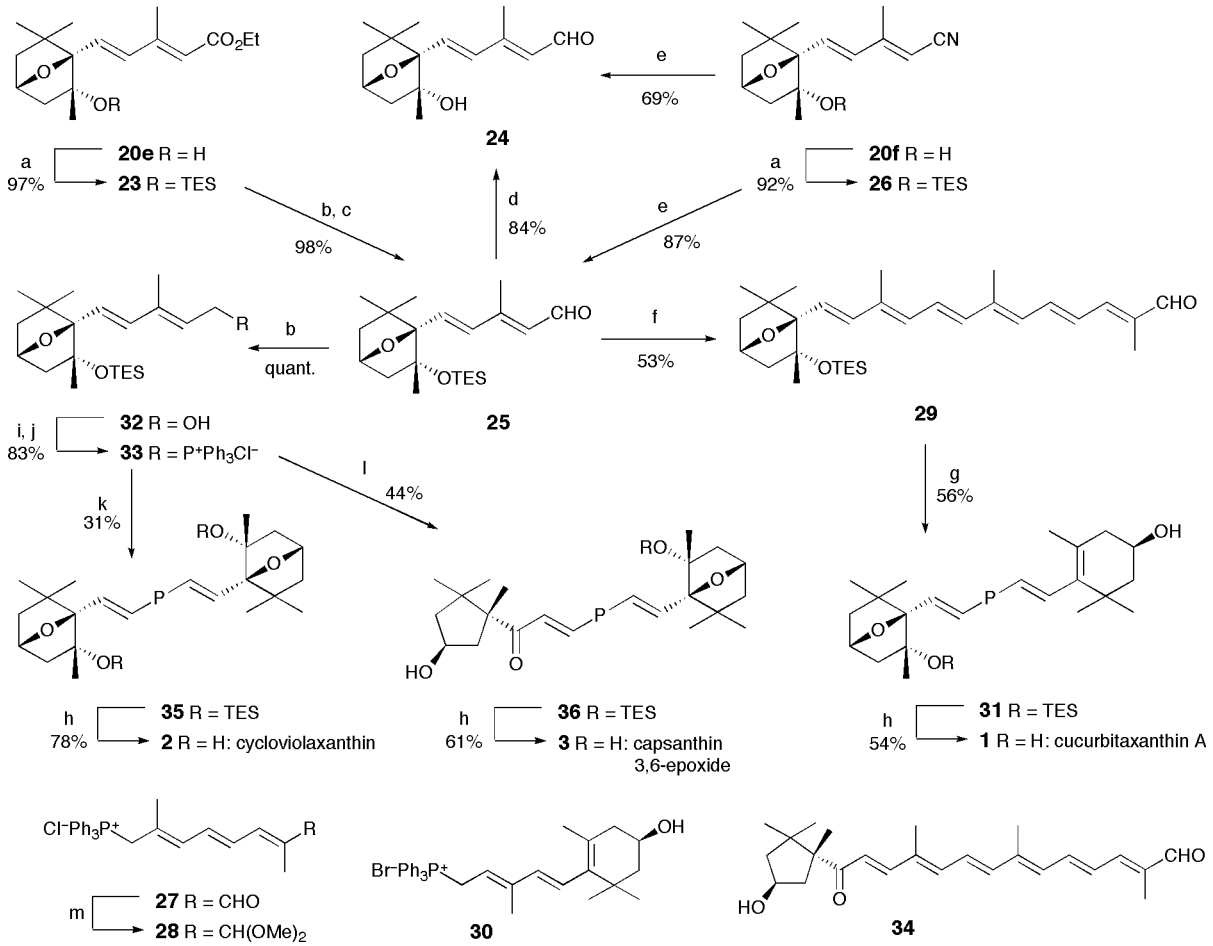
Entry	Substrate	Conditions	Isolated yield (%)		
			20	**21**[a]	**22**
1	**10a**	$SnCl_4$ (2 equiv.), rt, 1 h	—	—	25
2	**10a**	**19** (0.1 equiv.), rt, 3 h	—	—	6
3	**10b**	$SnCl_4$ (2 equiv.), rt, 1 h	—	—	20
4	**10c**	$SnCl_4$ (2 equiv.), 0 °C, 20 min	—	44	—
5	**10c**	**19** (0.1 equiv.), rt, 30 min	20	47	6
6	**10d**	**19** (0.1 equiv.), rt, 30 min	9	68	—
7	**10e**	$SnCl_4$ (2 equiv.), 0 °C, 15 min	16	32	—
8	**10e**	**19** (0.1 equiv.), rt, 20 min	45	35	—
9	**10f**	**19** (0.2 equiv.), rt, 2 h	54	—	—
10	**10f**	**19** (0.2 equiv.), 4 Å MS, rt, 2 h	78	—	—

[a] Mixture of 5,8-*trans*[15] and 5,8-*cis* isomers.

Then the 3,6-epoxy dienoate **20e** and dienonitrile **20f** respectively were transformed into the dienal **24** (Scheme 6). Reduction of the ester group in **20e** with $LiAlH_4$ and subsequent oxidation of the resulting alcohol with MnO_2 resulted in a complex mixture, probably due to oxidative cleavage of the C5–6 bond. Thus after protection (97%) of the C-5-hydroxy group in **20e** by a triethylsilyl (TES) group, the resulting silyl ether **23** was converted into the aldehyde **25** (98%), which was deprotected to give compound **24** (84%). In the case of the nitrile **20f**, the aldehyde **24** was obtained directly (69%) by reduction with diisobutylaluminium hydride (DIBAL-H).

Unfortunately, the Wittig condensation of the aldehyde **24** with the C_{10}-phosphonium salt **28**[17] was unsuccessful because of the instability of **24** under basic conditions. Thus, the TES-protected aldehyde **25**, which could be also derived in two steps (81%) from the nitrile **20f**, was condensed with the phosphonium salt **28** in the presence of NaOMe as a base, and then in the same pot treated with ion-exchange resin, Dowex 50W-X8 (H^+), leading to a mixture of the all-*E*-C_{25}-apocarotenal **29** (53%) accompanied by some isomers. Wittig condensation of compound **29** with the C_{15}-phosphonium salt **30**,[1,18] followed by purification of the condensed products by preparative HPLC provided the all-*E*-skeletal compound **31** (56%). Although desilylation of compound **31** with tetrabutylammonium fluoride (TBAF) or hydrogen fluoride pyridine (Py) complex was not successful, **31** could be deprotected by treatment with TBAF in the presence of an equimolar amount of acetic acid (AcOH) to furnish cucurbitaxanthin A **1** (54%) along with some recovery (32%) of **31**. The spectral data of synthetic **1** were in good agreement with those of the natural specimen.[2,3,19]

Next, aldehyde **25** was transformed into the C_{15}-Wittig salt **33** toward the synthesis of cycloviolaxanthin **2** and capsanthin 3,6-epoxide **3**. Reduction of **25** with $LiAlH_4$ provided the alcohol **32** (quant.), which was allowed to react with LiCl and methanesufonyl chloride (MsCl), followed by treatment of the resulting chloride with PPh_3 under reflux in CH_2Cl_2 to afford the phosphonium salt **33** in 83% yield from the aldehyde **25**. Finally, the Wittig salt **33** was condensed with the 3,6-epoxy apocarotenal **29** and the previously prepared[1,5] cyclopentylketo apocarotenal **34**, and then purification by preparative HPLC gave the all-*E* skeletal compounds **35** (31%) and **36** (44%) respectively, which were



Scheme 6 *Reagents and conditions*: a, TESOTf, lutidine; b, $LiAlH_4$; c, MnO_2; d, HF·Py; e, DIBAL-H; f, **28**, NaOMe then DOWEX (H^+); g, **30**, NaOMe; h, TBAF, AcOH; i, LiCl, γ-collidine, MsCl; j, PPh_3, CH_2Cl_2, reflux; k, **29**, NaOMe; l, **34**, NaOMe; m, $CH(OMe)_2$, H^+, MeOH.

desilylated to afford cycloviolaxanthin **2** (78%) and capsanthin 3,6-epoxide **3** (61%), respectively. The spectral data of the synthesized **2** and **3** were in good accordance with those reported.[2]

Conclusions

Consideration of the end-group formation in the biosynthesis of carotenoids has led us to apply the ring opening of 5,6-epoxides **10a–f** possessing a hydroxy group at C-3 to their synthesis. As a result, we found that the dienoate **10e** and the dienonitrile **10f**, having weak EWG, predominantly provided the 3,6-epoxides **20e** and **20f**, formed by ring opening at C-6 and subsequent ring closing by the C-3-hydroxy group. After protection of their hydroxy groups with TES groups, 3,6-epoxides **20e** and **20f** respectively were converted into the aldehyde **25** and the Wittig salt **33**. By the use of these synthons, the total synthesis of optically active cucurbitaxanthin A **1**, cycloviolaxanthin **2** and capsanthin 3,6-epoxide **3** was accomplished.

Experimental

UV spectra were recorded on a JASCO Ubest-55 instrument. IR spectra were measured on a Perkin Elmer FT-IR spectrometer, model Paragon 1000, with chloroform solutions. ^{1}H NMR and ^{13}C NMR spectra were determined on a Varian Gemini-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 spectrometer. Optical rotations were measured on a JASCO DIP-181 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. Column chromatography (CC) was performed on silica gel (Merck Art. 7734). Short CC was conducted on silica gel (Merck Art. 7739) under reduced pressure. Preparative HPLC was carried out on a Shimadzu LC-6A with a UV–vis detector. Standard work-up means that the organic layers were finally washed with brine, dried over anhydrous Na_2SO_4, filtered and evaporated. 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.

Treatment of the dienoate 10e with aminium salt 19

To a solution of the dienoate **10e** (550 mg, 1.87 mmol) in dry CH_2Cl_2 (20 ml) was added tris(4-bromophenyl)aminium hexachloroantimonate **19** (153 mg, 0.19 mmol) and the mixture

was stirred at rt for 30 min. The mixture was then concentrated to give a residue, which was purified by short CC (acetone–hexane, 1 : 9) to give the 3,6-epoxide **20e** (247 mg, 45%) and the 5,8-epoxide **21e** (193 mg, 35%).

Compound 20e. Pale yellow oil. $[\alpha]_D^{25}$ −24.6 (*c* 1.06, MeOH); λ_{max}(EtOH)/nm 268; ν_{max}/cm^{-1} 3609, 3489, 1702, 1683, 1620; δ_H(500 MHz) 0.87, 1.19 and 1.44 (each 3H, s), 1.28 (3H, t, *J* 7), 1.62 (1H, d, *J* 11.5), 1.68 (1H, d, *J* 12.5), 1.84 (1H, ddd, *J* 11.5, 6 and 2), 2.05 (1H, ddd, *J* 12.5, 6 and 2), 2.30 (3H, d, *J* 1), 4.17 (2H, q, *J* 7), 4.40 (1H, t, *J* 6), 5.80 (1H, br s), 6.15 (1H, d *J* 15.5), 6.36 (1H, dd, *J* 15.5, and 0.5); δ_C(125 MHz) 13.79, 14.35, 25.68, 31.43, 31.99, 44.05, 47.76, 48.44, 59.75, 75.52, 82.28, 91.46, 119.14, 130.26, 133.76, 151.39, 167.27; *m*/*z* (EI) 294.1831 (M$^+$, $C_{17}H_{26}O_4$ requires 294.1830).

Compound 21e (5,8-*trans* isomer). Colorless solid. $[\alpha]_D^{24}$ 124.0 (*c* 1.03, MeOH); λ_{max}(EtOH)/nm 216; ν_{max}/cm^{-1} 3608, 3487, 1708, 1656; δ_H(300 MHz) 1.16 and 1.33 (each 3H, s), 1.27 (3H, t, *J* 7), 1.49 (1H, dd, *J* 14 and 3.5), 1.63 (3H, s), 1.76 (1H, br dd, *J* 14 and 4), 1.96 (1H, dd, *J* 14 and 4.5), 2.08 (3H, s), 2.16 (1H, br dd, *J* 14 and 4), 4.16 (2H, q, *J* 7), 4.24 (1H, quint-like, *J* 4), 5.13 (1H, br s), 5.30 (1H, br s), 5.95 (1H, br s); *m*/*z* (EI) 294.1835 (M$^+$, $C_{17}H_{26}O_4$ requires 294.1830).

(2*E*,4*E*)-5-[(1*R*,2*R*,4*S*)-2-Hydroxy-2,6,6-trimethyl-7-oxabicyclo[2.2.1]hept-1-yl]-3-methylpenta-2,4-dienenitrile 20f

To a solution of the dienonitrile **10f** (937 mg, 3.79 mmol) in dry CH_2Cl_2 (35 ml) were added 4 Å MS (2 g). After being stirred at rt for 15 min, the aminium salt **19** (620 mg, 0.76 mmol) was added and the mixture was stirred at rt for 2 h. The mixture was filtered through Celite. Evaporation of the filtrate gave a residue, which was purified by short CC (acetone–hexane, 15 : 85 to 25 : 75) to give the 3,6-epoxide **20f** (735 mg, 78%) as a pale yellow oil; $[\alpha]_D^{25}$ −26.0 (*c* 1.00, MeOH); λ_{max}(EtOH)/nm 264; ν_{max}/cm^{-1} 3605, 3484, 2214, 1640, 1591; δ_H(300 MHz) 0.86, 1.19 and 1.44 (each 3H, s), 1.63 and 1.68 (each 1H, d, *J* 12), 1.84 and 2.06 (each 1H, ddd, *J* 12, 6 and 2), 2.18 (3H, d, *J* 1), 4.41 (1H, t, *J* 6), 5.23 (1H, br s), 6.15 (1H, d, *J* 16), 6.40 (1H, dd, *J* 15.5 and 0.5); *m*/*z* (EI) 247.1569 (M$^+$, $C_{15}H_{21}NO_2$ requires 247.1571).

Ethyl (2*E*,4*E*)-3-methyl-5-[(1*R*,4*S*,6*R*)-2,2,6-trimethyl-6-triethylsilyloxy-7-oxabicyclo[2.2.1]hept-1-yl]penta-2,4-dienenoate 23

To a solution of the alcohol **20e** (580 mg, 1.97 mmol) and lutidine (0.46 ml, 3.98 mmol) in dry CH_2Cl_2 (6 ml) was added triethylsilyl triflate (TESOTf) (0.67 ml, 2.96 mmol) at 0 °C and the mixture was stirred at 0 °C for 20 min. The reaction mixture was diluted with ether and followed by standard work-up to give a residue, which was purified by short CC (ether–hexane, 5 : 95) to yield the silyl ether **23** (790 mg, 97%) as a pale yellow oil; $[\alpha]_D^{21}$ −65.2 (*c* 0.97, MeOH); λ_{max}(EtOH)/nm 268; ν_{max}/cm^{-1} 1703, 1639, 1614; δ_H(300 MHz) 0.61 (6H, q, *J* 8), 0.84 (3H, s), 0.96 (9H, t, *J* 8), 1.17 (3H, s), 1.28 (3H, t, *J* 7), 1.37 (3H, s), 1.56 (1H, d, *J* 11.5), 1.62 (1H, d, *J* 12), 1.81 (1H, ddd, *J* 11.5, 6 and 2), 1.99 (1H, ddd, *J* 12, 6 and 2), 2.30 (3H, d, *J* 1), 4.17 (2H, q, *J* 7), 4.38 (1H, t, *J* 6), 5.77 (1H, br s), 6.15 (1H, d *J* 16), 6.33 (1H, dd, *J* 16 and 1); *m*/*z* (EI) 408.2713 (M$^+$, $C_{23}H_{40}O_4Si$ requires 408.2694).

(2*E*,4*E*)-3-Methyl-5-[(1*R*,4*S*,6*R*)-2,2,6-trimethyl-6-triethylsilyloxy-7-oxabicyclo[2.2.1]hept-1-yl]penta-2,4-dienal 25

A solution of the ester **23** (790 mg, 1.94 mmol) in dry ether (10 ml) was added dropwise to a stirred suspension of $LiAlH_4$ (96 mg, 2.53 mmol) in dry ether (20 ml) at 0 °C. After being stirred at 0 °C for 15 min, the excess $LiAlH_4$ was decomposed by the dropwise addition of water. The mixture was extracted with ether and followed by standard work-up to provide the crude alcohol, which was dissolved in ether–hexane (1 : 1) and shaken with active MnO_2 (10 g) at rt for 2 h. The mixture was filtered through Celite. Evaporation of the filtrate gave a residue, which was purified by short CC (acetone–hexane, 1 : 9) to give the aldehyde **25** (690 mg, 98%) as a pale yellow oil; $[\alpha]_D^{20}$ −77.8 (*c* 0.99, MeOH); λ_{max}(EtOH)/nm 286; ν_{max}/cm^{-1} 1662, 1634, 1598; δ_H(300 MHz) 0.62 (6H, q, *J* 8), 0.86 (3H, s), 0.97 (9H, t, *J* 8), 1.19 and 1.39 (each 3H, s), 1.57 (1H, d, *J* 11.5), 1.63 (1H, d, *J* 12), 1.82 (1H, ddd, *J* 11.5, 6 and 2), 2.00 (1H, ddd, *J* 12, 6 and 2), 2.28 (3H, d, *J* 1), 4.40 (1H, t, *J* 6), 5.97 (1H, br d, *J* 8), 6.32 (1H, d, *J* 16), 6.45 (1H, dd, *J* 16 and 0.5), 10.13 (1H, d, *J* 8); *m*/*z* (EI) 364.2444 (M$^+$, $C_{21}H_{36}O_3Si$ requires 364.2432).

(2*E*,4*E*)-3-Methyl-5-[(1*R*,4*S*,6*R*)-2,2,6-trimethyl-6-triethylsilyloxy-7-oxabicyclo[2.2.1]hept-1-yl]penta-2,4-dienenitrile 26

In the same manner as described for the preparation of the compound **23**, the alcohol **20f** (143 mg) was silylated to give a crude product, which was purified by short CC (acetone–hexane, 7 : 93) to provide compound **26** (193 mg, 92%) as a pale yellow oil; $[\alpha]_D^{27}$ −57.0 (*c* 0.91, MeOH); λ_{max}(EtOH)/nm 263; ν_{max}/cm^{-1} 2214, 1643, 1591; δ_H(300 MHz) 0.61 (6H, q, *J* 8), 0.83 (3H, s), 0.96 (9H, t, *J* 8), 1.16 and 1.37 (each 3H, s), 1.57 and 1.62 (each 1H, d, *J* 12), 1.81 and 1.99 (each 1H, ddd, *J* 12, 6 and 2), 2.17 (3H, d, *J* 1), 4.38 (1H, t, *J* 6), 5.20 (1H, br s), 6.15 and 6.37 (each 1H, d, *J* 16); *m*/*z* (EI) 361.2432 (M$^+$, $C_{21}H_{35}NO_2Si$ requires 361.2435).

Reduction of the nitrile 26

To a solution of the nitrile **26** (202 mg, 0.56 mmol) in dry ether (10 ml) was added DIBAL-H (1.0 M in hexane; 1.7 ml, 1.7 mmol) at −78 °C and the mixture was stirred at −78 °C for 1 h. Excess DIBAL-H was destroyed by the addition of moist silica gel (SiO_2–H_2O, 5 : 1) and the mixture was filtered through Celite. The filtrate was dried and evaporated to give a residue, which was purified by short CC (ether–hexane, 15 : 85) to give the aldehyde **25** (177 mg, 86%). The spectral data were identical with those of the aldehyde prepared from the ester **23**.

(2*E*,4*E*)-5-[(1*R*,2*R*,4*S*)-2-Hydroxy-2,6,6-trimethyl-7-oxabicyclo[2.2.1]hept-1-yl]-3-methylpenta-2,4-dienal 24

From the silyl ether 25. HF·Py (2 ml) was added to a solution of the silyl ether **25** (170 mg, 0.47 mmol) in THF (5 ml) at 0 °C. After being stirred at 0 °C for 30 min, the reaction mixture was diluted with ether. The organic layer was washed successively with brine, saturated aq. $NaHCO_3$ and then brine. Evaporation of the dried solution gave a residue, which was purified by short CC (acetone–hexane, 1 : 4) to afford compound **24** (98 mg, 84%) as a yellow oil; $[\alpha]_D^{25}$ −26.8 (*c* 1.12, MeOH); λ_{max}(EtOH)/nm 285; ν_{max}/cm^{-1} 3607, 3464, 1662, 1636, 1597; δ_H(300 MHz) 0.88, 1.21 and 1.46 (each

3H, s), 1.64 (1H, d, *J* 11.5), 1.70 (1H, d, *J* 12.5), 1.85 (1H, ddd, *J* 11.5, 6 and 2), 2.07 (1H, ddd, *J* 12.5, 6 and 2), 2.30 (3H, d, *J* 1), 4.42 (1H, t, *J* 6), 5.98 (1H, br d, *J* 8), 6.35 (1H, d, *J* 16), 6.47 (1H, dd, *J* 16 and 0.5), 10.12 (1H, d, *J* 8); *m*/*z* (EI) 250.1586 (M^+, $C_{15}H_{22}O_3$ requires 250.1567).

From the nitrile 20f. Following the procedure described for the reduction of the nitrile **26**, reduction of the nitrile **20f** (306 mg) with DIBAL-H provided the aldehyde **24** (215 mg, 69%).

(2*E*,4*E*,6*E*,8*E*,10*E*,12*E*)-2,7,11-Trimethyl-13-[(1*R*,4*S*,6*R*)-2,2,6-trimethyl-6-triethylsilyloxy-7-oxabicyclo[2.2.1]hept-1-yl]trideca-2,4,6,8,10,12-hexaenal 29

An acidic solution (0.4 ml) prepared from toluene-*p*-sulfonic acid (*p*-TsOH) (500 mg) and H_3PO_4 (725 mg) in MeOH (38 ml) and methyl orthoformate (0.8 ml) were added to a solution of the C_{10}-phosphonium chloride **27**[17] (690 mg, 1.54 mmol) in MeOH (5 ml). The reaction mixture was stirred at rt for 1.5 h then neutralized with NaOMe (1M in MeOH) until just before the red color of an ylide appeared, to give a solution of the Wittig salt **28**. To this solution were added a solution of the aldehyde **25** (90 mg, 0.25 mmol) in MeOH (3 ml) and NaOMe (1M in MeOH; 1.6 ml, 1.6 mmol) at rt. After being stirred at rt for 30 min, Dowex 50W-X8 (H^+) (1.5 g) was added to the reaction mixture and this was stirred at rt for 20 min. After the Dowex was filtered off, the filtrate was evaporated. The resulting residue was purified by short CC (acetone–hexane, 1 : 9) and then preparative HPLC [LiChrosorb Si 60 (7 μm) 1 × 30 cm; ether–hexane, 15 : 85] to provide all-*E*-apocarotenal **29** (65 mg, 53%) as an orange amorphous solid; λ_{max}(EtOH)/nm 419; ν_{max}/cm^{-1} 1660, 1610, 1600, 1549; δ_H(300 MHz) 0.59 (6H, q, *J* 8), 0.85 (3H, s), 0.96 (9H, t, *J* 8), 1.19 and 1.37 (each 3H, s), 1.55 (1H, d, *J* 11.5), 1.61 (1H, d, *J* 12), 1.81 (1H, ddd, *J* 11.5, 6 and 2), 1.88, 1.96 and 2.03 (each 3H, s), 2.00 (1H, ddd, *J* 12, 6 and 2), 4.37 (1H, t, *J* 6), 5.82 (1H, d, *J* 16), 6.18 (1H, br d, *J* 11.5), 6.30 (1H, br d, *J* 12), 6.36 (1H, d, *J* 16), 6.36 (1H, *J* 15), 6.68 (1H, dd, *J* 14.5 and 12), 6.78 (1H, dd, *J* 15 and 11.5), 6.96 (1H, br d, *J* 12), 7.02 (1H, dd, *J* 14.5 and 12), 9.45 (1H, s); *m*/*z* (EI) 496.3371 (M^+, $C_{31}H_{48}O_3Si$ requires 496.3371).

(3*R*,3′*S*,5′*R*,6′*R*)-3′,6′-Epoxy-5′,6′-dihydro-5′-triethylsilyloxy-β,β-caroten-3-ol 31

To a solution of the phosphonium salt **30**[1,18] (240 mg, 0.43 mmol) and the all-*E*-apocarotenal **29** (31 mg, 0.063 mmol) in CH_2Cl_2 (2 ml) was added NaOMe (1M in MeOH; 1.0 ml, 1.0 mmol) at rt. After being stirred at rt for 45 min, Dowex 50W-X8 (H^+) (1 g) was added to the reaction mixture and this was stirred at rt for 5 min. After the Dowex was filtered off, the filtrate was evaporated. The resulting residue was purified by short CC (acetone–hexane, 1 : 4) and then preparative HPLC [LiChrosorb Si 60 (7 μm) 1 × 30 cm; acetone–hexane, 12 : 88] to provide the all-*E*-skeletal compound **31** (24.5 mg, 56%) as a red solid, along with some isomeric mixtures; λ_{max}(EtOH)/nm 268, 424sh, 446, 474; δ_H(300 MHz) 0.61 (6H, q, *J* 8), 0.86 (3H, s), 0.97 (9H, t, *J* 8), 1.07 (6H, s), 1.19 and 1.36 (each 3H, s), 1.48 (1H, t, *J* 12), 1.55 (1H, d, *J* 11), 1.61 (1H, d, *J* 11.5), 1.74 (3H, s), 1.76 (1H, m), 1.80 (1H, ddd, *J* 11, 6 and 2), 1.94 (3H, s), 1.97 (9H, s), 1.96–2.10 (2H, m), 2.39 (1H, br dd, *J* 17 and 6), 4.00 (1H, m), 4.37 (1H, t, *J* 6), 5.75 (1H, d, *J* 16), 6.12 (2H, s), 6.15 and 6.17 (each 1H, br d, *J* 11.5), 6.25 (2H, m), 6.34 (2H, d, *J* 16), 6.36 (1H, d, *J* 15), 6.58–6.69 (4H, m); *m*/*z* (EI) 698.5100 (M^+, $C_{46}H_{70}O_3Si$ requires 698.5091).

Preparation of cucurbitaxanthin A 1

To a solution of the compound **31** (66 mg, 0.095 mmol) in THF (2 ml) were added AcOH (1.0 M in THF; 1.0 ml, 1.0 mmol) and TBAF (1.0 M in THF; 1.0 ml, 1.0 mmol) and the mixture was stirred at 50 °C for 20 h. The mixture was concentrated to give a residue, which was purified by short CC (acetone–hexane, 1 : 4) to yield cucurbitaxanthin A **1** (30 mg, 54%) as a red solid, along with recovered **31** (21 mg, 32%). The spectral data of synthetic **1** were in good agreement with those of a natural specimen.[2,3,19]

(2*E*,4*E*)-3-Methyl-5-[(1*R*,4*S*,6*R*)-2,2,6-trimethyl-6-triethylsilyloxy-7-oxabicyclo[2.2.1]hept-1-yl]penta-2,4-dienol 32

A solution of the aldehyde **25** (308 mg, 0.85 mmol) in dry ether (8 ml) was added dropwise to a stirred suspension of $LiAlH_4$ (32 mg, 0.84 mmol) in dry ether (10 ml) at 0 °C and the mixture was stirred for a further 5 min. The excess $LiAlH_4$ was decomposed by the dropwise addition of water and the mixture was filtered through Celite. The filtrate was evaporated to give a residue, which was purified by short CC (acetone–hexane, 3 : 7) to provide the alcohol **32** (310 mg, quant.) as a white solid; $[\alpha]_D^{26}$ −52.0 (*c* 0.96, MeOH); ν_{max}/cm^{-1} 3609, 3441, 1628; δ_H(300 MHz) 0.61 (6H, q, *J* 8), 0.85 (3H, s), 0.96 (9H, t, *J* 8), 1.19 and 1.36 (each 3H, s), 1.55 and 1.61 (each 1H, d, *J* 11.5), 1.80 and 1.98 (each 1H, ddd, *J* 11.5, 6 and 2), 1.82 (3H, br s), 4.29 (2H, br d, *J* 6), 4.36 (1H, t, *J* 6), 5.66 (1H, br t, *J* 6), 6.74 and 6.28 (each 1H, d, *J* 16); *m*/*z* (EI) 366.2586 (M^+, $C_{21}H_{38}O_3Si$ requires 366.2588).

Preparation of the Wittig salt 33

A solution of LiCl (58 mg, 1.36 mmol) in dry DMF (2 ml) was added to a stirred solution of the alcohol **32** (383 mg, 1.05 mmol) and γ-collidine (0.21 ml, 1.59 mmol) in DMF (1 ml) at 0 °C and the mixture was stirred at 0 °C for 10 min. To this mixture was added MsCl (0.11 ml, 1.42 mmol) and the mixture was stirred at 0 °C for a further 30 min. The mixture was poured into ice–water and extracted with ether. The extracts were washed successively with 3% aq. HCl, saturated aq. $NaHCO_3$ and brine. Evaporation of the dried solution provided a residue, which was expeditiously purified by short CC (acetone–hexane, 1 : 4) to afford the corresponding chloride (380 mg, 94%). Subsequently, triphenylphosphine (310 mg, 1.18 mmol) was added to a solution of this chloride in CH_2Cl_2 (10 ml) and the mixture was refluxed for 17 h. Evaporation of the solvent gave a residue, which was washed with ether to provide the phosphonium chloride **33** (564 mg, 88%) as a pale yellow foam; δ_H(300 MHz) 0.57 (6H, q, *J* 8), 0.79 (3H, s), 0.92 (9H, t, *J* 8), 1.12 and 1.32 (each 3H, s), 1.40 (3H, d, *J* 3.5), 1.54 and 1.59 (each 1H, d, *J* 12), 1.77 and 1.95 (each 1H, ddd, *J* 12, 6 and 2), 4.33 (1H, t, *J* 6), 4.92 (2H, m), 5.34 (1H, m), 5.63 (1H, dd, *J* 16 and 2). 6.14 (1H, d, *J* 16), 7.62–7.92 (15H, m).

(3*S*,3′*S*,5*R*,5′*R*,6*R*,6′*R*)-3,6,3′,6′-Diepoxy-5,5′,6,6′-tetrahydro-5,5′-di(triethylsilyloxy)-β,β-carotene 35

In the same manner as described for the preparation of compound **31**, Wittig reaction between the phosphonium salt **33** (564 mg, 0.87 mmol) and the apocarotenal **29** (108 mg, 0.22 mmol)

produced crude products, which were purified by short CC (ether–hexane, 1 : 4) and then preparative HPLC [LiChrosorb Si 60 (7 μm) 2 × 25 cm; ether–hexane, 8 : 92] to provide the all-*E*-skeletal compound **35** (56 mg, 31%) and its 11*Z* isomer (30 mg, 17%) as red solids, respectively.

Compound 35. λ_{max}(EtOH)/nm 266, 315, 329, 393sh, 416, 441, 470; δ_H(500 MHz) 0.61 (12H, q, *J* 8), 0.86 (6H, s), 0.97 (18H, t, *J* 8), 1.19 and 1.36 (each 6H, s), 1.55 and 1.61 (each 2H, d, *J* 11.5), 1.81 (2H, ddd, *J* 11.5, 6 and 2.5), 1.94 and 1.96 (each 6H, s), 1.98 (2H, ddd, *J* 11.5, 6 and 2.5), 4.37 (2H, t, *J* 6), 5.75 (2H, d, *J* 16), 6.17 (2H, br d, *J* 11.5), 6.25 (2H, m), 6.35 (2H, d, *J* 16), 6.35 (2H, dd, *J* 14.5 and 12), 6.62 (4H, m); *m*/*z* (EI) 828.5922 (M^+, $C_{52}H_{84}O_4Si_2$ requires 828.5904).

11*Z* Isomer of 35. λ_{max}(EtOH)/nm 231, 267, 316, 330, 394sh, 417, 440, 470; δ_H(500 MHz) 0.61 (12H, q, *J* 8), 0.86 and 0.87 (each 3H, s), 0.97 (18H, t, *J* 8), 1.19 and 1.21 (each 3H, s), 1.34 (6H, s), 1.55 and 1.57 (each 1H, d, *J* 11.5), 1.61 and 1.62 (each 1H, d, *J* 11.5), 1.81 (2H, m), 1.91, 1.94 and 1.96 (each 3H, s), 1.98 (2H, m), 2.08 (3H, s), 4.37 and 4.38 (each 1H, t, *J* 6), 5.75 and 5.79 (each 1H, d, *J* 16), 5.97 (1H, d, *J* 12), 6.17 (1H, br d, *J* 11.5), 6.25 (1H, br d, *J* 10), 6.29 (1H, d-like, *J* 10), 6.30 (1H, t, *J* 12), 6.35 (1H, d, *J* 16), 6.35 (1H, d, *J* 14.5), 6.37 (1H, d, *J* 16), 6.62 (3H, m), 6.72 (1H, br d, *J* 12); *m*/*z* (EI) 828.5922 (M^+, $C_{52}H_{84}O_4Si_2$ requires 828.5904).

Preparation of cycloviolaxanthin 2

In the same manner as described for the preparation of cucurbitaxanthin A **1**, desilylation of compound **35** (24.5 mg) gave crude products, which were purified by preparative HPLC [LiChrosorb Si 60 (7 μm) 1 × 30 cm; acetone–hexane, 17 : 83] to provide cycloviolaxanthin **2** (13.9 mg, 78%) as a red solid. The spectral data of synthetic **2** were in good agreement with those reported.[2]

(3*S*,3′*S*,5*R*,5′*R*,6*R*)-3,6-Epoxy-5,6-dihydro-3′-hydroxy-5-triethylsilyloxy-β,κ-caroten-6′-one 36

In the same manner as described for the preparation of compound **31**, Wittig reaction between the phosphonium salt **33** (600 mg, 0.93 mmol) and the apocarotenal **34**[1,5] (110 mg, 0.29 mmol) produced crude products, which were purified by short CC (acetone–hexane, 3 : 7) and then preparative HPLC [LiChrosorb Si 60 (7 μm) 2 × 25 cm; acetone–hexane, 18 : 82] to provide the all-*E*-skeletal compound **35** (90 mg, 44%) as a red solid, along with some isomeric mixtures; λ_{max}(EtOH)/nm 283, 358, 470; ν_{max}/cm^{-1} 3611, 3460, 1661, 1579, 1556, 1519; δ_H(500 MHz) 0.61 (6H, q, *J* 8), 0.84 and 0.86 (each 3H, s), 0.97 (9H, t, *J* 8), 1.19 and 1.21 (each 3H, s), 1.37 (6H, s), 1.49 (1H, dd, *J* 14.5 and 3), 1.56 (1H, d, *J* 11.5), 1.61 (1H, d, *J* 12), 1.71 (1H, dd, *J* 13.5 and 5), 1.81 (1H, ddd, *J* 11.5, 6 and 2.5), 1.95, 1.96, 1.97 and 1.98 (each 3H, s), 1.99 (1H), 2.00 (1H, dd, *J* 13.5 and 8), 2.96 (1H, dd, *J* 14.5 and 8.5), 4.37 (1H, t, *J* 6), 4.51 (1H, m), 5.77 (1H, d, *J* 16), 6.18, 6.26 and 6.35 (each 1H, br d, *J* 11), 6.35 (1H, d, *J* 15), 6.35 (1H, d, *J* 16), 6.44 (1H, d, *J* 15), 6.52 (1H, d, *J* 14.5), 6.55 (1H, br d, *J* 11), 6.61 and 6.62 (each 1H, dd, *J* 14.5 and 11), 6.66 (1H, dd, *J* 15 and 11), 6.70 (1H, dd, *J* 14.5 and 11), 7.33 (1H, d, *J* 15); *m*/*z* (EI) 714.5041 (M^+, $C_{46}H_{70}O_4Si$ requires 714.5041).

Preparation of capsanthin 3,6-epoxide 3

In the same manner as described for the preparation of cucurbitaxanthin A **1**, desilylation of the compound **36** (80 mg, 0.11 mmol) gave crude products, which were purified by preparative HPLC [LiChrosorb Si 60 (7 μm) 2 × 25 cm; THF–hexane–MeOH, 25 : 75: 1.5] to provide capsanthin 3,6-epoxide **3** (41 mg, 61%) as a red solid. The spectral data of synthetic **3** were in good agreement with those reported.[2]

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