Organic & Biomolecular Chemistry

Cite this: *Org. Biomol. Chem.*, 2012, **10**, 4103

www.rsc.org/obc

PAPER

Stereoselective total synthesis of the acetylenic carotenoids alloxanthin and triophaxanthin†

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Received 14th February 2012, Accepted 22nd March 2012
DOI: 10.1039/c2ob25321f

Stereoselective total synthesis of the C_{40}-diacetylenic carotenoid alloxanthin (**1**) and the C_{31}-acetylenic apocarotenoid triophaxanthin (**2**) was accomplished by Wittig condensation of C_{10}-dialdehyde **20** or C_{16}-keto aldehyde **19**, respectively, with C_{15}-acetylenic tri-n-butylphosphonium salt **12**.

Introduction

More than 20 different acetylenic carotenoids, including alloxanthin (**1**) and triophaxanthin (**2**) (Fig. 1), have been isolated from nature.[2] These natural products have all-*E* configurations in their conjugated double bonds, even though the 9*Z* (9′*Z*)[3] isomers are known to be more thermodynamically stable.[4–6]

The widely used Wittig condensation of C_{15}-acetylenic triphenylphosphonium salt **A**[7–9] (Fig. 2) with the aldehydes is known to provide 9*Z* isomers along with all-*E* and 11*Z* isomers in specific proportions.

To obtain all-*E* acetylenic carotenoids, the challenge lies in achieving two modes of stereocontrol. The first is *E*-selectivity at the C9–C10 double bond. We presumed that the generation of 9*Z* isomers was not attributed to the Wittig reaction but the phosphonium salts **A**, which included the 9*Z* isomer. Thus, the stereoselective preparation of 9*E* phosphonium salt **A** would enable predominant formation of the 9*E* condensation products. The second is *E*-selectivity at the C11–C12 double bond. It has been reported[10–12] that Wittig reaction of aldehydes with tri-n-butylphosphonium salts affords primarily *E*-olefins. Thus, the formation of 11*Z* isomers can be avoided by using tri-n-butylphosphonium salt **B** instead of triphenylphosphonium salt **A**.

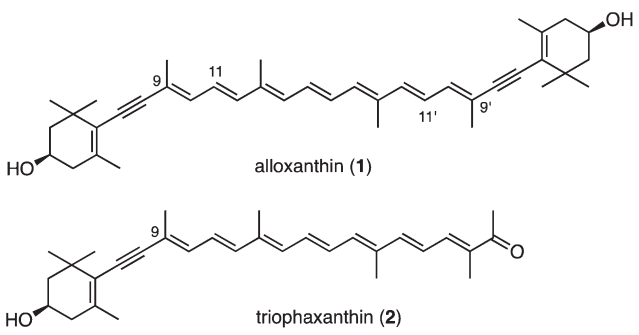

Fig. 1 Structure of acetylenic carotenoids

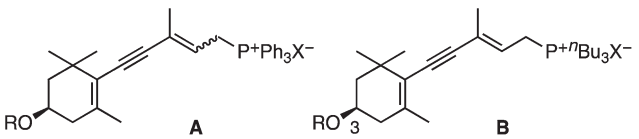

Fig. 2 Structure of C_{15}-acetylenic phosphonium salts

In this paper, we disclose the stereoselective preparation of C_{15}-acetylenic tri-n-butylphosphonium salt **B** and its application in the stereoselective total synthesis of the C_{40}-diacetylenic carotenoid alloxanthin (**1**) and the C_{31}-acetylenic apocarotenoid triophaxanthin (**2**).

Results and discussion

Preparation of C_{15}-acetylenic phosphonium salt 12 (B)

To establish a general protocol for stereoselective synthesis of various acetylenic carotenoids, we planned to prepare tri-n-butylphosphonium salt **12** (**B**), whose hydroxyl group at C-3 was protected by a triethylsilyl (TES) group (Scheme 1). The TES moiety was expected to tolerate the necessary reaction conditions and to undergo smooth deprotection without isomerization.

Through a known procedure,[13,14] (−)-actinol (**3**)[15] was converted into terminal alkyne **6**, which was then reduced with lithium aluminum hydride followed by treatment of the resulting alcohol **7** with TES chloride in the presence of triethylamine to provide the TES-protected terminal alkyne **8**.

By using tetrakis(triphenylphosphine) palladium (5 mol%) and copper(I) iodide (5 mol%) as catalysts in diisopropylamine and by degassing the reaction mixture in the presence of 2,6-*tert*-butyl-4-methylphenol (BHT, 5 mol%), Sonogashira cross-coupling between alkyne **8** and easily prepared vinylbromide **9**[16]

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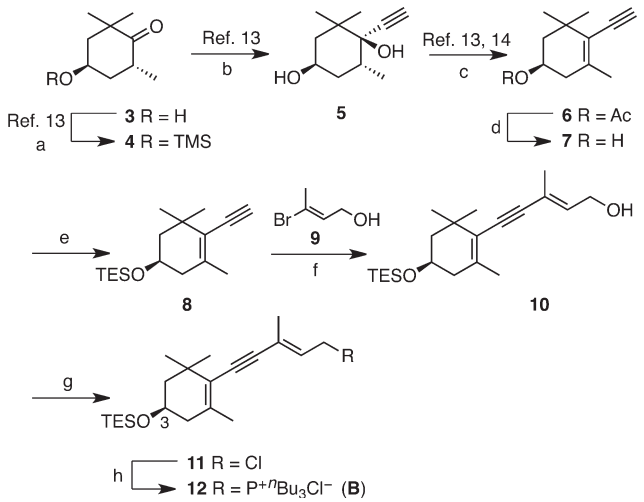
† Carotenoids and related polyenes. Part 13.[1]



Scheme 1 *Reagents and conditions*: (a) TMSCl, Et_3N, cat. DMAP, CH_2Cl_2, 0 °C (98%); (b) ethynyltrimethylsilane, ^nBuLi, THF, −50 °C then aq. KOH, MeOH, rt; (c) Ac_2O, pyridine, rt then cat. $CuSO_4$, xylene, reflux (Dean–Stark) (89% from **4**); (d) $LiAlH_4$, Et_2O, 0 °C (97%); (e) TESCl, Et_3N, cat. DMAP, CH_2Cl_2, 0 °C (94%); (f) cat. Pd-$(PPh_3)_4$, cat. CuI, cat. BHT, $^iPr_2NH$ (95%); (g) LiCl, MsCl, γ-collidine, DMF, −10 °C (83%); (h) P^nBu_3, Et_3N, CH_2Cl_2, rt (quant.).

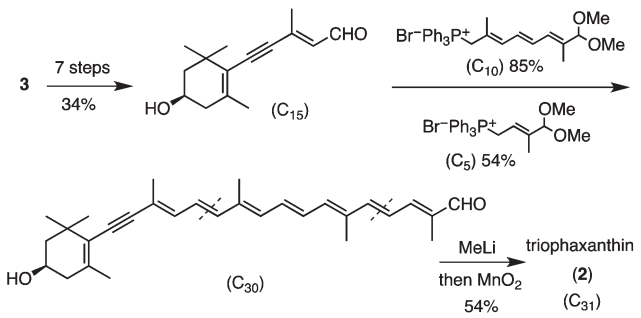
gave the desired cross-coupling product **10** in high yield. This reaction without degassing yielded a considerable amount of the alkyne homodimer.

Allylic alcohol **10** was then allowed to react with lithium chloride and methanesulfonyl chloride (MsCl) in the presence of γ-collidine as a base in *N*,*N*-dimethylformamide (DMF) at −10 °C to afford the corresponding allylic chloride **11** without isomerization. In this chlorination, the reaction temperature was found to be crucial for avoiding isomerization. Finally, the chloride was treated with tri-n-butylphosphine in the presence of triethylamine in dichloromethane to yield the desired phosphonium salt **12**. The transformation of the chloride **11** to the Wittig salt **12** in the absence of triethylamine resulted in partial deprotection of the TES group. The total yield of Wittig salt **12** from (−)-actinol (**3**) was 63%.

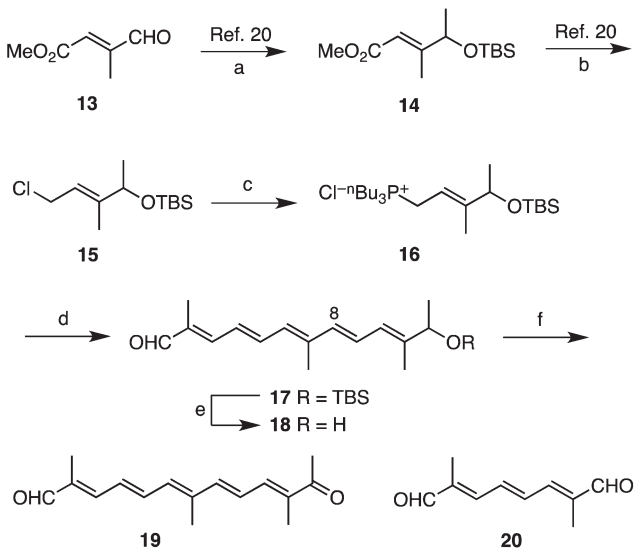
Improved preparation of C_{16}-keto aldehyde 19 and total synthesis of triophaxanthin (2)

The C_{15}-acetylenic phosphonium salt **12** was next applied to the stereoselective synthesis of triophaxanthin (**2**), which was first isolated[17] as the major carotenoid (more than 52% of the total pigments) from the nudibranch *Triopha carpenteri*. Matsuno *et al.* reported[18] that it was formed *via* retro-aldol cleavage of the marine acetylenic carotenoid amarouciaxanthin B by treatment with methanolic potassium hydroxide.

Completely synthetic triophaxanthin (**2**: Scheme 2) has been obtained only once previously by Haugan,[19] who noted that using the C_{15}-acetylenic aldehyde was selected for the synthesis of **2** to avoid the formation of the 9*Z* isomer. However, that synthesis was achieved over 13 linear steps from (−)-actinol (**3**) through a $C_{15} + C_{10} + C_5 + C_1 = C_{31}$ strategy, in which the stereoselectivity of the two Wittig condensations remained to be improved.



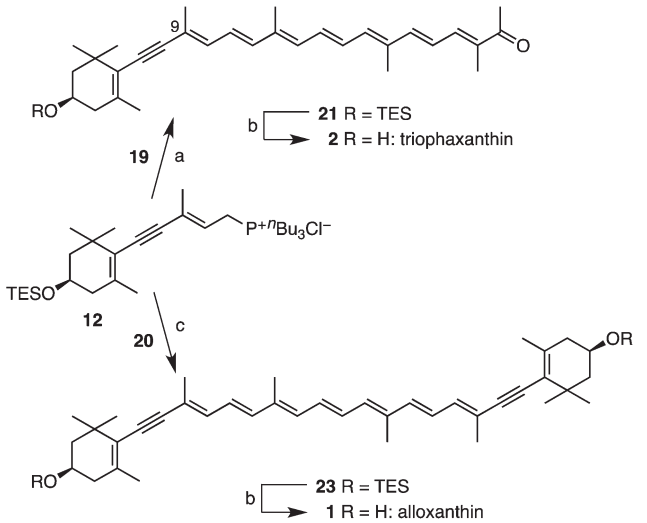
Scheme 2



Scheme 3 *Reagents and conditions*: (a) MeMgBr, THF, −20 °C then TBSOTf, γ-collidine, CH_2Cl_2, 0 °C (86%); (b) $LiAlH_4$, Et_2O, 0 °C then LiCl, MsCl, γ-collidine, DMF, −10 °C; (c) P^nBu_3, CH_2Cl_2, rt (75% from **14**); (d) **20**, NaOMe, CH_2Cl_2, rt (87%); (e) TBAF, THF, rt (88%); (f) IBX, DMSO, rt (98%).

We planned the convergent total synthesis of **2** *via* the condensation between C_{15}-acetylenic phosphonium salt **12** and C_{16}-keto aldehyde **19** (Scheme 3). Although we previously reported[20] the preparation of aldehyde **19** *via* the Wittig reaction of C_{10}-dialdehyde **20** with the corresponding triphenylphosphonium salt of C_6-phosphonium salt **16**, HPLC separation of the isomers of **19** was troublesome. To overcome this problem, we used tri-n-butylphosphonium salt **16** (Scheme 3).

Allyl chloride **15**, prepared by a previously reported procedure,[20] was treated with tri-n-butylphosphine to give phosphonium salt **16**, which was condensed with C_{10}-dialdehyde **20**[21] to yield the all-*E* pentaenal **17** in high yield. After deprotection of the *tert*-butyldimethylsilyl (TBS) group on **17** by treatment with tetrabutylammonium fluoride (TBAF), the resulting alcohol **18** was oxidized with 2-iodoxybenzoic acid (IBX) in dimethylsulfoxide (DMSO) to provide the desired all-*E* C_{16}-keto aldehyde **19** in high yield; in contrast, the previously reported MnO_2 oxidation[20] of **18** requires a large excess of oxidant and a long reaction time, and oxidation of **18** with Dess–Martin periodinane was accompanied by a considerable amount of the acetylated product.



Scheme 4 *Reagents and conditions*: (a) NaOMe, CH_2Cl_2, 0 °C (92%); (b) TBAF, AcOH, THF, rt (quant.); (c) NaOMe, CH_2Cl_2, rt (61%); (d) TBAF, AcOH, THF, rt (90%).

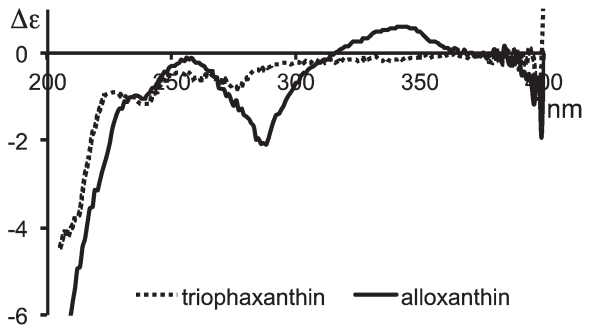


Fig. 3 CD spectra in Et_2O–isopentane–EtOH (5 : 5 : 2) of synthesized alloxanthin (**1**) and triophaxanthin (**2**).

As expected, the Wittig reaction of C_{16}-keto aldehyde **19** with C_{15}-phosphonium salt **12** by using sodium methoxide as a base in dichloromethane stereoselectively proceeded to afford the all-*E* C_{31}-condensed product **21** in high yield (Scheme 4). The 9*E*-geometry of **21** was confirmed from the chemical shift[22] of the methyl carbon (18.11 ppm) at the C-9 position in the compound's ^{13}C NMR spectrum. Desilylation of **21** with TBAF in the presence of acetic acid quantitatively provided all-*E* triophaxanthin (**2**) without isomerization.[23] Its spectral data were in good accordance with those reported.[19] Although the circular dichroism (CD) spectrum of the prepared compound (Fig. 3) showed weak Cotton effects, it was similar to that of reported natural product.[18]

Total synthesis of alloxanthin (1)

Alloxanthin (**1**),[24] isolated from flagellates of the algal class *Cryptophyceae*, was the first natural acetylenic carotenoid to be discovered. This compound has subsequently been isolated from various marine sources.[2] The first and only synthesis of alloxanthin (**1**) was achieved by Weedon *et al.* in 1984[7] *via* Wittig condensation of C_{10}-dialdehyde **20** with C_{15}-acetylenic triphenylphosphonium salt **A** (R = Ac, Fig. 2) in the presence of potassium hydroxide in 2-propanol. Although the condensation was carried out at −30 °C to avoid the formation of the thermodynamically more stable 9*Z* isomer, they obtained all-*E* alloxanthin (**1**) (3.6%) accompanied by an equal amount of its 9*Z* isomer.

In contrast, Wittig condensation of C_{10}-dialdehyde **20** with C_{15}-acetylenic tri-n-butylphosphonium salt **12** in the presence of sodium methoxide in dichloromethane at room temperature (rt) proceeded almost stereoselectively to afford the all-*E* condensed product **23** in 61% yield. We observed that in a protic solvent such as methanol, this condensation required a long reaction time. Selection of a suitable solvent was crucial for accelerating the reaction, especially the second step (C_{25}-apocarotenal to C_{40}-alloxanthin). Finally desilylation of **23** with TBAF in the presence of acetic acid yielded all-*E* alloxanthin (**1**) in high yield (Scheme 4). Its ^{13}C NMR spectral data were in good accordance with those reported.[25] The CD spectrum of the synthesized compound (Fig. 3) was similar to that of the natural product.[18]

In summary, we have achieved the stereoselective total synthesis of the C_{40}-diacetylenic carotenoid alloxanthin (**1**) and the C_{31}-acetylenic apocarotenoid triophaxanthin (**2**) *via* Wittig condensation of C_{10}-dialdehyde **20** or C_{16}-keto aldehyde **19**, respectively, with C_{15}-acetylenic tri-n-butylphosphonium salt **12**. This phosphonium salt **12** would be an efficient synthon for the synthesis of various acetylenic carotenoids.

Experimental

UV-vis spectra were recorded on a JASCO Ubest-55 instrument. IR spectra were measured on a Perkin-Elmer FT-IR spectrometer, spectrum 100, using chloroform solution. ^1H and ^{13}C NMR spectra were determined on a Varian Gemini-300 superconducting FT-NMR spectrometer, using deuteriochloroform solutions (tetramethylsilane as internal reference). *J* values are given in Hz. Mass spectra were taken on a Thermo Fisher Scientific Exactive spectrometer. Optical rotations were measured on a JASCO DIP-181 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. 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.

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 carotenoid numbering system.

(4*R*)-4-Ethynyl-3,5,5-trimethylcyclohex-3-enol (7)

A solution of the acetate **6** (3.60 g, 17.5 mmol) in ether (50 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (498 mg, 13.1 mmol) at 0 °C and the mixture was stirred at 0 °C for 15 min. The excess $LiAlH_4$ was decomposed by dropwise addition of water. The mixture was filtered through Celite and the filtrate was dried and evaporated. The resulting residue was purified by recrystallization from ether–hexane (1 : 10) to give

the alcohol **7** (2.78 g, 97%) as colorless needles: mp 71–72 °C; $[\alpha]_D^{23}$ −131.90 (*c* 0.98, MeOH); IR ν 3605 and 3451 (OH), 3307 (≡CH), 2088 (C≡C), 1625 and 1602 (C═C); ^{1}H NMR (300 MHz) δ 1.13 and 1.19 (each 3H, s, *gem*-Me), 1.45 (1H, t, *J* 12, 2-Hβ), 1.78 (1H, br s, OH), 1.82 (1H, ddd, *J* 12, 4,5 and 2, 2-Hα), 1.91 (3H, br s, 5-Me), 2.03 (1H, ddquint, *J* 17.5, 10 and 1, 4-Hβ), 2.40 (1H, ddm, 17.5 and 5.5, 4-Hα), 3.10 (1H, s, 8-H), 3.97 (1H, m, 3-H); ^{13}C NMR (75 MHz) δ 21.69, 27.73, 29.54, 35.65, 40.61, 45.92, 64.08, 80.70, 81.04, 122.34, 138.77; Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.55; H, 10.10.

Triethyl[(4*R*)-4-ethynyl-3,5,5-trimethylcyclohex-3-en-1-yl]-oxysilane (8)

TESCl (4.95 mL, 29.5 mmol) was added to a stirred solution of the alcohol **7** (3.23 g, 19.7 mmol), *N*,*N*-dimethylaminopyridine (DMAP, 1.20 g, 9.84 mmol) and Et_3N (4.54 mL, 32.5 mmol) in CH_2Cl_2 (25 mL) at 0 °C. After being stirred at rt for 45 min, the mixture was poured into chilled water and extracted with ether. The extracts were washed successively with aq. 5% HCl, saturated aq. $NaHCO_3$ and brine. Evaporation of the dried solution gave a residue, which was purified by flash CC (ether–hexane, 5 : 95) to afford the TES ether **8** (5.17 g, 94%) as a colorless oil: $[\alpha]_D^{24}$ −62.5 (*c* 0.72, MeOH); IR *ν* 3307 (≡CH), 2087 (C═C), 1625 (C═C); ^{1}H NMR (300 MHz) δ 0.60 (6H, q, *J* 8, SiC*H*$_2$ × 3), 0.97 (9H, t, *J* 8, SiCH$_2$*Me* × 3), 1.12 and 1.16 (each 3H, s, *gem*-Me), 1.45 (1H, t, *J* 12, 2-Hβ), 1.72 (1H, ddd, *J* 12, 3.5 and 2, 2-Hα), 1.89 (3H, t, *J* 0.5, 5-Me), 2.07 (1H, ddquint, *J* 18, 9 and 1, 4-Hβ), 2.26 (1H, ddd, 18, 6 and 2, 4-Hα), 3.08 (1H, d, *J* 0.5, 8-H), 3.91 (1H, m, 3-H); ^{13}C NMR (75 MHz) δ 5.00, 6.97, 22.48, 28.39, 30.28, 36.35, 42.09, 47.17, 65.13, 81.22, 81.99, 122.89, 140.21; HRMS (ESI) *m*/*z* calcd for $C_{17}H_{31}OSi$ $(MH)^+$ 279.2139, found 279.2139.

(2*E*)-3-Methyl-5-[(4*R*)-2,6,6-trimethyl-4-triethylsilyloxycyclohex-1-en-1-yl]pent-2-en-4-yn-1-ol (10)

BHT (110 mg, 0.5 mmol), $Pd(PPh_3)_4$ (578 mg, 0.5 mmol) and CuI (95 mg, 0.5 mmol) were added to a stirred, degassed mixture of the terminal alkyne **8** (2.78 g, 10 mmol) and the vinyl bromide **9** (2.26 g, 15 mmol) in diisopropylamine (35 mL). After being stirred at rt for a further 2 h, the mixture was poured into saturated aq. NH_4Cl and extracted with AcOEt. The extract was washed with brine, dried and evaporated to give a residue, which was purified by flash CC (AcOEt–hexane, 3 : 7) to provide the alcohol **10** (3.31 g, 95%) as a pale yellow oil: $[\alpha]_D^{24}$ −57.9 (*c* 0.31, MeOH); IR *ν* 3608 and 3434 (OH), 2186 (C≡C), 1661 and 1617 (C═C); ^{1}H NMR (300 MHz) δ 0.60 (6H, q, *J* 8, SiC*H*$_2$ × 3), 0.97 (9H, t, *J* 8, SiCH$_2$*Me* × 3), 1.12 and 1.15 (each 3H, s, *gem*-Me), 1.27 (1H, t, *J* 6, OH), 1.47 (1H, t, *J* 12, 2-Hβ), 1.72 (1H, ddd, *J* 12, 3.5 and 2, 2-Hα), 1.88 (6H, br s, 5-Me and 9-Me), 2.09 (1H, ddd, *J* 18, 9 and 1, 4-Hβ), 2.27 (1H, ddd, *J* 18, 5 and 2, 4-Hα), 3.92 (1H, m, 3-H), 4.25 (2H, br t, *J* 6, 11-H$_2$), 5.96 (1H, tq, *J* 7 and 2, 10-H); ^{13}C NMR (75 MHz) δ 4.87, 6.84, 17.80, 22.44, 28.54, 30.39, 36.54, 42.06, 47.10, 59.23, 65.09, 86.33, 95.85, 121.73, 123.55, 133.56, 138.41; HRMS (ESI) *m*/*z* calcd for $C_{21}H_{36}O_2NaSi$ $(M + Na)^+$ 371.2377, found 371.2372.

[(1*R*)-4-((3*E*)-5-Chloro-3-methylpent-3-en-1-ynyl)-3,5,5-trimethylcyclohex-3-en-1-yloxy]triethylsilane (11)

A solution of LiCl (200 mg, 4.74 mmol) in dry DMF (5 mL) was added to a stirred mixture of the alcohol **10** (1.50 g, 4.31 mmol) and γ-collidine (1.30 mL, 9.48 mmol) at −10 °C and the mixture was stirred at −10 °C for 10 min. MsCl (0.60 mL, 7.75 mmol) was added to this mixture and the mixture was stirred at −10 to 0 °C for 1.5 h. The mixture was poured into chilled brine and extracted with ether. Evaporation of the dried extract provided a residue, which was purified by short CC (ether–hexane, 5 : 95) to afford the chloride **11** (1.31 g, 83%) as a pale yellow oil: $[\alpha]_D^{22}$ −62.4 (*c* 0.59, $CHCl_3$); IR *ν* 2185 (C≡C), 1612 (C═C); ^{1}H NMR (300 MHz) δ 0.60 (6H, q, *J* 8, SiC*H*$_2$Me × 3), 0.97 (9H, t, *J* 8, SiCH$_2$*Me* × 3), 1.11 and 1.15 (each 3H, s, *gem*-Me), 1.47 (1H, t, *J* 12, 2-Hβ), 1.73 (1H, ddd, *J* 12, 3.5 and 2, 2-Hα), 1.88 (3H, d, *J* 1, 5-Me), 1.94 (3H, d, *J* 1.5, 9-Me), 2.09 (1H, ddd, *J* 18, 9 and 1, 4-Hβ), 2.28 (1H, ddd, *J* 18, 5 and 1, 4-Hα), 3.92 (1H, m, 3-H), 4.15 (2H, d, *J* 7, 11-H$_2$), 5.96 (1H, tq, *J* 7 and 1.5, 10-H); ^{13}C NMR (75 MHz) δ 4.88, 6.84, 17.57, 22.47, 28.57, 30.39, 36.51, 40.15, 42.09, 47.07, 65.04, 88.16, 95.38, 123.47, 124.66, 129.51, 139.07; HRMS (ESI) *m*/*z* calcd for $C_{21}H_{35}OSi$ $(M - Cl)^+$ 331.2452, found 331.2445.

Preparation of the Wittig salt 12

^{n}Bu$_3$P (0.90 mL, 3.62 mmol) was added dropwise at rt to a stirred solution of the chloride **11** (1.30 g, 3.29 mmol) and Et_3N (0.23 mL, 1.65 mmol) in dry CH_2Cl_2 (12 mL) and the mixture was stirred at rt for 1.5 h. Evaporation of the solvent gave a residue, which was washed with ether to provide the phosphonium chloride **12** (1.87 g, quant.) as colorless solids: $[\alpha]_D^{22}$ −38.1 (*c* 0.92, $CHCl_3$); IR *ν* 2185 (C≡C), 1612 (C═C); ^{1}H NMR (300 MHz) δ 0.60 (6H, q, *J* 8, SiC*H*$_2$ × 3), 0.97 (18H, t, *J* 8, CH$_2$*Me* × 6), 1.11 and 1.14 (each 3H, s, *gem*-Me), 1.47 (1H, t, *J* 12, 2-Hβ), 1.54 (12H, m, C*H*$_2$ × 6), 1.74 (1H, ddd, *J* 12, 3.5 and 2, 2-Hα), 1.88 (3H, br s, 5-Me), 2.04 (3H, d, *J* 4, 9-Me), 2.12 (1H, ddd, *J* 18, 9 and 1, 4-Hβ), 2.29 (1H, br dd, *J* 18 and 5, 4-Hα), 2.48 (6H, m, PCH$_2$ × 3), 3.76 (2H, dd, *J* 16.5 and 8, 11-H$_2$), 3.92 (1H, m, 3-H), 5.56 (1H, q-like, *J* 7, 10-H); HRMS (ESI) *m*/*z* calcd for $C_{33}H_{62}OPSi$ $(M - Cl)^+$ 533.4302, found 533.4306.

Preparation of the Wittig salt 16

In the same manner as described for the preparation of the Wittig salt **12**, the chloride **15** (3.55 g, 14.3 mmol) was treated with ^{n}Bu$_3$P to give the Wittig salt **16** (4.82 g, 75%) as colorless solids: ^{1}H NMR (300 MHz) δ −0.06 and −0.02 (each 3H, s, SiMe × 2), 0.81 (9H, s, *tert*-Bu), 0.89 (9H, t *J* 7, CH$_2$*Me* × 3), 1.19 (3H, d, *J* 6, CH*Me*), 1.38–1.54 (12H, m, CH$_2$ × 6), 1.70 (3H, d, *J* 3,═CMe), 2.32–2.46 (6H, m, CH$_2$ × 3), 3.42 (2H, dd, *J* 16 and 8, PCH$_2$), 4.10 (1H, qd, *J* 6 and 3, OC*H*Me), 5.28

(br q-like, *J* 7.5,=CH); HRMS (ESI) *m*/*z* calcd for $C_{24}H_{52}OPSi$ $(M - Cl)^+$ 415.3519, found 415.3509.

(2*E*,4*E*,6*E*,8*E*,10*E*)-12-*tert*-Butyldimethylsilyloxy-2,7,11-trimethyltrideca-2,4,6,8,10-pentaenal (17)

NaOMe (1 M in MeOH; 2.0 mL, 2.0 mmol) was added to a solution of the phosphonium salt **16** (726 mg, 1.61 mmol) and C_{10}-dialdehyde **20** (220 mg, 1.34 mmol) in CH_2Cl_2 (10 mL) at rt. After being stirred at rt for 1.5 h, the mixture was poured into saturated aq. NH_4Cl and extracted with AcOEt. The extracts were washed with brine, dried and evaporated to afford a residue, which was purified by flash CC (AcOEt–hexane, 1 : 4) to give the pentaenal **17** (420 mg, 87%) as an orange oil: UV-VIS (EtOH) λ 398; IR ν 1660 (conj. CO), 1611 and 1562 (C=C); ^{1}H NMR (300 MHz) δ 0.02 and 0.05 (each 3H, s, SiMe × 2), 0.94 (9H, s, *tert*-Bu), 1.22 (3H, d, *J* 6.5, 13-H_3), 1.80 (3H, br s, 11-Me), 1.88 (3H, br s, 2-Me), 2.02 (3H, br s, 7-Me), 4.23 (1H, q, *J* 6.5, 12-H), 6.15 (1H, br d, *J* 11.5, 10-H), 6.27 (1H, br d, *J* 11.5, 6-H), 6.30 (1H, d, *J* 15, 8-H), 6.64 (1H, dd, *J* 15 and 11.5, 9-H), 6.67 (1H, dd, *J* 14.5 and 11.5, 4-H), 6.96 (1H, br d, *J* 11.5, 3-H), 7.02 (1H, dd, *J* 14.5 and 11.5, 5-H); HRMS (ESI) *m*/*z* calcd for $C_{22}H_{37}O_2Si$ $(MH)^+$ 361.2557, found 361.2551.

(2*E*,4*E*,6*E*,8*E*,10*E*)-12-Hydroxy-2,7,11-trimethyltrideca-2,4,6,8,10-pentaenal (18)

TBAF (1 M in THF; 2.35 mL, 2.35 mmol) was added to a solution of the TBS ether **17** (420 mg, 1.17 mmol) in THF (10 mL) and the mixture was stirred at 40 °C for 1.5 h. The mixture was concentrated to give a residue, which was purified by flash CC (MeOH–AcOEt–hexane, 5 : 35 : 60) to provide the alcohol **18** (255 mg, 89%) as an orange oil: UV-VIS (EtOH) λ 396; IR ν 3605 and 3463 (OH), 1660 (conj. CO), 1610 and 1563 (C=C); ^{1}H NMR (300 MHz) δ 1.29 (3H, d, *J* 6.5, 13-H_3), 1.83 (3H, br s, 11-Me), 1.87 (3H, br s, 2-Me), 2.01 (3H, br s, 7-Me), 4.29 (1H, q, *J* 6.5, 12-H), 6.19 (1H, br d, *J* 11, 10-H), 6.27 (1H, br d, *J* 11.5, 6-H), 6.32 (1H, d, *J* 15.5, 8-H), 6.62 (1H, dd, *J* 15.5 and 11, 9-H), 6.67 (1H, dd, *J* 14 and 11.5, 4-H), 6.95 (1H, br d, *J* 11.5, 3-H), 7.01 (1H, dd, *J* 14 and 11.5, 5-H); HRMS (ESI) *m*/*z* calcd for $C_{16}H_{23}O_2$ $(MH)^+$ 247.1692, found 247.1692.

(2*E*,4*E*,6*E*,8*E*,10*E*)-2,7,11-Trimethyl-12-oxotrideca-2,4,6,8,10-pentaenal (19)

IBX (854 mg, 3.05 mmol) was added to a solution of the alcohol **18** (250 mg, 1.02 mmol) in DMSO (5 mL) and the mixture was stirred at rt for 15 min. The mixture was poured into chilled water and extracted with AcOEt. The extracts were washed with 10% aq. $Na_2S_2O_3$ and then brine, dried and evaporated to give a residue, which was purified by flash CC (MeOH–AcOEt–CH_2Cl_2, 2 : 10 : 90) to provide the alcohol **19** (243 mg, 98%) as pale yellow solids. Its spectral data were in agreement with those previously reported.[20]

(3*E*,5*E*,7*E*,9*E*,11*E*,13*E*,15*E*)-3,7,12,16-Tetramethyl-18-[(4*R*)-2,6,6-trimethyl-4-triethylsilyloxycyclohex-1-en-1-yl]octadeca-3,5,7,9,11,13,15-heptaen-17-yn-2-one (21)

NaOMe (1 M in MeOH; 0.57 mL, 0.57 mmol) was added to a solution of the phosphonium salt **12** (240 mg, 0.43 mmol) and C_{16}-keto aldehyde **19** (70 mg, 0.27 mmol) in CH_2Cl_2 (5 mL) at 0 °C. After being stirred at 0 °C for 15 min, the mixture was poured into saturated aq. NH_4Cl and extracted with AcOEt. The extracts were washed with brine, dried and evaporated to afford a residue, which was purified by flash CC (AcOEt–hexane, 1 : 4) to give the compound **21** (420 mg, 87%) as an orange oil: UV-VIS (EtOH) λ 278, 451, 472sh; IR ν 2170 (C≡C), 1648 (conj. CO), 1608, 1575 and 1532 (C=C); ^{1}H NMR (500 MHz) δ 0.61 (6H, q, *J* 7.5, SiCH_2 × 3), 0.97 (9H, t, *J* 7.5, $SiCH_2Me$ × 3), 1.14 and 1.18 (each 3H, s, *gem*-Me), 1.48 (1H, t, *J* 12, 2-Hβ), 1.74 (1H, ddd, *J* 12, 3.5 and 1.5, 2-Hα), 1.91 (3H, d, *J* 1, 5-Me), 1.94 (3H, d, *J* 1, 9′-Me), 1.98 (3H, br s, 13-Me), 2.00 (3H, d, *J* 1, 13′-Me), 2.01 (3H, d, *J* 1, 9-Me), 2.11 (1H, ddd, *J* 17.5, 9 and 1, 4-Hβ), 2.29 (1H, ddd, *J* 17.5, 6 and 1.5, 4-Hα), 2.36 (3H, s, COMe), 3.92 (1H, m, 3-H), 6.28 (1H, br d, *J* 11.5, 14-H), 6.36 (1H, d, *J* 14.5, 12-H), 6.39 (1H, br d, *J* 11.5, 14′-H), 6.45 (1H, dd-like, *J* 11.5 and 1, 10-H), 6.56 (1H, dd, *J* 14.5 and 11.5, 11-H), 6.59 (1H, dd, *J* 15 and 10.5, 11′-H), 6.64 (1H, dd, *J* 14 and 11.5, 15′-H), 6.66 (1H, d, *J* 15, 12′-H), 6.73 (1H, dd, *J* 14 and 11.5, 15-H), 7.14 (1H, dd-like, *J* 10.5 and 1, 10′-H); ^{13}C NMR (125 MHz) δ 4.90 (SiCH_2), 6.85 ($SiCH_2CH_3$), 11.67 (9′-Me), 12.76 and 12.83 (13-Me and 13′-Me), 18.11 (9-Me), 22.54 (5-Me), 25.58 ($COCH_3$), 28.66 and 30.50 (*gem*-Me), 36.59 (C1), 42.17 (C4), 47.14 (C2), 65.10 (C3), 89.60 (C7), 98.40 (C8), 119.77 (C9), 123.87 (C11′), 123.97 (C6), 124.97 (C11), 129.79 (C15′), 132.13 (C15), 132.99 (C14), 134.89 (C10), 135.64 and 135.76 (C9′ and C13′), 136.17 (C14′), 137.69 (C12 and C13), 138.29 (C5), 139.91 (C10′), 144.43 (C12′),199.36 (CO); HRMS (ESI) *m*/*z* calcd for $C_{37}H_{55}O_2Si$ $(MH)^+$ 559.3960, found 559.3959.

Preparation of triophaxanthin (2)

AcOH (1 M in THF; 0.13 mL, 0.13 mmol) and then TBAF (1 M in THF; 0.40 mL, 0.40 mmol) were added to a solution of the TBS ether **21** (74 mg, 0.13 mmol) in THF (10 mL) and the mixture was stirred at rt for 20 min. The mixture was concentrated to give a residue, which was purified by flash CC (MeOH–AcOEt–hexane, 5 : 35 : 60) to provide triophaxanthin (**2**) (57 mg, 98%) as red solids. Its spectral data were in agreement with those reported.[19]

[((1*R*,1′*R*)-(3*E*,5*E*,7*E*,9*E*,11*E*,13*E*,15*E*)-3,7,12,16-Tetramethyloctadeca-3,5,7,9,11,13,15-heptaen-1,17-diyne-1,18-diyl)bis(3,5,5-trimethylcyclohex-3-ene-4,1-diyl)bisoxy]bis-(triethylsilane) (23)

NaOMe (1 M in MeOH; 2.0 mL, 2.0 mmol) was added to a solution of the phosphonium salt **12** (960 mg, 1.72 mmol) and C_{10}-dialdehyde **20** (65 mg, 0.40 mmol) in CH_2Cl_2 (10 mL) at rt. After being stirred at rt for 1.5 h, the mixture was poured into saturated aq. NH_4Cl and extracted with AcOEt. The extracts were washed with brine, dried and evaporated to afford a

residue, which was purified by flash CC (AcOEt–hexane, 8 : 92) to give the compound **23** (192 mg, 61%) as orange solids: UV-VIS (EtOH) λ 430sh, 453, 482; IR ν 2169 (C≡C), 1618, 1601 and 1565 (C=C); ^{1}H NMR (500 MHz) δ 0.59 (12H, q, J 8, SiCH_2 × 6), 0.95 (18H, t, J 8, SiCH$_2$*Me* × 6), 1.12 and 1.16 (each 6H, s, 1-*gem*-Me and 1′-*gem*-Me), 1.46 (2H, t, J 12, 2-Hβ and 2′-Hβ), 1.71 (1H, ddd, J 12, 3 and 2, 2-Hα and 2′-Hα), 1.89 (6H, br s, 5-Me and 5′-Me), 1.94 (6H, br s, 13-Me and 13′-Me), 1.98 (6H, br s, 9-Me and 9′-Me), 1.99 (2H, br dd, J 18 and 9, 4-Hβ and 4′-Hβ), 2.27 (2H, br dd, J 18 and 5.5, 4-Hα and 4′-Hα), 3.91 (2H, m, 3-H and 3′-H), 6.25 (2H, br d-like, J 10, 14-H and 14′-H), 6.33 (2H, d, J 14.5, 12-H and 12′-H), 6.43 (2H, dd, J 11.5 and 1.5, 10-H and 10′-H), 6.50 (2H, dd, J 14.5 and 11.5, 11-H and 11′-H), 6.62 (2H, m, 15-H and 15′-H); ^{13}C NMR (125 MHz) δ 4.86 (SiCH_2), 6.84 (SiCH$_2$$CH_3$), 12.74 (13-Me and 13′-Me), 18.06 (9-Me and 9′-Me), 22.53 (5-Me and 5′-Me), 28.63 and 30.48 (1-*gem*-Me and 1′-*gem*-Me), 36.58 (C1 and C1′), 42.13 (C4 and C′4), 47.12 (C2 and C2′), 65.10 (C3 and C3′), 89.25 (C7 and C7′), 98.46 (C8 and C8′), 119.13 (C9 and C9′), 123.96 (C6 and C6′), 124.28 (C11 and C11′), 130.31 (C15 and C15′), 133.35 (C14 and C14′), 135.04 (C10 and C10′), 136.42 (C13 and C13′), 137.92 (C12 and C12′), 138.09 (C5 and C5′); HRMS (ESI) m/z calcd for $C_{51}H_{81}O_2Si_2$ $(MH)^+$ 793.5770, found 793.5757.

Preparation of alloxanthin (1)

AcOH (1 M in THF; 0.30 mL, 0.30 mmol) and then TBAF (1 M in THF; 0.60 mL, 0.60 mmol) were added to a solution of the TBS ether **23** (103 mg, 0.13 mmol) in THF (10 mL) and the mixture was stirred at rt for 1 h. The mixture was concentrated to give a residue, which was purified by flash CC (MeOH–AcOEt–hexane, 5 : 50 : 45) to provide alloxanthin (**2**) (66 mg, 90%) as red solids: UV-VIS (EtOH) λ 430sh, 453, 482; IR ν 3606 and 3457 (OH), 2172 (C≡C), 1617, 1602 and 1567 (C=C); ^{1}H NMR (500 MHz) δ 1.15 and 1.20 (each 6H, s, 1-*gem*-Me and 1′-*gem*-Me), 1.46 (2H, t, J 12, 2-Hβ and 2′-Hβ), 1.83 (2H, br d, J 12, 2-Hα and 2′-Hα), 1.92 (6H, br s, 5-Me and 5′-Me), 1.96 (6H, br s, 13-Me and 13′-Me), 2.01 (6H, br s, 9-Me and 9′-Me), 2.07 (2H, br dd, J 18 and 9, 4-Hβ and 4′-Hβ), 2.43 (2H, br dd, J 18 and 5.5, 4-Hα and 4′-Hα), 3.99 (2H, m, 3-H and 3′-H), 6.27 (2H, br d-like, J 8.5, 14-H and 14′-H), 6.35 (2H, d, J 14.5, 12-H and 12′-H), 6.46 (2H, br d, J 11.5, 10-H and 10′-H), 6.52 (2H, dd, J 14.5 and 11.5, 11-H and 11′-H), 6.64 (2H, m, 15-H and 15′-H); ^{13}C NMR (125 MHz) δ 12.77 (13-Me and 13′-Me), 18.07 (9-Me and 9′-Me), 22.50 (5-Me and 5′-Me), 28.77 and 30.51 (1-*gem*-Me and 1′-*gem*-Me), 36.63 (C1 and C1′), 41.46 (C4 and C′4), 46.68 (C2 and C2′), 64.89 (C3 and C3′), 89.04 (C7 and C7′), 98.61 (C8 and C8′), 119.06 (C9 and C9′), 124.21 (C6 and C6′), 124.28 (C11 and C11′), 130.36 (C15 and C15′), 133.42 (C14 and C14′), 135.18 (C10 and C10′), 136.45 (C13 and C13′), 137.33 (C5 and C5′), 138.04 (C12 and C12′); HRMS (ESI) m/z calcd for $C_{40}H_{53}O_2$ $(MH)^+$ 565.4040, found 565.4031.

Acknowledgements

We thank Mr H. Yanou and Miss M. Hotta for technical assistance.

Notes and references

1 Part 12: Y. Yamano, M. V. Chary and A. Wada, *Chem. Pharm. Bull.*, 2010, **58**, 1362.
2 *Key to Carotenoids*, ed. H. Pfander, Birkhäuser, Basel, 2nd edn, 1987.
3 W have employed the numbering system used in carotenoids.
4 A. Fiksdahl, J. D. Tauber, S. Liaaen-Jensen, G. Saucy and G. F. Weber, *Acta Chem. Scand., Ser. B*, 1979, **33**, 192.
5 J. A. Haugan and S. Liaaen-Jensen, *Acta Chem. Scand.*, 1994, **48**, 899.
6 B. Vaz, M. Domínguez, R. Álvarez and A. R. de Lera, *J. Org. Chem.*, 2006, **71**, 5914.
7 A. J. Davies, A. Khare, A. K. Mallams, R. A. Massy-Westropp, G. P. Moss and B. C. L. Weedon, *J. Chem. Soc., Perkin Trans. 1*, 1984, 2147.
8 A. K. Chopra, G. P. Moss and B. C. L. Weedon, *J. Chem. Soc., Chem. Commun.*, 1977, 467; A. K. Chopra, A. Khare, G. P. Moss and B. C. L. Weedon, *J. Chem. Soc., Perkin Trans. 1*, 1988, 1383.
9 C. Tode, Y. Yamano and M. Ito, *Chem. Pharm. Bull.*, 2000, **48**, 1833; C. Tode, Y. Yamano and M. Ito, *J. Chem. Soc., Perkin Trans. 1*, 2002, 1581.
10 C. W. Spangler, R. K. McCoy, A. A. Dembek, L. S. Sapochak and B. D. Gates, *J. Chem. Soc., Perkin Trans. 1*, 1989, 151.
11 D. A. Evans and J. S. Johnson, *J. Org. Chem.*, 1997, **62**, 786.
12 Y. Yamano, Y. Sato, Y. Watanabe, K. Namikawa, W. Miki and M. Ito, *J. Chem. Soc., Perkin Trans. 1*, 2001, 1862.
13 Y. Yamano and M. Ito, *J. Chem. Soc., Perkin Trans. 1*, 1993, 1599; Y. Yamano, C. Tode and M. Ito, *J. Chem. Soc., Perkin Trans. 1*, 1998, 2569.
14 M. Soukup, E. Widmer and T. Lukác, *Helv. Chim. Acta*, 1990, **73**, 868.
15 H. G. W. Leuenberger, W. Bouguth, E. Widmer and R. Zell, *Helv. Chim. Acta*, 1976, **59**, 1832.
16 W. R. Roush and B. B. Brown, *J. Am. Chem. Soc.*, 1993, **115**, 2268.
17 J. W. McBeth, *Comp. Biochem. Physiol.*, 1972, **41B**, 55.
18 T. Matsuno, M. Ookubo and T. Komori, *J. Nat. Prod.*, 1985, **48**, 606.
19 J. A. Haugan, *Acta Chem. Scand.*, 1997, **51**, 1096.
20 Y. Yamano, M. Mimuro and M. Ito, *J. Chem. Soc., Perkin Trans. 1*, 1997, 2713.
21 P. Mildner and B. C. L. Weedon, *J. Chem. Soc.*, 1953, 3294.
22 G. Englert, *Pure Appl. Chem.*, 1985, **57**, 801.
23 Deprotection of TBS group on an acetylenic synthon by treatment with TBAF was reported[6] to be accompanied by isomerization.
24 A. K. Mallams, E. S. Waight, B. C. L. Weedon, D. J. Chapman, F. T. Haxo, T. W. Goodwin and D. M. Thomas, *Chem. Commun.*, 1967, 301.
25 G. P. Moss, *Pure Appl. Chem.*, 1976, **47**, 97.