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Synthesis of labile all-*trans*-7,8,7′,8′-bis-acetylenic carotenoids by bi-directional Horner–Wadsworth–Emmons condensation†

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A new stereoselective synthesis of the C_{40}-bis-acetylenic carotenoids all-*trans*-(3*R*,3′*R*)-alloxanthin and all-*trans*-3,4,7,8,3′,4′,7′,8′-octadehydro-β,β-carotene, both compounds featuring a stereochemically labile C7–C10 enyne, based on a bi-directional Horner–Wadsworth–Emmons (HWE) reaction of a C_{15}-phosphonate and a central C_{10}-dialdehyde, is reported. The triene unit of the latter fragment was synthesized using the acyclic metathesis/dimerization reaction.

Introduction

Carotenoids[1] are naturally occurring pigments ubiquitously present in plants and in other photosynthetic organisms.[2,3] They play multiple roles in Nature,[4] most importantly in photosynthesis and photoprotection, and hold potential as disease chemopreventive agents in humans by acting as antioxidants.[5] All these functions are causally linked to the presence of a central polyene chain that empowers carotenoids with unmatched light absorption and radical quenching features.[6] Arguably the polyenic nature of these compounds is a synthetic challenge since building the desired stereoisomer faces the intrinsic sensitivity of the intermediates and the final product under the reaction conditions.[7] Synthetic methodologies designed towards the total synthesis of carotenoids must consider how to progress within these constrains and overcome the shortcomings of previous strategies.

The acetylenic (7,8-didehydro) carotenoids,[8] which contain one or two alkynes at the C7–C8 position, constitute a small (over 20 members) subgroup within this family of polyterpenoids.[9,10] Even though the all-*trans* are, with a few exceptions, the exclusive stereoisomers found in Nature, the acetylenic carotenoids are considered the stereochemically most labile members of this family of natural products due to their propensity to isomerize to the more stable 9-*cis* isomers. Stereomutation at the C7–C10 enyne moiety to afford the 9-*cis* isomers has been reported to occur rapidly upon irradiation of solutions of all-*trans*-7,8-acetylenic carotenoids in the presence of catalytic quantities of iodine.[11] In particular, the C_2-symmetrical all-*trans*-7,8,7′,8′-bis-acetylenic compounds undergo complete isomerization under these conditions forming exclusively the 9*Z*,9′*Z* isomers. Extensive isomerization of the C9–C10 double bond has also been reported to take place on attempts to synthesize these compounds using condensation reactions[12–14] or palladium-catalyzed cross-coupling processes.[15] Within the first group, however, a modification of the classical (non-stereoselective) Wittig condensation that uses instead tri-*n*-butyl phosphoranes, has led to the formation of polyenes with improved *trans* stereoselectivity, including (3*R*,3′*R*)-alloxanthin **1**.[16]

We have explored the same bidirectional approach (a C_{15} + C_{10} + C_{15} = C_{40} condensation scheme)[1,7] to C_2-symmetrical bis-acetylenic carotenoids and found that the scarcely used[1] Horner–Wadsworth–Emmons (HWE) reaction[17–20] of two C_{15}-phosphonate anions with a central C_{10}-dialdehyde is an equally efficient synthetic procedure. We exemplify the finding with the new stereoselective synthesis of (3*R*,3′*R*)-alloxanthin **1** and the first synthesis of the highly unsaturated 3,4,7,8,3′,4′,7′,8′-octadehydro-β,β-carotene **2** (Fig. 1). In addition, we report a new preparation of the C_{10}-dialdehyde, based on the acyclic metathesis/dimerization[21–23] of precursor functionalized dienes.

Results and discussion

Due to the prevalence of an intact polyene on the central region of most C_{40}-carotenoids, the use of symmetrical difunctionalized building blocks (such as the C_{10}-dialdehyde, Fig. 1) simplifies the synthetic approaches to these compounds. Thus, various practical syntheses have been developed over the years to access these functionalized fragments.[7] A selection of

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†Electronic supplementary information (ESI) available: This includes general experimental procedures, alternative synthesis of dialdehyde **8a**, and copies of ^{13}C- and ^{1}H-NMR spectra of key compounds. See DOI: 10.1039/c4ob02144d

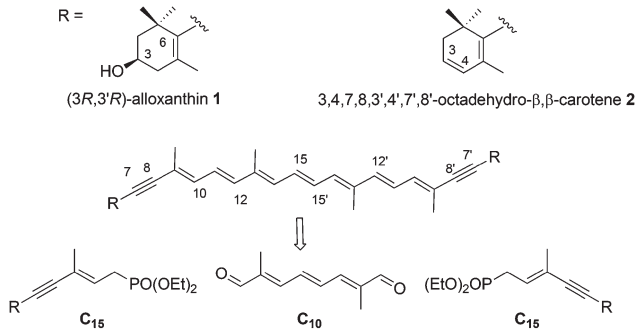


Fig. 1 Strategy for the synthesis of C_2-symmetric acetylenic carotenoids using a double HWE reaction.

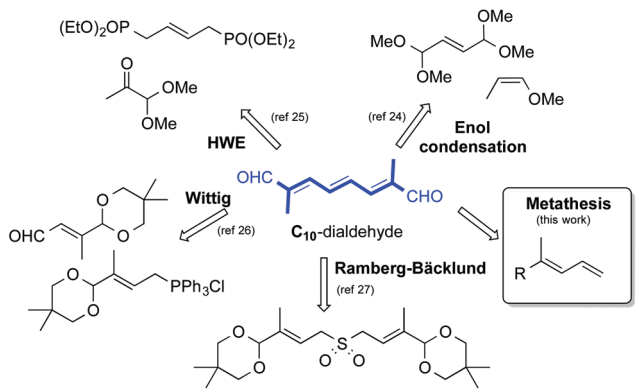
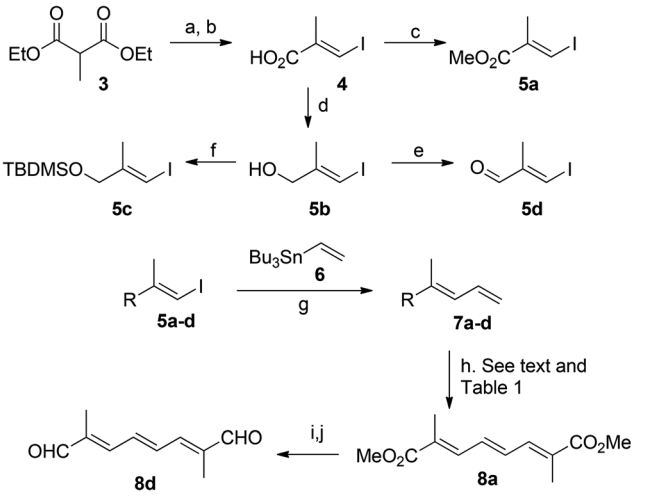


Fig. 2 Summary of the synthetic methodologies employed for the synthesis of the C_{10}-dialdehyde.

the routes followed for the preparation of the C_{10}-dialdehyde are summarized in Fig. 2. The first approach[24] relied on a double Mukaiyama condensation of an enol ether and a bis-acetal followed by hydrolysis and elimination. The industrial route developed by BASF[25] was based on a double HWE reaction of the C_4-bis-phosphonate with pyruvic aldehyde dimethylacetal, and deprotection. Alternatively, the Wittig condensation of a C_5-phosphonium salt and a C_5-aldehyde followed by hydrolysis was also employed in the industrial setting.[26] A more recent synthesis of the C_{10}-dialdehyde is based on the Ramberg–Bäcklund reaction of diallylsulphones and deprotection.[27]

As an alternative, we have explored a new approach to this triene-dialdehyde based on the metathesis reaction of precursor dienes. We[21,22] and others[28] have previously found that the acyclic metathesis/dimerization of hexaenes is a valuable method for the synthesis of highly conjugated polyenes such as the carotenoids, since it takes place with high chemoselectivity (a preference for the metathesis of the terminal monosubstituted olefin *vs.* the di-, tri- and tetrasubstituted ones). In the case of the C_{10}-trienedialdehyde, we expected a similar selectivity, but concerns about the effect of the functional group(s) on the metathesis reaction remained. Consequently the performance of the common metathesis catalysts



Scheme 1 Reagents and conditions: a. CHI_3, NaH, Et_2O, reflux, 20 h, 60%. b. KOH, EtOH–H_2O, reflux, 24 h, 69%. c. $TMSCHN_2$, MeOH, benzene, 25 °C, 5 min, 89%. d. $LiAlH_4$, THF, 25 °C, 2 h, 47%. e. MnO_2, Et_2O, 0 °C, 5 h, 76%. f. TBDMSCl, imidazole, DMF, 25 °C, 1 h, 77%. g. $Pd_2(dba)_3$, $AsPh_3$, NMP, 25 °C, 2 h, 81% **7a**, 97% **7b**, 76% **7c**, 50% **7d**. i. DIBAL-H, THF, from −78 to −20 °C. j. MnO_2, Na_2CO_3, acetone, 97% (two steps).

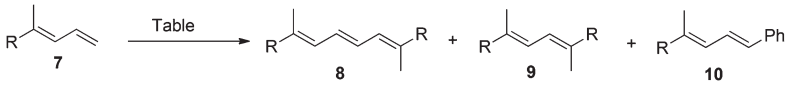
with functionalized terminal conjugated dienes that differ in the nature of the functional group (**7a–d**) was surveyed.

The synthesis of these dienes started with the known (*E*)-3-iodo-2-methacrylic acid **4** obtained from diethyl 2-methylmalonate **3** by the reaction of the enolate with iodoform and subsequent decarboxylation/elimination.[29,30] Ester formation using trimethylsilyldiazomethane in MeOH afforded **5a**, and reduction of **4** with $LiAlH_4$ gave (*E*)-3-iodo-2-methylprop-2-en-1-ol **5b**. Protection of **5b** by treatment with TBDMSCl and imidazole provided **5c**, whereas its oxidation with MnO_2 afforded aldehyde **5d** (Scheme 1). Stille cross-coupling of iodides (**5a–d**) with commercial tributylvinylstannane **6** under Farina's conditions[31] provided the corresponding terminal dienes **7**.

The metathesis–dimerization reaction was first carried out using Grubbs' second-generation catalyst in CH_2Cl_2, at 25 or 50 °C.[32] As shown in Table 1, the outcome of the reaction was found to depend on the nature of the diene functional group. In most of the cases, the desired triene product was accompanied by dienes **9** (Table 1, entries 1, 3 and 4), resulting from the cleavage of the trisubstituted double bond of the starting diene and subsequent cross-metathesis with **7**, and **10** (entries 8–10), generated by the alternative cross-metathesis with styrene (formed from the ruthenium precatalyst), as well as by partially recovered starting dienes.

Treatment of **7d** with Grubbs' second-generation catalyst in CH_2Cl_2 at room temperature for 5 h led to C_{10}-dialdehyde **8d** albeit in poor yield (12%), accompanied by minor amounts of diene **9d** and a reactant (entry 1). Due to the problems encountered with the dienal we decided to carry out the reaction at the alcohol oxidation stage. Since the conditions that had been successful before for hexaenes[21,22] (entry 2) gave disappointing yields, the reaction was performed at room tempera-

Table 1 Optimization of conditions for the homometathesis/dimerization reaction of functionalized dienes **7a–d**



Entry	R	Conditions	8a–d	9a–d	10a–d	7a–d
1	CHO (**7d**)	Grubbs II (5 mol%), CH_2Cl_2, 25 °C, 5 h.	12%	Trace[a]	—	Trace
2	CH_2OH (**7b**)	Grubbs II (5 mol%), CH_2Cl_2, 50 °C, 6.5 h.	Trace	—	—	16%[b]
3	CH_2OH (**7b**)	Grubbs II (5 mol%), CH_2Cl_2, 25 °C, 7 h.	34%	16%	—	34%
4	CH_2OH (**7b**)	Grubbs II (4 mol%), CuI (6 mol%) Et_2O, 25 °C, 7.5 h.	20%	21%	—	13%
5	$CH_2OTBDMS$ (**7c**)	Grubbs II (5 mol%), CH_2Cl_2, 50 °C, 6.5 h.	—	—	—	—
6	$CH_2OTBDMS$ (**7c**)	Grubbs II (5 mol%), CH_2Cl_2, 25 °C, 6.5 h.	—	—	—	—
7	CO_2Me (**7a**)	Grubbs II (5 mol%), CH_2Cl_2, 25 °C, 6 h.	24%	—	—	37%
8	CO_2Me (**7a**)	Grubbs II (10 mol%), CH_2Cl_2, 25 °C, 6.5 h.	59%	—	4%	9%
9	CO_2Me (**7a**)	Grubbs II (10 mol%), CH_2Cl_2, 25 °C, 22 h.	52%	—	8%	Trace
10	CO_2Me (**7a**)	Grubbs II (15 mol%), CH_2Cl_2, 25 °C, 6.5 h.[c]	64%	—	18%	11%
11	CO_2Me (**7a**)	Hoveyda–Grubbs (15 mol%), CH_2Cl_2, 25 °C, 8.5 h.	66%	—	—	—

[a] Mixture of diene **9d**, triene **8d** and starting material. [b] Mixture of isomers. [c] Catalyst degradation was observed.

ture, and this modification led to the desired product in 34% yield, although the conversion was incomplete (13% starting material was recovered) and the undesired diene **9b** was also obtained in 21% yield (entry 3). Using CuI as a cocatalyst,[33] which is considered to play a beneficial role as a catalyst activator (offering in addition faster rates and avoiding chlorinated solvents), did not improve the results. The desired triene **8b** was obtained in only 20% yield, together with similar amounts of diene **9b** (21%, entry 4). The presence of the silyl ether was detrimental and the expected product was not detected even when the reaction was carried out at room temperature (entries 5 and 6).

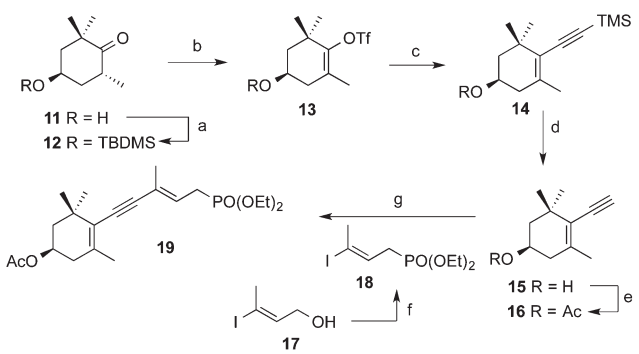
Fortunately, the yields increased when **7a** and higher amounts of the catalyst (between 10 mol% and 15 mol%) were used (entries 7–10). In these cases, we did not detect the presence of diene **9a** in the reaction mixture probably due to the electronic deactivation of the trisubstituted double bond of the substrate.[34,35] The more robust Hoveyda–Grubbs catalyst[36] led to a slight increase in yield (66%) and higher selectivity since side products were not isolated (entry 11). In all cases, the trienes were obtained as the most stable *trans* isomers with these catalysts (recent procedures with modified catalysts, however, allow the homo- and cross-coupling of (*E*)-1,3-dienes to (*E*,*Z*,*E*)-trienes[37–39]).

A parallel study on the cross-metathesis of electron-deficient polyenes (up to four double bonds) has recently been published by Sammakia *et al.*[40] These authors likewise obtained unsatisfactory results with dienals (poor selectivity for the terminal alkenes regardless of the catalyst), but also with dienoic esters (conversion to unidentified by-products). The reasons behind the contrasting results obtained with dienoates in both settings are unclear at this moment, but it is worth mentioning that Sammakia found that lower or higher vinylogous substrates (acrylate or trienoate analogues) afforded excellent yields using the less-reactive first-generation Grubbs catalyst.

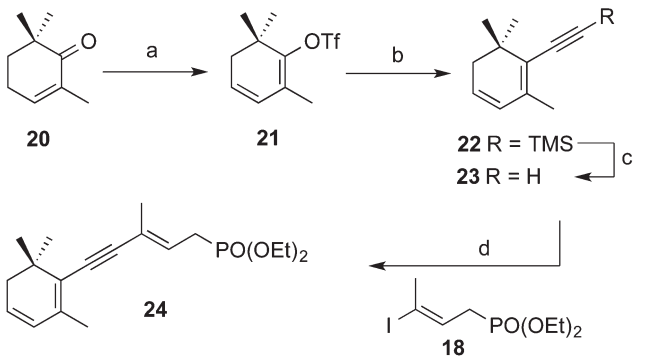
To complete the synthesis of the C_{10}-dialdehyde, treatment of trienoate **8a** with DIBAL-H followed by oxidation of the trienol **8b** with MnO_2 under basic conditions afforded **8d** in 97% combined yield (10% overall yield for the seven-steps sequence, Scheme 1; for larger scale approaches to **8d**, see Scheme 5 below).[41,42]

The synthesis of the C_{15} fragment required for the synthesis of alloxanthin **1** started from the known terminal alkyne **16**[16,43,44] derived from (−)-actinol **11**[45] by a modified procedure. Treatment of the *tert*-butyldimethylsilyl ether of (−)-actinol **12** in the presence of LDA with *N*-phenyltrifluoromethanesulfonimide (Tf_2NPh) gave the enoltriflate **13**,[46] which underwent a Sonogashira coupling with TMS-acetylene to afford alkyne **14**. Subsequent silyl deprotection followed by acetylation afforded acetate **16**[16,43,44] in good yield. Sonogashira coupling of alkyne **16** with diethyl (*E*)-3-iodobut-2-enylphosphonate **18**, which was prepared from vinyliodide **17** in 84% yield following the procedure of Wiemer,[47] provided the desired phosphonate **19** in 73% yield. The overall yield for the six-step synthesis of phosphonate **19** from (−)-actinol **11** was 45% (Scheme 2).

An analogous sequence allowed the preparation of phosphonate **24** required for the synthesis of 3,4,7,8,3′,4′,7′,8′-



Scheme 2 Reagents and conditions: a. TBDMSCl, imidazole, DMF, 25 °C, 6 h, 98%. b. LDA, Tf_2NPh, THF, −78 to 0 °C, 14 h, 87%. c. TMS-acetylene, K_2CO_3, $Pd(PPh_3)_4$, DMF, 60 °C, 95%. d. *n*-Bu_4NF, THF, 25 °C, 2.5 h, 99%. e. Ac_2O, pyridine, 25 °C, 14 h, 77%. f. ZnI_2, $P(OEt)_3$, THF, 85 °C, 16 h, 84%. g. $Pd(PPh_3)_4$, CuI, Et_3N, THF, 25 °C, 4 h, 73%.



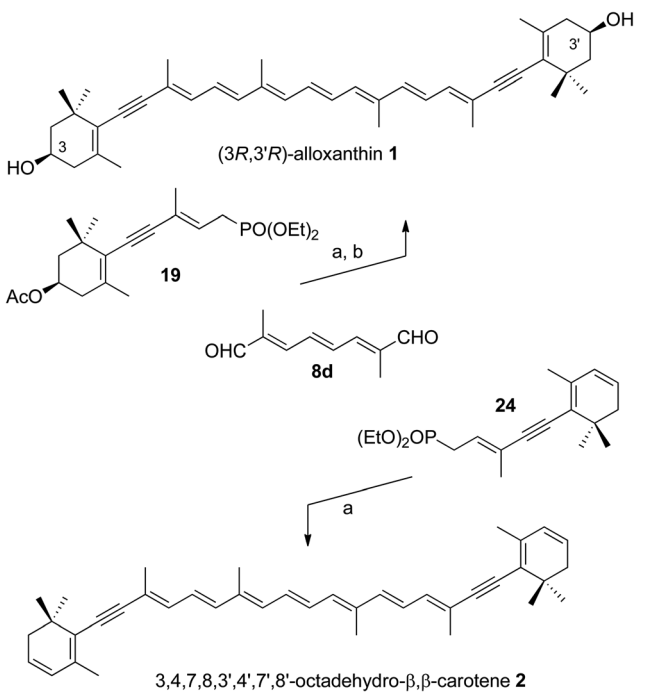
Scheme 3 Reagents and reaction conditions: a. iPr_2NH, *n*BuLi, HMPA; then Tf_2NPh, THF, 66%. b. TMS-acetylene, K_2CO_3, $Pd(PPh_3)_4$, DMF, 93%. c. TBAF, 40 min, 25 °C, 79%. d. $Pd(PPh_3)_4$, CuI, Et_3N, THF, 25 °C, 66%.

octadehydro-β,β-carotene **2**. The transformation of 2,2,6-trimethylcyclohex-2-en-1-one **20** into dienyl triflate **21**[48] and the subsequent Sonogashira coupling to TMS-acetylene followed by deprotection of the alkyne provided the C_{11} terminal alkyne **23**. The C_{15}-phosphonate was prepared by a second Sonogashira coupling reaction of **23** with phosphonate **18**, which produced **24** as a single stereoisomer (Scheme 3).

Finally, the bi-directional HWE reaction between two units of appropriate C_{15}-phosphonates **19** or **24** and C_{10}-dialdehyde **8d** was performed using NaHMDS in THF, and led to the expected (3*R*,3′*R*)-diacetylalloxanthin and 3,4,7,8,3′,4′,7′,8′-octadehydro-β,β-carotene **2** (Scheme 4). The former was converted under mild conditions (MeLi, Et_2O, −15 °C) into *all-trans*-(3*R*,3′*R*)-alloxanthin **1** in 78% (combined) yield.

All-*trans*-3,4,7,8,3′,4′,7′,8′-octadehydro-β,β-carotene **2** has been isolated, admixed with the 9*Z* and 9*Z*,9′*Z* isomers, from the euglenophyte alga *Euglena viridis*,[49] and from the sponge *Polymastia granulosa*.[50] The NMR spectroscopic data of our synthetic 3,4,7,8,3′,4′,7′,8′-octadehydro-β,β-carotene **2** could not be compared with the existing ^{1}H-NMR literature data, since these are reported in $CDCl_3$.[49] In our experience traces of acid formed adventitiously when this solvent is used with these polyenes rapidly catalyze the stereomutation of the all-*trans* to the thermodynamically more stable (9*Z*,9′*Z*)-7,8,7′,8′-bis-acetylenic carotenoid isomer. To ensure that the geometry of the synthetic product **2** was the desired one, and that the reaction conditions had not induced the formation of the thermodynamically more stable (9*Z*,9′*Z*) stereoisomer or of a mixture of isomers, as is commonly found in substrates endowed with the C7–C10 enyne skeleton (for example, pyrrhoxanthin[15]), NOE correlations in C_6D_6 solution (shown in ESI†) demonstrated that carotenoid **2** had been acquired with total stereocontrol.

Alloxanthin **1** was the first acetylenic carotenoid isolated from dinoflagellates of the algal class *Cryptophyceae*.[51] Chromatographic comparison of natural extracts from microalgae *Rhodomonas lens* containing alloxanthin in its lipophilic pigment signature, with the synthetic (3*R*,3′*R*)-alloxanthin described in this work (Fig. 3) provided additional proof of the all-*trans* geometry of the synthetic carotenoid, also confirmed by NOE correlations (see ESI†). The first synthesis of this xanthophyll employed a bi-directional Wittig condensation of C_{10}-dialdehyde **8d** and C_{15}-tri-triphenylphosphoranes and afforded in low yield (7%) a mixture of the all-*trans* and 9-*cis* isomers in roughly equal amounts.[14] The recent approach to (3*R*,3′*R*)-alloxanthin **1** using a bi-directional Wittig condensation of C_{10}-dialdehyde **8d** and analogous C_{15}-tri-*n*-butylphosphoranes[16] was, similar to the HWE reported here, also stereoselective.



Scheme 4 Reagents and conditions: a. NaHMDS, THF, −78 °C, 1 h, 47% for **2**. b. MeLi, Et_2O, −15 °C, 30 min, 78% for **1** (two steps).

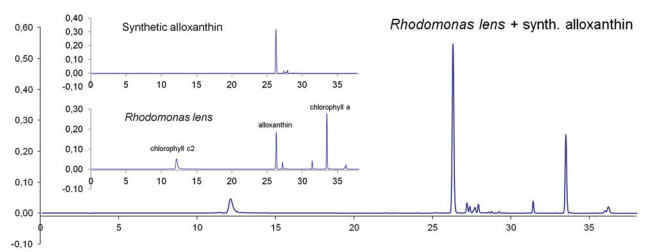


Fig. 3 HPLC chromatogram obtained from the mixture of a natural extract and a sample of synthetic (3*R*,3′*R*)-alloxanthin **1**. The method was run in a C_8 monomeric column using aqueous pyridine as a mobile phase modifier, showing the co-elution of natural and synthetic alloxanthin (26.2 min). The inset shows also the chromatograms obtained from the synthetic carotenoid (top) and the natural extract (bottom) under the same chromatographic method.

Summary and conclusions

The HWE condensation reaction using a synthetic scheme based on a C_{15} + C_{10} + C_{15} pattern has been demonstrated to be a powerful tool for the preparation of the configurationally labile C_{40} symmetrical carotenoids that possess C7,C8 alkyne moieties inserted into their polyenic structures. A new stereocontrolled synthesis of (3*R*,3′*R*)-alloxanthin **1**, and the first stereocontrolled synthesis of highly unsaturated 3,4,7,8,3′,4′,7′,8′-octadehydro-β,β-carotene **2** have been achieved using as common fragments a central C_{10}-dialdehyde and terminal C_{15}-phosphonates. The former was made by metathesis/dimerization of the precursor dienoate followed by functional group interconversions. C_{15}-phosphonates were stereoselectively synthesized using consecutive Pd/Cu-cocatalyzed Sonogashira reactions of TMS-acetylene, the first to attach the unsaturated cyclic end group and the second to connect the allylphosphonate. The otherwise facile isomerization of the C9–C10 double bond (carotenoid numbering) was prevented using this scheme. Compared to traditional condensation reactions (Wittig or Julia/Julia–Kocienski olefination reactions),[1] the improved stereoselectivity, the ready availability of the precursor phosphonates, as well as the easy removal of secondary by-products (phosphoric acid/esters) make the HWE reaction highly recommended for the formation of disubstituted double bonds in polyenes, in particular for the construction of the C11═C12 bond as the last step in the total synthesis of carotenoids.

Experimental

Dimethyl (2*E*,4*E*,6*E*)-2,7-dimethylocta-2,4,6-trienedioate 8a

To a degassed solution of methyl (*E*)-2-methylpenta-2,4-dienoate **5a** (0.068 g, 0.054 mmol) in CH_2Cl_2 (10 mL) was added the Hoveyda–Grubbs catalyst (0.051 g, 0.081 mmol). After stirring at 25 °C for 8.5 h the solvent was evaporated and the residue was purified by column chromatography (silica gel, from 95 : 5 hexane–EtOAc to 90 : 10 hexane–EtOAc) to afford 0.040 g (66%) of a white solid identified as dimethyl (2*E*,4*E*,6*E*)-2,7-dimethylocta-2,4,6-trienedioate **8a**.[17] ^{1}H-NMR (400.13 MHz, $CDCl_3$): δ 7.28 (ddd, J = 7.8, 2.9, 1.3 Hz, 2H, H_3 + H_6), 6.79 (dd, J = 7.8, 3.0 Hz, 2H, H_4 + H_5), 3.77 (s, 6H, 2 × OCH_3), 2.00 (d, J = 1.2 Hz, 6H, 2 × CH_3) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ 168.6 (s, 2×), 137.5 (d, 2×), 133.7 (d, 2×), 130.1 (s, 2×), 52.1 (c, 2×), 13.1 (c, 2×) ppm.

(*E*)-Diethyl (3-iodobut-2-en-1-yl)phosphonate 18

To a solution of ZnI_2 (1.03 g, 3.23 mmol) in THF (1.6 mL) was added triethyl phosphite (1 mL, 6.45 mmol), and a solution of (*E*)-3-iodobut-2-en-1-ol **17** (0.43 g, 2.15 mmol) in THF (1.8 mL) *via* cannula. After stirring overnight at 85 °C, the solvent was evaporated and the reaction mixture was washed with a 2 M aqueous solution of NaOH (3×). The aqueous layer was extracted with Et_2O (3×) and the combined organic layers were dried (Na_2SO_4) and the solvent removed. Purification by column chromatography (C-18 silica gel, 55 : 45 CH_3CN–H_2O) afforded 0.58 g (84%) of a colorless oil identified as diethyl (*E*)-(3-iodobut-2-en-1-yl)phosphonate **18**. ^{1}H-NMR (400.13 MHz, $CDCl_3$): δ 6.11 (dtq, J = 6.5, 1.4 Hz, $^3J_{H-P}$ = 8.0, 1H, H_2), 4.14–3.96 (m, 4H, 2 × $CO_2CH_2CH_3$), 2.49 (ddd, J = 8.0, 1.0 Hz, $^2J_{H-P}$ = 21.9 Hz, 2H, $2H_1$), 2.34 (d, $^5J_{H-P}$ = 4.4 Hz, 3H, CH_3), 1.26 (t, J = 7.1 Hz, 6H, 2 × $CO_2CH_2CH_3$) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ 129.1 (d, $^2J_{P-C}$ = 10.8 Hz), 97.6 (s, $^3J_{P-C}$ = 17.7 Hz), 62.1 (t, $^2J_{P-C}$ = 6.8 Hz, 2×), 28.9 (t, $^1J_{P-C}$ = 141.0 Hz), 27.7 (q, $^4J_{P-C}$ = 2.5 Hz), 16.5 (q, $^3J_{P-C}$ = 6.0 Hz, 2×) ppm. HRMS (ESI^+): calcd for $C_8H_{17}IO_3P$ ($[M + H]^+$), 318.9954; found, 318.9958. IR (NaCl): ν 2980 (m, C–H), 2919 (w, C–H), 1390 (w), 1253 (s) cm^{-1}.

(*R*,*E*)-4-[5′-(Diethoxyphosphoryl)-3′-methylpent-3′-en-1-ynyl]-3,5,5-trimethylcyclohex-3-enyl acetate 19

To a degassed solution of $Pd(PPh_3)_4$ (3.9 mg, 0.003 mmol) in THF (0.5 mL) was added CuI (1.9 mg, 0.010 mmol). To this reaction mixture were added a degassed solution of diethyl (*E*)-3-iodobut-2-enylphosphonate **18** (0.032 g, 0.112 mmol) in THF (1.0 mL), freshly distilled Et_3N (0.039 mL, 0.280 mmol) and a solution of (*R*)-4-ethynyl-3,5,5-trimethylcyclohex-3-enyl acetate **16**[16,43,44] (0.030 g, 0.145 mmol) in THF (1.0 mL). The mixture was stirred for 4 h at 25 °C, then the mixture was filtered through a pad of Celite® and the solvent was evaporated. The residue was purified by column chromatography (silica gel-NH_2, from 90 : 10 hexane–CH_2Cl_2 to CH_2Cl_2) to afford 0.03 g (73%) of an oil identified as (*R*,*E*)-4-[5-(diethoxyphosphoryl)-3-methylpent-3-en-1-ynyl]-3,5,5-trimethylcyclohex-3-enyl acetate **19**. ^{1}H-NMR (400.13 MHz, C_6D_6): δ 6.03 (q, J = 8.2 Hz, $^3J_{H-P}$ = 1.5 Hz, 1H, $H_{4'}$), 5.19–5.11 (m, 1H, H_1), 3.95–3.84 (m, 4H, 2 × OCH_2CH_3), 2.47 (d, J = 8.2 Hz, $^2J_{H-P}$ = 23.0 Hz, 2H, $H_{2'}$), 2.29 (dd, J = 17.6, 5.6 Hz, 1H, H_2), 1.97 (dd, J = 17.6, 9.1 Hz, 1H, H_2), 1.83–1.78 (m, 7H, H_6 + 2 × CH_3), 1.71 (s, 3H, CH_3), 1.51 (t, J = 11.9 Hz, 1H, H_6), 1.23 (s, 3H, CH_3), 1.19 (s, 3H, CH_3), 1.01 (t, J = 7.1 Hz, 6H, OCH_2CH_3) ppm. ^{13}C-NMR (100.62 MHz, C_6D_6): δ 169.7 (s), 136.7 (s, $^6J_{C-P}$ = 1.4 Hz), 125.2 (d, $^2J_{C-P}$ = 12.7 Hz), 124.6 (s, $^5J_{C-P}$ = 3.3 Hz), 122.8 (s, $^2J_{C-P}$ = 15.4 Hz), 96.9 (s, $^4J_{C-P}$ = 6.5 Hz), 86.2 (s, $^7J_{C-P}$ = 1.3 Hz), 67.8 (d), 61.8 (t, $^3J_{C-P}$ = 6.7 Hz, 2×), 42.7 (t), 37.6 (t), 36.3 (s), 30.4 (q), 28.8 (q), 27.9 (t, $^1J_{C-P}$ = 140.0 Hz), 22.4 (q), 21.0 (q), 17.9 (q, $^4J_{C-P}$ = 2.9 Hz), 16.5 (q, $^3J_{C-P}$ = 5.7 Hz, 2×) ppm. MS (EI): m/z (%). HRMS (ESI^+): calcd for $C_{21}H_{34}O_5P$ ($[M + H]^+$), 397.2152; found, 397.2132. IR (NaCl): ν 2965 (m, C–H), 2927 (m, C–H), 1736 (s, C═O), 1442 (w), 1365 (m), 1241 (s), 1027 (s) cm^{-1}. $[\alpha]_D^{26}$ −39.5 (c 0.895, MeOH).

Trimethyl[(2,6,6-trimethylcyclohexa-1,3-dien-1-yl)ethynyl]-silane 22

To a degassed solution of 1-[(trifluoromethanesulfonyl)oxy]-2,6,6-trimethylcyclohexa-1,3-diene **21**[48] (0.7 g, 2.59 mmol) in DMF (31.2 mL) was added $Pd(PPh_3)_4$ (299 mg, 0.26 mmol) followed by anhydrous K_2CO_3 (1.07 g, 7.78 mmol), and trimethylsilylacetylene (1.1 mL, 7.78 mmol). After stirring for 5 h at 60 °C, Et_2O was added and the organic layer was washed with H_2O (3×). The combined organic layers were dried (Na_2SO_4) and the solvent was evaporated. The residue was purified by

column chromatography (silica gel, hexane) to afford 0.57 g (93%) of a pale yellow oil identified as trimethyl[(2,6,6-trimethylcyclohexa-1,3-dien-1-yl)ethynyl]silane **22**. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 5.86 (dt, J = 9.6, 1.5 Hz, 1H, H_3), 5.80 (dt, J = 9.6, 4.2 Hz, 1H, H_4), 2.09 (dd, J = 4.2, 1.5 Hz, 2H, $2H_5$), 1.95 (s, 3H, CH_3), 1.07 (s, 6H, 2 × CH_3), 0.21 (s, 9H, 3 × CH_3). ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 137.6 (s), 127.7 (d), 126.8 (d), 123.6 (s), 103.8 (s), 101.7 (s), 38.2 (t), 32.4 (s), 27.0 (q, 2×), 20.7 (q), 0.2 (q, 3×). IR (NaCl): ν 2958 (s, C–H), 2128 (s, C≡C), 859 (s, Si–C), 842 (s, Si–C) cm^{-1}. HRMS (ESI$^+$): calcd for $C_{14}H_{23}Si$ ([M + H]$^+$), 219.1564; found, 219.1569.

1-Ethynyl-2,6,6-trimethylcyclohexa-1,3-diene 23. To a solution of trimethyl[(2,6,6-trimethylcyclohexa-1,3-dien-1-yl)-ethynyl]silane **22** (0.53 g, 2.42 mmol) in THF (24 mL) was added TBAF (3.63 mL, 1 M in hexane, 3.63 mmol). After stirring for 40 min at 25 °C the reaction mixture was poured over a saturated aqueous $NaHCO_3$ solution and extracted with Et_2O (3×). The combined organic layers were dried (Na_2SO_4) and the solvent was evaporated. Purification by column chromatography (silica gel, hexane) afforded 0.28 g (79%) of a yellow oil identified as 1-ethynyl-2,6,6-trimethylcyclohexa-1,3-diene **23**. ^{1}H-NMR (400.13 MHz, $CDCl_3$): δ 5.87 (dt, J = 9.6, 1.4 Hz, 1H, H_3), 5.83 (dt, J = 9.6, 4.0 Hz, 1H, H_4), 3.32 (s, 1H), 2.11 (dd, J = 4.0, 1.4 Hz, 2H, $2H_5$), 1.96 (s, 3H, C_2–CH_3), 1.09 (s, 6H, 2 × C_6–CH_3). ^{13}C-NMR (100.62 MHz, $CDCl_3$): δ 138.1 (s), 127.6 (d), 126.9 (d), 122.6 (s), 110.0 (s), 84.1 (d), 38.1 (t), 32.4 (s), 26.9 (q, 2×), 20.5 (q). IR (NaCl): ν 3306 (s, C≡C–H), 2958 (s, C–H), 2920 (s, C–H), 2859 (s, C–H), 2080 (w, C≡C) cm^{-1}.

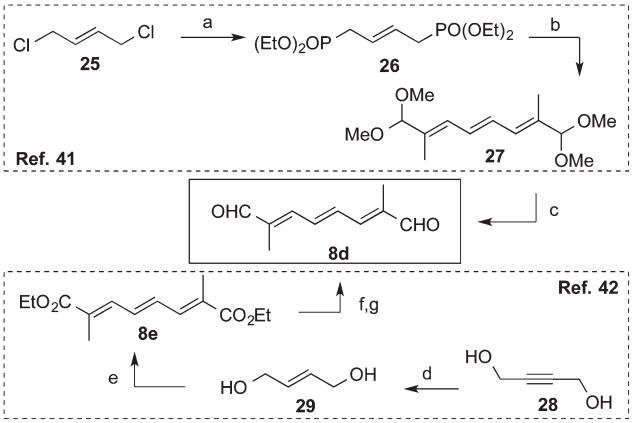
Diethyl (*E*)-[3-methyl-5-(2,6,6-trimethylcyclohexa-1,3-dien-1-yl]-pent-2-en-4-yn-1-yl)phosphonate 24

To a degassed solution of $Pd(PPh_3)_4$ (14.0 mg, 0.01 mmol) in THF (1.4 mL) was added CuI (6.8 mg, 0.036 mmol) and a solution of **18** (127 mg, 0.40 mmol) in THF (2.8 mL) *via* cannula. To the described mixture was added Et_3N (0.14 mL, 1.00 mmol) and a solution of 1-ethynyl-2,6,6-trimethylcyclohexa-1,3-diene **23** (87.6 mg, 0.60 mmol) in THF (2.8 mL). The reaction mixture was stirred for 2 h 30 min at 25 °C. Then it was filtered with AcOEt through a pad of Celite® and the solvent was evaporated. The residue was purified by column chromatography (C-18 silica gel, from 65 : 35 to 100 : 0 CH_3CN–H_2O) to afford 88.8 mg (66%) of a pale yellow oil identified as diethyl (*E*)-[3-methyl-5-(2,6,6-trimethylcyclohexa-1,3-dien-1-yl]-pent-2-en-4-yn-1-yl)phosphonate **24**. ^{1}H-NMR (400.13 MHz, C_6D_6): δ 6.12–6.00 (m, 1H, $H_{4'}$), 5.79 (dt, J = 9.5, 1.7 Hz, 1H, $H_{3'}$), 5.63 (dt, J = 9.3, 4.5 Hz, 1H, H_2), 3.97–3.83 (m, 4H, 2 × O$CH_2$$CH_3$), 2.49 (dd, J = 23.6, 8.3 Hz, 2H, $2H_1$), 1.98 (dd, J = 4.5, 1.7 Hz, 2H, $2H_{5'}$), 1.96 (s, 3H, $C_{2'}$–CH_3), 1.82 (d, J = 4.5 Hz, 3H, C_3–CH_3), 1.18 (s, 6H, 2 × C_6–CH_3), 1.01 (t, J = 6.9 Hz, 6H, 2 × OCH_2CH_3) ppm. ^{13}C-NMR (100.62 MHz, C_6D_6): δ 136.3 (s, J_{P-C} = 2.0 Hz), 127.9 (d), 126.5 (d), 125.2 (d, $^2J_{P-C}$ = 12.8 Hz), 124.6 (s, J_{P-C} = 2.1 Hz), 123.0 (s, J_{P-C} = 15.9 Hz), 100.4 (s, J_{P-C} = 6.5 Hz), 87.2 (s, J_{P-C} = 3.6 Hz), 61.7 (t, J_{P-C} = 6.4 Hz), 38.5 (t), 33.2 (s), 27.9 (t, $^1J_{P-C}$ = 139.3 Hz), 20.4 (q, 2×), 17.9 (q, J_{P-C} = 2.8 Hz), 16.5 (q, J_{P-C} = 5.5 Hz, 2×) ppm. IR (NaCl): ν 2966 (s, C–H), 2912 (s, C–H), 2865 (s, C–H), 1251 (m, P=O), 1050–1027 (s, P–O–C) cm^{-1}. HRMS (ESI$^+$): calcd for $C_{19}H_{29}NaO_3P$ ([M + H]$^+$), 359.1747; found, 359.1745.

(3*R*,3′*R*)-Alloxanthin 1. To a cooled (−78 °C) solution of (*R*,*E*)-4-[5-(diethoxyphosphoryl)-3-methylpent-3-en-1-ynyl]-3,5,5-trimethylcyclohex-3-enyl acetate **19** (28 mg, 0.070 mmol) in THF (0.9 mL) was added NaHMDS (0.08 mL, 1 M in hexane, 0.08 mmol). After stirring for 30 min, a solution of (2*E*,4*E*,6*E*)-2,7-dimethylocta-2,4,6-triene-1,8-dial **8d** (5.2 mg, 0.032 mmol) in THF (1.1 mL) was added. After stirring for 2 h at the same temperature a saturated aqueous solution of NH_4Cl was added and the mixture was extracted with a 90 : 10 EtOAc–CH_2Cl_2 mixture. The combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$, dried (Na_2SO_4) and the solvent was evaporated. The residue was used in the next reaction without further purification. To a cooled (−15 °C) solution of alloxanthin acetate (0.021 g, 0.032 mmol) in Et_2O (0.5 mL) was added MeLi (0.1 mL, 1.6 M, 0.16 mmol) and the mixture was stirred for 30 min at the same temperature. Then the mixture was warmed to 25 °C and a solution of saturated aqueous solution of $NaHCO_3$ was added. The mixture was extracted with a 90 : 10 EtOAc–CH_2Cl_2 mixture, dried (Na_2SO_4) and the solvent was evaporated. The residue was purified by column chromatography (C18 silica gel, CH_3CN) to afford 14 mg (78%) of a red solid identified as (3*R*,3′*R*)-alloxanthin **1**. ^{1}H-NMR (400.13 MHz, C_6D_6): δ 6.79 (d, J = 11.4 Hz, 2H, $2H_{10}$), 6.64–6.55 (m, 4H, $2H_{11}$ + $2H_{14}$), 6.36 (d, J = 14.8 Hz, 2H, $2H_{12}$), 6.27–6.24 (m, 2H, $2H_{15}$), 3.75–3.68 (m, 2H, $2H_3$), 2.16 (dd, J = 18.2, 5.1 Hz, 2H, $2H_4$), 1.98 (s, 6H, 2 × CH_3), 1.92 (s, 6H, 2 × CH_3), 1.88 (dd, J = 18.2, 8.3 Hz, 2H, $2H_4$), 1.79 (s, 6H, 2 × CH_3), 1.65 (ddd, J = 12.2, 3.2, 1.7 Hz, 2H, $2H_2$), 1.39 (d, J = 12.0 Hz, 2H, $2H_2$), 1.35 (s, 6H, 2 × CH_3), 1.23 (s, 6H, 2 × CH_3) ppm. ^{13}C-NMR (100.62 MHz, C_6D_6): δ 138.5 (d, 2×), 137.8 (s, 2×), 136.7 (s, 2×), 135.7 (d, 2×), 134.1 (d, 2×), 130.9 (d, 2×), 124.8 (s, 2×), 124.7 (d, 2×), 119.7 (s, 2×), 99.2 (s, 2×), 90.2 (s, 2×), 64.5 (d, 2×), 47.0 (t, 2×), 41.7 (t, 2×), 36.8 (s, 2×), 30.9 (q, 2×), 29.0 (q, 2×), 22.7 (q, 2×), 18.3 (q, 2×), 12.9 (q, 2×) ppm. HRMS (ESI$^+$): calcd for $C_{40}H_{53}O_2$ ([M + H]$^+$), 565.4040; found, 565.4039. $[\alpha]_D^{24}$ −106.0 (*c* 0.01, $CHCl_3$).

3,4,7,8,3′,4′,7′,8′-Octadehydro-β,β-carotene 2

To a cooled (−78 °C) solution of diethyl (*E*)-[3-methyl-5-(2,6,6-trimethylcyclohexa-1,3-dien-1-yl]pent-2-en-4-yn-1-yl)phosphonate (C_{15}-alkynylphosphonate) **24** (24.5 mg, 0.07 mmol) in THF (1 mL) was added NaHMDS (0.083 mL, 1 M in hexane, 0.08 mmol). After stirring for 30 min, a solution of (2*E*,4*E*,6*E*)-2,7-dimethylocta-2,4,6-triene-1,8-dial **8d** (5.4 mg, 0.03 mmol) in THF (1 mL) was added. The mixture was stirred at −78 °C for 1.5 h. Then, a saturated aqueous solution of NH_4Cl was added at −78 °C and the mixture was allowed to reach room temperature and extracted with 90 : 10 EtOAc–CH_2Cl_2. The combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$, dried (Na_2SO_4) and the solvent was evaporated. The crude was purified by column chromatography (silicagel-CN, from 100 : 0 to 90 : 10 hexane–EtOAc) afforded 8.2 mg (47%) of an orange solid identified as octadehydro-β,β-carotene **2**. ^{1}H-NMR (400.13 MHz, C_6D_6): δ 6.81 (d,



Scheme 5 Reagents and reaction conditions: a. $P(OEt)_3$, from 25 to 180 °C, 97%. b. Methyl glyoxal dimethyl acetal, *t*-BuOK, THF-DMSO, 56%. c. Acid-catalyzed acetal removal (see text). d. $LiAlH_4$, THF, 85 °C, 87%. e. MnO_2, ethyl 2-(triphenyl-λ^5-phosphanylidene)propanoate, Na_2CO_3, CH_2Cl_2, from 0 to 25 °C, 74%. f. DIBAL-H, THF, from −78 to −20 °C. g. MnO_2, Na_2CO_3, acetone.

J = 11.4 Hz, 2H, H_{10} + $H_{10'}$), 6.63 (dd, J = 8.0, 2.9 Hz, 2H, H_{14} + $H_{14'}$), 6.60 (dd, J = 14.9, 11.4 Hz, 2H, H_{11} + $H_{11'}$), 6.37 (d, J = 14.9 Hz, 2H, H_{12} + $H_{12'}$), 6.26 (dd, J = 8.0, 2.0 Hz, 2H, H_{15} + $H_{15'}$), 5.86 (dt, J = 9.5, 1.9 Hz, 2H, H_4 + $H_{4'}$), 5.67 (dt, J = 9.5, 4.5 Hz, 2H, H_3 + $H_{3'}$), 2.07 (s, 3H, CH_3), 2.03 (dd, J = 4.5, 1.9 Hz, 4H, $2H_2$ + $2H_{2'}$), 1.99 (d, J = 2.0 Hz, 6H, 2 × CH_3), 1.79 (s, 6H, 2 × CH_3), 1.28 (s, 12H, 4 × CH_3). ^{13}C-NMR (100.62 MHz, C_6D_6): δ 138.6 (d, 2×), 136.8 (s, 2×), 136.4 (s, 2×), 135.9 (d, 2×), 134.2 (d, 2×), 131.0 (d, 2×), 128.7 (d, 2×), 126.7 (d, 2×), 125.1 (s, 2×), 124.8 (d, 2×), 119.8 (s, 2×), 103.3 (s, 2×), 91.2 (s, 2×), 38.6 (t, 2×), 33.4 (s, 2×), 27.5 (q, 4×), 20.9 (q, 2×), 18.2 (q, 2×), 12.8 (q, 2×) ppm. IR (NaCl): ν 3031 (w, C–H), 2956 (s, C–H), 2919 (s, C–H), 2857 (w, C–H), 2148 (w, C≡C) cm^{-1}. UV (MeOH)(ε M^{-1} cm^{-1}): λ_{max} 380 (547 000); 470 (453 000). HRMS (ESI$^+$): calcd for $C_{40}H_{48}$ ([M + H]$^+$), 528.3750; found, 528.3749.

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