JOURNAL OF NATURAL PRODUCTS

Article

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Stereoselective Synthesis by Olefin Metathesis and Characterization of η-Carotene (7,8,7′,8′-tetrahydro-β,β-carotene)

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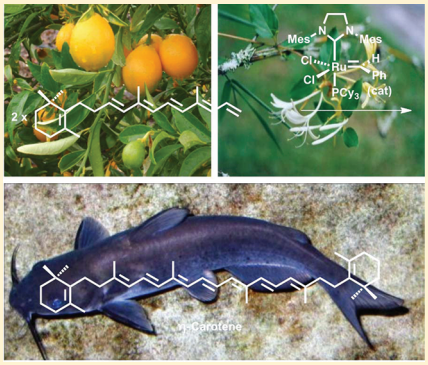
Supporting Information

ABSTRACT: The purported structure of the elusive η-carotene (7,8,7′,8′-tetrahydro-β,β-carotene), a natural C_{40} carotenoid first detected in the berries of *Lonicera japonica* and in citrus fruits sixty years ago, has been synthesized by olefin cross-metathesis/dimerization of a C_{21} polyene derived from *trans*-7,8-dihydroretinal, thus allowing the full characterization of this highly unstable natural product.



A number of the more than 700 different carotenoids isolated thus far[1−3] are incompletely characterized due to their instability or as a consequence of the scarcity of material isolated from the natural source. 7,8,7',8'-Tetrahydro-β,β-carotene (η-carotene; **1g**) (Figure 1) stands out from the subgroup of carotenoids whose identity remains uncertain. It was isolated sixty years ago as a very minor carotenoid (1.3%) from berries of *Lonicera japonica*[4] and later also from the flavedo of the fruit of the trigeneric hybrid Sinton citrangequat[5] and other citrus fruits[6−8] and in the Siluridae family of catfish.[9] However, only UV absorption data and insufficient (signals in the aliphatic region, δ ∼1.01−2.12 ppm) ^{1}H NMR data[9] have been reported; thus, no confirmation of its structure has been provided. Moreover, the presence of η-carotene in natural sources appears to depend upon the ripening period of the fruits, and therefore "a full investigation into this pigment must await the availability of larger amounts of ripe *Lonicera* berries at a time when it is feasible to examine them".[4] Synthesis is invaluable in providing larger amounts of material to fully characterize and confirm or correct the proposed structures of natural products.

The inherent instability of carotenoids derives from the reactive nature of the highly conjugated polyene skeleton when subjected to a variety of reaction conditions. In contrast, the producing organisms exquisitely handle the basic C_{40} tetraterpenoid and also the diverse carotenoids generated by biosynthetic modifications including cyclizations, oxidations, dehydrogenations, and rearrangement reactions. The photophysical and photochemical properties of these polyenes are responsible for much of the coloration in Nature, as well as for the photoprotection of plants and microorganisms, where they also function as accessory pigments in photosynthesis.[10] Unable to biosynthesize carotenoids, humans ingest them in the diet, and we may use their antioxidant properties for prevention of certain cardiovascular diseases and cancer.[10]

In the past few years palladium-catalyzed cross-coupling processes[11] (primarily Negishi,[12,13] Stille,[14] and Suzuki[15]) for C−C single bond formation have found a niche in the polyene field, as they complement traditional C−C double bond condensation methods such as Wittig, Horner−Wadsworth−Emmons (HWE), and Julia−Kocienski olefination reactions.[16,17] Olefin metathesis[18−21] is a powerful tactic for the preparation of a great variety of natural products[22,23] and its use has been extended to the synthesis of the conjugated carotenoid polyene chain.[24,25] Four fully conjugated C_{40} undecaene carotenoids, namely, β,β-carotene (**1a**), (*R*,*R*)-zeaxanthin (**1b**), *rac*-iso-zeaxanthin (**1c**), and lycopene (ψ,ψ-carotene; **1d**)[25] (Figure 1), and two symmetrical conjugated nonaene carotenoids, namely, violaxanthin (**1e**) and mimulaxanthin (**1f**),[24] have been prepared by metathesis−dimerization of precursors **2a**−**f**.

In this $C_{21} + C_{21} - C_2 = C_{40}$ approach to carotenoids **1**, the C_{21} heptaene/hexaene precursors **2** are obtained by Wittig olefination of *trans*-retinal and ring/chain-modified or acyclic analogues.[25] Application of the same strategy to η-carotene (**1g**) requires the preparation of stereochemically homogeneous nonconjugated hexaene **2g**, itself obtained from 7,8-dihydroretinal (**12**) (Scheme 1). Compounds with the general 7,8-dihydroretinal structure but with 11-*cis* geometry have been described previously,[26] but no synthesis of the *trans* isomer has been reported.

Received: March 26, 2012
Published: May 15, 2012

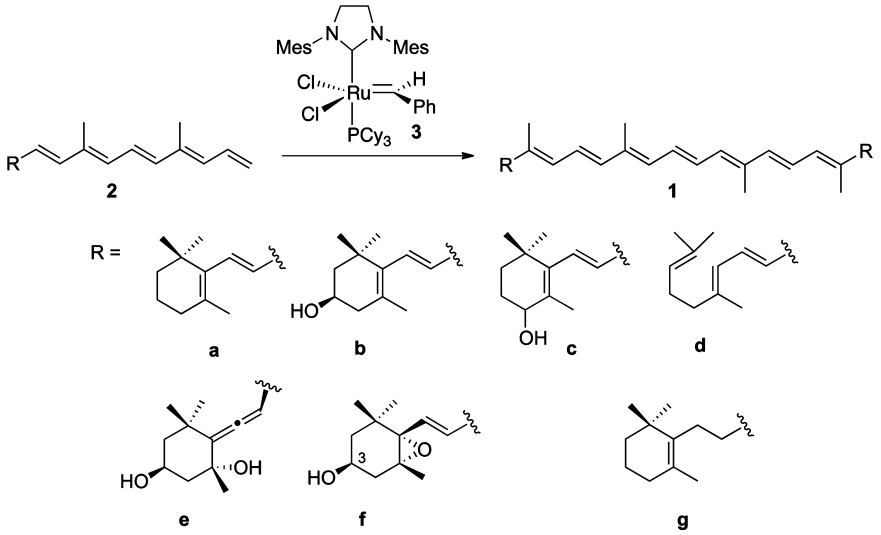
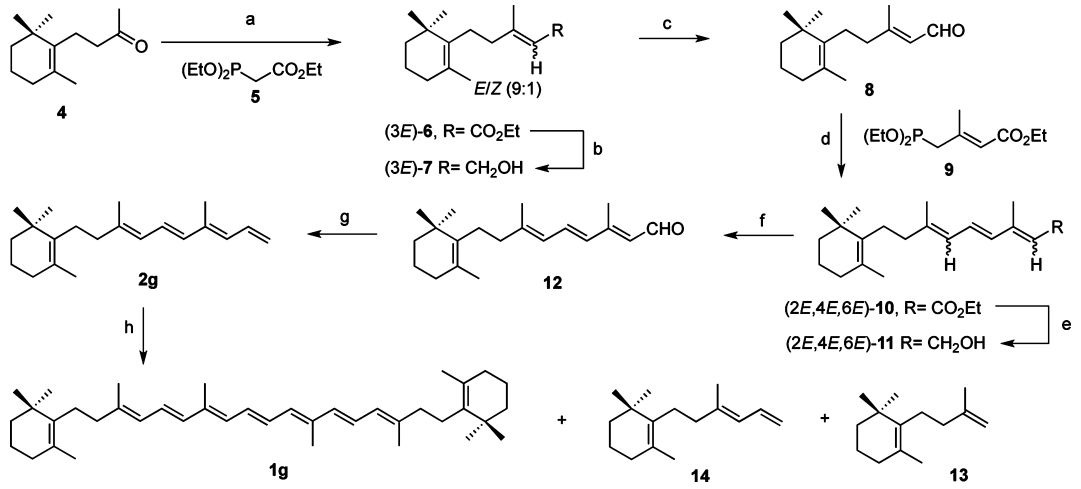


Figure 1. Symmetrical carotenoids **1a–f** previously prepared by acyclic cross-metathesis/dimerization and the proposed structure of *η*-carotene (**1g**).

Scheme 1[a]



[a]Reagents and conditions: (a) *n*-BuLi, DMPU, THF, −78 °C, 47 h, 90%, 9:1 *E/Z*; (b) DIBAL-H, THF, −78 °C, 30 min, 97%; (c) MnO_2, Na_2CO_3, CH_2Cl_2, 25 °C, 3 h, 85%; (d) *n*-BuLi, DMPU, THF, −78 to 25 °C, 2 h, 97%, 20:3:1 mixture of (2*E*,4*E*,6*E*)/(2*E*,4*E*,6*Z*)/(2*Z*,4*E*,6*E*) isomers; (e) DIBAL-H, THF, −78 °C, 45 min, 91%; (f) MnO_2, Na_2CO_3, CH_2Cl_2, 25 °C, 1 h, 82%; (g) CH_3PPh_3Br, NaHMDS or *n*-BuLi, HMPA, THF, −78 °C, 2 h, 80%; (h) 2nd-generation Grubbs' catalyst **3**, CH_2Cl_2, 50 °C, 6.5 h (**1g**, 60%; **13**, 9%; **14**, 5%; **2g**, 9%).

RESULTS AND DISCUSSION

The synthesis of *trans*-7,8-dihydroretinal (**12**)[26] (Scheme 1) started with the HWE reaction of commercial 7,8-dihydro-*β*-ionone (**4**) (which can also be obtained from *β*-ionone using Bu_3SnH and catalytic amounts of $Pd(PPh_3)_4$[27]) and 2-(diethoxyphosphoryl)acetate (**5**) using *n*-BuLi as base in THF and DMPU as cosolvent. Ester **6** was obtained in 90% yield as a 9:1 mixture of double-bond isomers, which were separated by chromatography. Subsequent reduction of **6** with DIBAL-H, followed by MnO_2 oxidation, provided aldehyde **8** in good yield as a mixture of *all-trans*/9-*cis* isomers in a ≥37:1 ratio. A second HWE olefination with ethyl (*E*)-4-(diethoxyphosphoryl)-3-methylbut-2-enoate (**9**) led in excellent yield (97%) to ester **10** as a 20:3:1 mixture of (2*E*,4*E*,6*E*)/(2*E*,4*E*,6*Z*)/(2*Z*,4*E*,6*E*) isomers. Subsequent reduction of the purified *trans* isomer with DIBAL-H in THF followed by MnO_2 oxidation afforded *trans*-7,8-dihydroretinal (**12**) in good yield. Wittig olefination of **12** with methyltriphenylphosphonium bromide (**13**) using NaHMDS or *n*-BuLi as base and HMPA or DMPU as cosolvent afforded hexaene **2g**.

Polyene **2g** was subjected to the optimized conditions for cross-metathesis described for *β*,*β*-carotene (**1a**),[25] yielding 7,8,7′,8′-tetrahydro-*β*,*β*-carotene (*η*-carotene; **1g**) in 60% yield together with small amounts of unreacted **2g** (9%) and the shorter nonconjugated diene **13** (9%) and triene **14** (5%) products, which must form through alternative metathesis of other double bonds in the starting pentaene or in **1g**. The structures of **13** and **14** were confirmed by independent synthesis by Wittig reaction of **4** and **8**, respectively. Similar to previous examples (**1a–f**), the greater reactivity of the ruthenium carbenes with the terminal monosubstituted double bond when compared to the sterically more hindered tetra-, tri-, and disubstituted double bonds of **2g** produced the desired symmetrical polyene **1g** with remarkable site-selectivity and *trans* stereoselectivity. When nonstereochemically homogeneous *trans/cis* mixtures of **2g** were used in the metathesis reaction, the mixtures of double-bond isomers of **1g** obtained

dx.doi.org/10.1021/np300230t | *J. Nat. Prod.* 2012, 75, 975–979

proved difficult to separate by HPLC (Develosil C30-UG or Spherisorb CN columns). Moreover, the reactivity of the allylic positions makes **1g** highly prone to oxidation and decomposition. In fact, attempts to acquire MS data (ESI^+ or EI ionization) of **1g** were complicated by the appearance of a [M + 16] peak corresponding to an oxidized derivative. Likewise, samples left under air showed red-shifted UV spectra indicative of allylic oxidations.

The UV spectrum of synthetic **1g** [λ_{max} in acetone (ε) 380 (103 500), 402 (131 500), and 427 (121 000)] was coincidental with that published for the product isolated from natural sources.[4,6−8] The extinction coefficients, although not reported in the original disclosure, are also similar to those described for the acyclic analogue 7,8,7′,8′-tetrahydro-ψ,ψ-carotene (ζ-carotene),[2,28,29] and therefore we surmise that the proposed natural product structure must correspond to **1g**. From the biogenetic perspective[30] it is possible that, in the natural sources, ζ-carotene functions as a substrate for lycopene β-cyclase to first produce monocyclic dihydro-β-zeacarotene and then dicyclic η-carotene. In fact, both η-carotene and ζ-carotene were isolated as products of the lycopene cyclase gene *crtY* from the epiphytic bacterium *Erwinia uredovora* expressed in *E. coli*.[31]

In summary, we have achieved the first total synthesis of the purported structure of 7,8,7′,8′-tetrahydro-β,β-carotene (η-carotene) using the acyclic cross-metathesis/dimerization reaction, thus making possible complete spectroscopic characterization of this nonaene with a central conjugated chain of seven double bonds.

EXPERIMENTAL SECTION

General Experimental Procedures. For general procedures, see ref 25.

General Procedure for the Horner−Wadsworth−Emmons Reaction. A cooled (0 °C) solution of ethyl 2-(diethoxyphosphoryl)-acetate (**5**, 0.94 g, 4.192 mmol) in THF (2.3 mL) was treated with *n*-BuLi (2.56 mL, 1.5 M in hexane, 3.843 mmol) and DMPU (6.98 mL, 57.722 mmol) and stirred for 30 min. The mixture was cooled to −78 °C, and a solution of 4-(2′,6′,6′-trimethylcyclohex-1′-en-1′-yl)butan-2-one (**4**, 0.34 g, 1.747 mmol) in THF (4.7 mL) was added. The resulting mixture was stirred for 30 min at −78 °C and then allowed to warm to 25 °C for 47 h. The reaction mixture was quenched with H_2O, and the aqueous layer was extracted with ethyl ether (3×). The combined organic layers were washed with water (2×) and brine (2×) and dried (Na_2SO_4), and the solvent was evaporated. The residue was purified by column chromatography (CC) (silica gel, 98:2 hexane/EtOAc) to afford 0.378 g (82%) of a colorless oil identified as ethyl (*E*)-3-methyl-5-(2′,6′,6′-trimethylcyclohex-1′-en-1′-yl)pent-2-enoate (*E*-**6**) and 0.039 g (8%) of ethyl (*Z*)-3-methyl-5-(2′,6′,6′-trimethylcyclohex-1′-en-1′-yl)pent-2-enoate (*Z*-**6**). An aliquot of the mixture of isomers was purified by HPLC (Prep Novapak HR silica, 6 μm, 19 × 300 mm, 98/2 hexane/EtOAc, 3 mL/min; $t_R(Z)$ = 23.1 min and $t_R(E)$ = 27.0 min).

*Ethyl (E)-3-methyl-5-(2′,6′,6′-trimethylcyclohex-1′-en-1′-yl)pent-2-enoate (E-**6**):* colorless oil; IR (NaCl) ν 2928 (m, C−H), 2865 (m, C−H), 1717 (s, C═O), 1649 (m), 1445 (w), 1222 (s), 1144 (s) cm^{-1}; ^1H NMR (C_6D_6, 400 MHz) δ 5.93 (1H, s, H_2), 4.08 (2H, q, J = 7.1 Hz, $CO_2\underline{CH_2}CH_3$), 2.29 (3H, d, J = 1.0 Hz, CH_3), 2.07 (4H, app s, 2 × CH_2), 1.83 (2H, t, J = 6.2 Hz, CH_2), 1.56−1.49 (2H, m, CH_2), 1.47 (3H, s, CH_3), 1.40−1.37 (2H, m, CH_2), 1.04 (3H, t, J = 7.1 Hz, $CO_2CH_2\underline{CH_3}$), 0.94 (6H, s, 2 × CH_3); ^{13}C NMR (C_6D_6, 100 MHz) δ 166.6 (C), 160.2 (C), 136.5 (C), 127.9 (C), 115.8 (CH), 59.4 (CH_2), 41.7 (CH_2), 40.1 (CH_2), 35.2 (C), 33.0 (CH_2), 28.7 (CH_3, 2×), 27.4 (CH_2), 19.9 (CH_3), 19.9 (CH_2), 18.9 (CH_3), 14.5 (CH_3); HRMS (ESI^+) m/z 265.2159 (calcd for $C_{17}H_{29}O_2$ [M + H]$^+$, 265.2162).

*Ethyl (Z)-3-methyl-5-(2′,6′,6′-trimethylcyclohex-1′-en-1′-yl)pent-2-enoate (Z-**6**):* colorless oil; IR (NaCl) ν 2927 (m, C−H), 2864 (m, C−H), 1717 (s, C═O), 1648 (m), 1442 (w), 1236 (m), 1200 (m), 1156 (s) cm^{-1}; ^1H NMR (C_6D_6, 400 MHz) δ 5.75 (1H, s, H_2), 4.03 (2H, q, J = 7.1 Hz, $CO_2CH_2CH_3$), 2.92−2.88 (2H, m, $\underline{CH_2}$), 2.30−2.26 (2H, m, CH_2), 1.91 (2H, t, J = 6.0 Hz, CH_2), 1.81 (3H, s, CH_3), 1.62 (3H, d, J = 1.2 Hz, CH_3), 1.59−1.55 (2H, m, CH_2), 1.48−1.45 (2H, m, CH_2), 1.19 (6H, s, 2 × CH_3), 1.00 (3H, t, J = 7.1 Hz, $CO_2CH_2\underline{CH_3}$); ^{13}C NMR (C_6D_6, 100 MHz) δ 166.0 (C), 160.1 (C), 137.1 (C), 128.2 (C), 116.5 (CH), 59.4 (CH_2), 40.4 (CH_2), 35.4 (C), 34.4 (CH_2), 33.3 (CH_2), 28.9 (CH_3, 2×), 27.5 (CH_2), 25.0 (CH_3), 20.1 (CH_3), 20.0 (CH_2), 14.4 (CH_2); HRMS (ESI^+) m/z 265.2167 (calcd for $C_{17}H_{29}O_2$ [M + H]$^+$, 265.2162). Double-bond geometry assignment was based on NOE measurements.

General Procedure for the DIBAL-H Reduction. To a solution of *E*-**6** (0.337 g, 1.274 mmol) in THF (12.8 mL) was added dropwise diisobutylaluminum hydride (5.1 mL, 1 M in hexane, 5.1 mmol) at −78 °C. After stirring for 30 min at the same temperature, a saturated aqueous solution of potassium sodium (+)-tartrate was added, and the mixture was stirred for 4 h. The mixture was extracted with ethyl ether (1×), and the aqueous layer was saturated with NaCl and then extracted with ethyl ether (3×). The organic extracts were dried (Na_2SO_4), and the solvent was evaporated, affording 0.271 g (97%) of an oil identified as (*E*)-3-methyl-5-(2′,6′,6′-trimethylcyclohex-1′-en-1′-yl)pent-2-en-1-ol (*E*-**7**), which was used in the next reaction without further purification.

General Procedure for the MnO_2 Oxidation. To a cooled (0 °C) solution of (*E*)-3-methyl-5-(2′,6′,6′-trimethylcyclohex-1′-en-1′-yl)-pent-2-en-1-ol (*E*-**7**) (0.263 g, 1.181 mmol) obtained above in THF (23 mL) were added activated manganese dioxide (1.912 g, 21.256 mmol) and sodium carbonate (2.253 g, 21.256 mmol). The reaction mixture was stirred at 25 °C for 5 h and then filtered through a pad of Celite. The solvent was evaporated to afford 0.220 g (85%) of a white solid identified as (*E*)-3-methyl-5-(2′,6′,6′-trimethylcyclohex-1′-en-1′-yl)pent-2-enal (*E*-**8**).

*(E)-3-Methyl-5-(2′,6′,6′-trimethylcyclohex-1′-en-1′-yl)pent-2-enal (E-**8**):* white solid; UV (MeOH) λ_{max} 237 nm; IR (NaCl) ν 2930 (m, C−H), 2867 (m, C−H), 1675 (s, C═O), 1445 (w), 1192 (w), 1119 (w) cm^{-1}; ^1H NMR (C_6D_6, 400 MHz) δ 9.92 (1H, d, J = 7.7 Hz, CHO), 5.93 (1H, d, J = 7.7 Hz, H_2), 1.94 (4H, app s, 2 × CH_2), 1.82 (2H, t, J = 6.3 Hz, CH_2), 1.58 (3H, d, J = 1.2 Hz, CH_3), 1.55−1.50 (2H, m, CH_2), 1.40−1.37 (3H, s, CH_3), 1.4−1.3 (2H, m, CH_2), 0.93 (6H, s, 2 × CH_3); ^{13}C NMR (C_6D_6, 100 MHz) δ 190.0 (CH), 162.1 (C), 136.3 (C), 128.1 (C), 127.2 (CH), 41.2 (CH_2), 40.1 (CH_2), 35.2 (C), 33.0 (CH_2), 28.7 (CH_3, 2×), 26.9 (CH_2), 19.9 (CH_3), 19.9 (CH_2), 17.0 (CH_3); HRMS (ESI^+) m/z 221.1897 (calcd for $C_{15}H_{25}O$ [M + H]$^+$, 221.1899).

Ethyl (2*E*,4*E*,6*E*)-(3,7-Dimethyl-9-(2′,6′,6′-trimethylcyclohex-1′-en-1′-yl)nona-2,4,6-trienoate (2*E*,4*E*,6*E*-10). Following the general procedure for the HWE reaction, the reaction of *E*-**9** (0.308 g, 1.168 mmol), *n*-BuLi (0.78 mL, 1.37 M in hexane, 1.07 mmol), DMPU (0.33 mL, 2.724 mmol), and (*E*)-3-methyl-5-(2′,6′,6′-trimethylcyclohex-1′-en-1′-yl)pent-2-enal (*E*-**8**) (0.214 g, 0.973 mmol) in THF (1.75 mL) afforded, after purification by CC (silica gel, from 97.5:2.5 hexane/Et_3N to 97.5:2.5 hexane/EtOAc), 0.312 g (97%) of a colorless oil identified as a 20:3:1 mixture of (2*E*,4*E*,6*E*)/(2*E*,4*E*,6*Z*)/(2*Z*,4*E*,6*E*) isomers of the title compound, which were separated by HPLC (Prep Novapak HR silica 60 Å, 19 × 300 mm, 98/2 hexane/EtOAc, 3 mL/min; t_R(2*Z*,4*E*,6*E*) = 24.5 min, t_R(2*E*,4*E*,6*Z*) = 26.4 min, and t_R(2*E*,4*E*,6*E*) = 28.7 min).

*Ethyl (2E,4E,6E)-3,7-dimethyl-9-(2′,6′,6′-trimethylcyclohex-1′-en-1′-yl)nona-2,4,6-trienoate (2E,4E,6E-**10**):* colorless oil; UV (MeOH) λ_{max} 314 nm; IR (NaCl) ν 2925 (m, C−H), 2865 (m, C−H), 1711 (s, C═O), 1603 (s), 1441 (w), 1237 (m), 1148 (s) cm^{-1}; ^1H NMR (C_6D_6, 400 MHz) δ 6.81 (1H, dd, J = 15.2, 11.0 Hz, H_5), 6.11 (1H, d, J = 15.2 Hz, H_4), 5.99 (1H, d, J = 11.0 Hz, H_6), 5.98 (1H, s, H_2), 4.08 (2H, q, J = 7.1 Hz, $CO_2\underline{CH_2}CH_3$), 2.49 (3H, s, CH_3), 2.18 (4H, app s, 2 × CH_2), 1.89 (2H, t, J = 6.2 Hz, CH_2), 1.65 (3H, s, CH_3), 1.61 (3H, s, CH_3), 1.69−1.55 (2H, m, CH_2), 1.46−1.43 (2H, m, CH_2), 1.05 (6H, m, 2 × CH_3), 1.01 (3H, t, J = 7.1 Hz, $CO_2CH_2\underline{CH_3}$); ^{13}C NMR (C_6D_6, 100 MHz) δ 166.9 (C), 153.1 (C), 144 (C), 136.9 (C), 134.2 (CH), 131.1 (CH), 127.7 (C), 125.2 (CH), 119.0 (CH), 59.6 (CH_2),

41.3 (CH_2), 40.2 (CH_2), 35.3 (C), 33.1 (CH_2), 28.8 (CH_3, 2×), 28.0 (CH_2), 20.0 (CH_3), 19.9 (CH_2), 17.0 (CH_3), 14.5 (CH_3), 13.9 (CH_3); HRMS (ESI^+) m/z 331.2631 (calcd for $C_{22}H_{35}O_2$ $[M + H]^+$, 331.2632). Double-bond geometry assignment was based on NOE measurements.

*Ethyl (2E,4E,6Z)-3,7-dimethyl-9-(2′,6′,6′-trimethylcyclohex-1′-en-1′-yl)nona-2,4,6-trienoate (2E,4E,6Z-**10**):* colorless oil; ^1H NMR (C_6D_6, 400 MHz) δ 7.05−6.98 (1H, m, H_5), 6.13 (1H, d, J = 15.3 Hz, H_4), 5.98 (1H, s, H_2), 5.85 (1H, d, J = 10.8 Hz, H_6), 4.08 (2H, q, J = 7.1 Hz, $CO_2\underline{CH_2}CH_3$), 2.54 (3H, d, J = 1.0 Hz, CH_3), 2.28−2.24 (2H, m, CH_2), 2.10−2.06 (2H, m, CH_2), 1.87−1.81 (2H, m, CH_2), 1.74 (3H, s, CH_3), 1.59 (3H, s, CH_3), 1.57−1.53 (2H, m, CH_2), 1.43−1.40 (2H, m, CH_2), 1.05 (6H, m, 2 × CH_3), 1.01 (3H, t, J = 7.1 Hz, $CO_2CH_2\underline{CH_3}$).

*Ethyl (2Z,4E,6E)-3,7-dimethyl-9-(2′,6′,6′-trimethylcyclohex-1′-en-1′-yl)nona-2,4,6-trienoate (2Z,4E,6E-**10**):* colorless oil; ^1H NMR (C_6D_6, 400 MHz) δ 8.42 (1H, d, J = 15.6 Hz, H_4), 6.86 (1H, dd, J = 15.5, 11.0 Hz, H_5), 6.25 (1H, d, J = 11.0 Hz, H_6), 5.77 (1H, s, H_2), 4.05 (2H, q, J = 7.1 Hz, $CO_2\underline{CH_2}CH_3$), 2.14 (4H, app s, 2 × CH_2), 1.88 (2H, t, J = 6.4 Hz, CH_2), 1.77 (3H, s, CH_3), 1.69 (3H, s, CH_3), 1.58−1.55 (5H, m, CH_3 + CH_2), 1.45−1.42 (2H, m, CH_2), 1.05 (6H, m, 2 × CH_3), 1.01 (3H, t, J = 7.1 Hz, $CO_2CH_2\underline{CH_3}$).

(2*E*,4*E*,6*E*)-3,7-Dimethyl-9-(2′,6′,6′-trimethylcyclohex-1′-en-1′-yl)nona-2,4,6-trienal (2*E*,4*E*,6*E*-12). Following the general procedure for the DIBAL-H reduction, the reaction of 2*E*,4*E*,6*E*-**10** (0.31 g, 0.938 mmol) and diisobutylaluminum hydride (3.75 mL, 1 M in hexane, 3.75 mmol) in THF (9.4 mL) afforded, after purification by column chromatography (silica gel, from 95:2:3 hexane/EtOAc/Et_3N to 80:20 hexane/EtOAc), 0.246 g (91%) of (2*E*,4*E*,6*E*)-3,7-dimethyl-9-(2′,6′,6′-trimethylcyclohex-1′-en-1′-yl)nona-2,4,6-trien-1-ol (2*E*,4*E*,6*E*-**11**).

Following the general procedure for the MnO_2 oxidation, the reaction of 2*E*,4*E*,6*E*-**11** (0.245 g, 0.849 mmol), manganese dioxide (1.375 g, 15.288 mmol), and sodium carbonate (1.62 g, 15.287 mmol) in THF (16.3 mL) afforded 0.199 g (82%) of a white solid identified as (2*E*,4*E*,6*E*)-3,7-dimethyl-9-(2′,6′,6′-trimethylcyclohex-1′-en-1′-yl)-nona-2,4,6-trienal (2*E*,4*E*,6*E*-**12**), which was used in the next step without further purification.

*(2E,4E,6E)-3,7-Dimethyl-9-(2′,6′,6′-trimethylcyclohex-1′-en-1′-yl)-nona-2,4,6-trienal (2E,4E,6E-**12**):* white solid; UV (MeOH) λ_{max} 341 nm; IR (NaCl) ν 2927 (m, C−H), 2865 (w, C−H), 1661 (s, C═O), 1630 (w), 1594 (m) cm^{-1}; ^1H NMR (C_6D_6, 400 MHz) δ 10.03 (1H, d, J = 7.9 Hz, CHO), 6.73 (1H, dd, J = 15.1, 11.3 Hz, H_5), 6.00−5.94 (3H, m, H_2 + H_4 + H_6), 2.18 (4H, app s, 2 × CH_2), 1.90 (2H, t, J = 6.0 Hz, CH_2), 1.74 (3H, s, CH_3), 1.65 (3H, s, CH_3), 1.61 (3H, s, CH_3), 1.58−1.55 (2H, m, CH_2), 1.47−1.44 (2H, m, CH_2), 1.05 (6H, s, 2 × CH_3); ^{13}C NMR (C_6D_6, 100 MHz) δ 189.9 (CH), 153.6 (C), 145.5 (C), 136.8 (C), 133.7 (CH), 132.0 (CH), 129.4 (CH), 127.8 (C), 125.1 (CH), 41.3 (CH_2), 40.2 (CH_2), 35.3 (C), 33.1 (CH_2), 28.8 (CH_3, 2×), 27.9 (CH_2), 20.0 (CH_3), 20.1 (CH_2), 17.1 (CH_3), 12.6 (CH_3); HRMS (ESI^+) m/z 287.2365 (calcd. for $C_{20}H_{31}O$ ($[M + H]^+$), 287.2369).

(3′*E*,5′*E*,7′*E*)-2-(3′,7′-Dimethyldeca-3′,5′,7′,9′-tetraen-1′-yl)-1,3,3-trimethylcyclohex-1-ene (3′*E*,5′*E*,7′*E*-2g). To a suspension of methyltriphenylphosphonium bromide (0.227 g, 0.635 mmol) in THF (0.6 mL) were added dropwise *n*-BuLi (0.25 mL, 2.27 M in hexane, 0.564 mmol) and DMPU (0.07 mL, 0.529 mmol), and the resulting mixture was stirred for 30 min at 25 °C. The mixture was cooled to −78 °C, and a solution of (2*E*,4*E*,6*E*)-3,7-dimethyl-9-(2′,6′,6′-trimethylcyclohex-1′-en-1′-yl)nona-2,4,6-trienal (0.101 g, 0.353 mmol) in THF 4.5 mL) was added. After stirring for 1 h at −78 °C the reaction was allowed to warm to 25 °C for 1 h, and hexane was added. The combined organic layers were washed with brine (3×) and water (3×) and dried (Na_2SO_4), and the solvent was evaporated. The residue was purified by CC (silica gel, from 99:1 hexane/Et_3N to 99:1 hexane/EtOAc) to afford 0.080 g (80%) of a yellow oil identified as (3′*E*,5′*E*,7′*E*)-2-(3′,7′-dimethyldeca-3′,5′,7′,9′-tetraen-1′-yl)-1,3,3-trimethylcyclohex-1-ene (3′*E*,5′*E*,7′*E*-**2g**).

(3′E,5′E,7′E)-2-(3′,7′-Dimethyldeca-3′,5′,7′,9′-tetraen-1′-yl)-1,3,3-trimethylcyclohex-1-ene (3′E,5′E,7′E-2g): yellow oil; UV (MeOH) λ_{max} 321, 307 nm; IR (NaCl) ν 3040 (w, C−H), 2927 (s, C−H), 2865 (m, C−H), 1610 (w), 1471 (w), 1441 (w), 983 (m), 954 (m), 897 (m) cm^{-1}; ^1H NMR (C_6D_6, 400 MHz) δ 6.75−6.60 (2H, m, $H_{5'}$ + $H_{9'}$), 6.32 (1H, d, J = 15.2 Hz, $H_{6'}$), 6.17 (2H, d, J = 11.1 Hz, $H_{4'}$ + $H_{8'}$), 5.20 (1H, d, J = 16.7 Hz, $H_{10a'}$), 5.07 (1H, d, J = 10.2 Hz, $H_{10b'}$), 2.24 (4H, app s, 2 × CH_2), 1.90 (2H, t, J = 6.2 Hz, CH_2), 1.81 (3H, s, CH_3), 1.77 (3H, s, CH_3), 1.63 (3H, s, CH_3), 1.61−1.55 (2H, m, CH_2), 1.47−1.44 (2H, m, CH_2), 1.06 (6H, s, 2 × CH_3); ^{13}C NMR (C_6D_6, 100 MHz) δ 139.9 (C), 137.1 (C), 136.5 (C), 135.8 (CH), 133.8 (CH), 131.6 (CH), 127.5 (C), 125.9 (CH), 125.7 (CH), 117.0 (CH_2), 41.3 (CH_2), 40.2 (CH_2), 35.3 (C), 33.1 (CH_2), 28.8 (CH_3, 2×), 28.2 (CH_2), 20.1 (CH_3), 20.0 (CH_2), 17.0 (CH_3), 12.8 (CH_3); MS (EI^+) m/z (%) 284 $[M]^+$ (16), 147 (100), 137 (42), 119 (56), 105 (80), 95 (62), 91 (43); HRMS (EI^+) m/z 284.2507 (calcd for $C_{21}H_{32}$, 284.2504).

7,8,7′,8′-Tetrahydro-*β*,*β*-carotene (1g). To a degassed solution of (3′*E*,5′*E*,7′*E*-**2g**) (0.047 g, 0.165 mmol) in CH_2Cl_2 (3.1 mL) was added Grubbs' second-generation catalyst (0.014 g, 0.016 mmol). After stirring for 5 h at 50 °C, the reaction mixture was filtered through Celite, which was washed with acetone, and the solvent was evaporated. The residue was purified by CC (C_{18} silica gel, from 90:10 CH_3CN/CH_2Cl_2 to 70:30 CH_3CN/CH_2Cl_2 containing small amounts of BHT, butylated hydroxytoluene (2,6-di-*tert*-butyl-*p*-cresol)) to afford 0.027 g (60%) of a reddish solid identified as 7,8,7′,8′-tetrahydro-*β*,*β*-carotene (**1g**) and a mixture, which was purified by a second CC (silica gel, from hexane to 99:1 hexane/EtOAc) to afford, in order of elution, 2.8 mg (9%) of an oil identified as 1,3,3-trimethyl-2-(3′-methylbut-3′-en-1′-yl)cyclohex-1-ene (**13**), 2.0 mg (5%) of another oil identified as (*E*)-1,3,3-trimethyl-2-(3′-methylhexa-3′,5′-dien-1′-yl)cyclohex-1-ene (*E*-**14**), and 4.1 mg (9% recovered) of starting material.

*7,8,7′,8′-Tetrahydro-β,β-carotene (**1g**):* reddish solid; UV (acetone) λ_{max} (log ε) 380 (5.01), 402 (5.12), 427 (5.08) nm; (hexane) λ_{max} 378, 400, 426 nm. IR (NaCl) ν 3027 (w, C−H), 2924 (s, C−H), 2851 (m, C−H), 1441 (m), 1061 (m) cm^{-1}; ^1H NMR (C_6D_6, 400 MHz) δ 6.72−6.66 (4H, m, $2H_{11}$ + $2H_{15}$), 6.45 (2H, d, J = 15.0 Hz, $2H_{12}$), 6.35 (2H, d, J = 9.6 Hz, $2H_{14}$), 6.25 (2H, d, J = 11.0 Hz, $2H_{10}$), 2.28−2.25 (8H, m, 4 × CH_2), 1.92−1.89 (10H, m, 2 × CH_3 + 2 × CH_2), 1.81 (6H, s, 2 × CH_3), 1.64 (6H, s, 2 × CH_3), 1.62−1.55 (4H, m, 2 × CH_2), 1.47−1.45 (4H, m, 2 × CH_2), 1.08 (6H, s, 2 × CH_3) (signals of BHT stabilizer are not reported); ^{13}C NMR (C_6D_6, 100 MHz) δ 139.9 (C), 137.2 (C), 136.4 (C), 136.2 (CH), 132.3 (CH), 130.3 (CH), 127.5 (C), 126.2 (CH), 125.4 (CH), 41.4 (CH_2), 40.2 (CH_2), 35.3 (C), 33.1 (CH_2), 28.9 (CH_3, 2×), 28.3 (CH_2), 20.1 (CH_3), 20.0 (CH_2), 17.0 (CH_3), 13.0 (CH_3) (signals of BHT stabilizer are not reported); HRMS (ESI^+) m/z 540.4703 (calcd for $C_{40}H_{60}$ $[M]^+$, 540.4689).

The ^1H NMR data coincide with those described previously[9] for signals corresponding to the aliphatic region of this compound in $CDCl_3$: δ 2.12 (8H, m), 1.97 (6H, s), 1.86 (6H, s), 1.66 (6H, s), 1.01 (12H, s).

*1,3,3-Trimethyl-2-(3′-methylbut-3′-en-1′-yl)cyclohex-1-ene (**13**):* colorless oil; IR (NaCl) ν 2966 (s, C−H), 2929 (s, C−H), 2909 (s, C−H), 2865 (m), 1649 (w), 1472 (w), 1455 (w), 885 (m) cm^{-1}; ^1H NMR (C_6D_6, 400 MHz) δ 4.88 (1H, s, $H_{4a'}$), 4.83 (1H, s, $H_{4B'}$), 2.25−2.14 (4H, m, 2 × CH_2), 1.90 (2H, t, J = 6.3 Hz, CH_2), 1.72 (3H, s, CH_3), 1.58−1.53 (5H, m, CH_3 + CH_2), 1.45−1.42 (2H, m, CH_2), 1.05 (6H, t, J = 0.5 Hz, 2 × CH_3); ^{13}C NMR (C_6D_6, 100 MHz) δ 146.5 (C), 137.3 (C), 127.3 (C), 109.8 (CH_2), 40.3 (CH_2), 38.9 (CH_2), 35.3 (C), 33.1 (CH_2), 28.8 (CH_3, 2×), 27.8 (CH_2), 22.7 (CH_3), 20.0 (CH_2), 19.9 (CH_3); MS (EI^+) m/z 192 $[M]^+$ (13), 177 (20), 137 (83), 121 (18), 107 (22), 95 (100), 93 (21), 91 (19), 81 (49), 79 (20); HRMS (EI^+) m/z 192.1882 (calcd. for $C_{14}H_{24}$, 192.1878).

This compound was alternatively synthesized from dihydro-*β*-ionone **4**: Following the general procedure for the Wittig reaction, the reaction of methyltriphenylphosphonium bromide (0.652 g, 1.825 mmol) with *n*-BuLi (1.10 mL, 1.46 M in hexane, 1.622 mmol), DMPU (0.18 mL, 1.521 mmol), and 4-(2′,6′,6′-trimethylcyclohex-1′-en-1′-yl)butan-2-one) (**4**) (0.197 g, 1.014 mmol) in THF (15 mL) afforded, after purification by CC (silica gel, from 95:3:2 hexane/EtOAc/Et_3N

to 95:5 hexane/EtOAc), 0.120 g (62%) of a colorless oil identified as 1,3,3-trimethyl-2-(3′-methylbut-3′-en-1′-yl)cyclohex-1-ene (**13**).

(E)-1,3,3-Trimethyl-2-(3′-methylhexa-3′,5′-dien-1-yl)cyclohex-1-ene (E-14): colorless oil; UV (MeOH) λ_{max} 237 nm; IR (NaCl) ν 3083 (w, C−H), 2952 (s, C−H), 2928 (s, C−H), 2865 (m, C−H), 2829 (w, C−H), 1650 (w), 1472 (w), 895 (m) cm^{-1}; ^1H NMR (C_6D_6, 400 MHz) δ 6.64 (1H, ddd, J = 16.8, 10.8, 10.2 Hz, $H_{5'}$), 6.08 (1H, d, J = 10.8 Hz, $H_{4'}$), 5.17 (1H, d, J = 16.8 Hz, $H_{6a'}$), 5.03 (1H, d, J = 10.2 Hz, $H_{6b'}$), 2.18 (4H, app s, 2 × CH_2), 1.87 (2H, t, J = 6.1 Hz, CH_2), 1.68 (3H, s, CH_3), 1.59−1.53 (5H, m, CH_3 + CH_2), 1.45−1.42 (2H, m, CH_2), 1.03 (6H, s, 2 × CH_3); ^{13}C NMR (C_6D_6, 100 MHz) δ 139.9 (C), 137.1 (C), 133.9 (CH), 127.4 (C), 125.8 (CH), 114.9 (CH_2), 40.9 (CH_2), 40.2 (CH_2), 35.3 (C), 33.1 (CH_2), 28.8 (CH_3, 2×), 28.0 (CH_2), 20.0 (CH_3), 19.9 (CH_2), 16.7 (CH_3) ppm; MS (EI^+) m/z 218 $[M]^+$ (3), 137 (100), 95 (97), 81 (54), 79 (22); HRMS (EI^+) m/z 218.2042 (calcd for $C_{16}H_{26}$, 218.2035).

This compound was alternatively synthesized from dihydro-β-ionylideneacetaldehyde (**8**). Following the general procedure for the Wittig reaction, the reaction of methyltriphenylphosphonium bromide (0.277 g, 0.776 mmol) with *n*-BuLi (0.47 mL, 1.46 M in hexane, 0.690 mmol), DMPU (0.08 mL, 0.646 mmol), and (*E*)-3-methyl-5-(2′,6′,6′-trimethylcyclohex-1′-en-1′-yl)pent-2-enal (*E*-**8**) (0.095 g, 0.431 mmol) in THF (6.5 mL) afforded, after purification by CC (silica gel saturated with 2% Et_3N, 99:1 hexane/EtOAc), 0.055 g (59%) of a colorless oil identified as (*E*)-1,3,3-trimethyl-2-(3′-methylhexa-3′,5′-dien-1′-yl)cyclohex-1-ene (*E*-**14**).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of spectra of the compounds described in the text. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors are grateful to the Ministerio de Economía y Competitividad-Spain (SAF2010-17935-FEDER-Fondos Europeos para el Desarrollo Regional; FPU Fellowship to N.F.) and Xunta de Galicia (Grant 08CSA052383PR from DXI+D+i; Consolidación 2006/15 and from DXPCTSUG; INBIOMED) for financial support.

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