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Total synthesis of prolycopene, a novel 7,9,7′,9′-tetra-*cis*(*Z*) carotenoid and main pigment of the tangerine tomato *Lycopersicon esculentum*

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This paper is dedicated to the memory of Basil C. L. Weedon, 1923–2003

Abstract—A total synthesis of the 7,9,7′,9′-tetra-*cis*(*Z*) isomer of lycopene, also known as 'prolycopene', produced as the major carotenoid pigment in fruits of the tangerine tomato *Lycopersicon esculentum* ('Tangella') is described. The synthesis is based on: (i) a modified Sonogashira coupling reaction between the *E*-alkenyl bromide **6** and the *Z*-enynol **7**, leading to the 2*Z*-trienynol **8**, followed by (ii) a Wittig reaction between the phosphonium salt **4** and the C_{10}-triene dialdehyde **5** producing the symmetrical 9,9′-*Z* isomer of the bis-acetylene **3** and (iii) semi-hydrogenation of **3** in the presence of Lindlar's catalyst, and chromatography.
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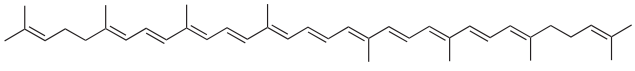
1. Introduction

Prolycopene **2** is the tetra-*cis*(*Z*) isomer of the more familiar carotenoid, all-*E*-lycopene **1**, found in commercial tomatoes. It was first isolated by Zechmeister et al. in 1941[1] from the tangerine tomato *Lycopersicon esculentum* var, known as 'Tangella'. Although the stereochemistry of prolycopene was investigated extensively by Zechmeister et al. over two decades, it was not until NMR spectroscopy, and particularly carbon NMR spectroscopy, became routinely available that the intriguing tetra-*Z* geometry of the pigment was established independently by Englert et al.[2] and ourselves[3] in 1979. In contemporaneous studies we also separated and characterised the *Z*-isomers of the carotenoid pigments phytoene, phytofluene, ζ-carotene and neurosporene, congeners to prolycopene, in *L. esculentum*.[4] Later we described the total synthesis of prolycopene,[5] Hengartner, Englert and co-workers, in 1992, presented the syntheses of six bis- and three tris-*Z*-isomers of lycopene.[6] In this paper we describe full details of our synthesis of natural (tetra-*Z*) prolycopene **2**.



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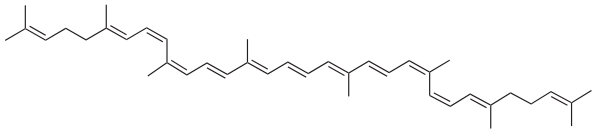

2

The synthesis of conjugated polyisopenoids with one or more *Z*-double bonds has been a formidable challenge since the early beginnings of carotenoid chemistry.[7] Without doubt, the Wittig reaction and its variants have been the cornerstone of polyene synthesis in recent years.[8] This is in spite of the fact that the stereochemical outcomes of these reactions are less predictable, and often lead to mixtures of *Z*- and *E*-isomers at the newly introduced double bonds. Prolycopene **2** has a symmetrical structure and accommodates two *Z*-disubstituted and two *Z*-trisubstituted double bonds. This led us to design a synthesis of the compound based on semi-hydrogenation of the bis-acetylenic precursor **3**, which we planned to elaborate from the *Z*-allylphosphonium salt **4** and the known C_{10}-triene dialdehyde **5**. There is considerable precedent for the formation of *Z*-disubstituted bonds from semi-hydrogenations of acetylene precursors in the carotenoid field, since the early work of Lindlar in

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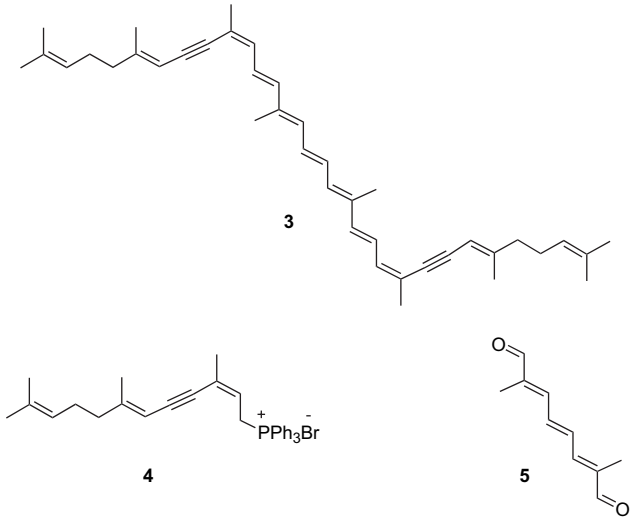
1952, i.e., Pd on $CaCO_3$ deactivated by quinoline.[9] Furthermore, the *Z*-pentenynol **7** is readily available, and we planned to use this precursor in a palladium-catalysed coupling reaction with the *E*-vinyl bromide **6**, to produce the C_{15}-2*Z*,6*E*-trienynol intermediate **8**, en route to the corresponding phosphonium salt **4**.



2. Results and discussion

Thus, a Wittig reaction between 6-methyl-5-hepten-2-one and bromomethyltriphenylphosphonium bromide, in the presence of $KOBu^t$ at −60 °C to 25 °C gave a 3:1 mixture of *E*- and *Z*-isomers of the vinyl bromide **6**,[10] from which the *E*-isomer was easily separated by gas chromatography (Scheme 1). An sp^2–sp coupling reaction between the vinyl bromide **6** and the enynol **7** under modified Sonogashira conditions, i.e., Ph_4Pd–CuI–$PrNH_2$,[11] next gave the 2*Z*-trienynol **8** in 72% yield. The stereochemistry assigned to **8** followed from analysis and comparison of its PMR and CMR spectroscopic data with those of its 2*Z*,6*Z*-, 2*E*,6*Z*- and 2*E*,6*E*-isomers, which were prepared from corresponding sp^2–sp coupling reactions involving **6** and the *Z*-vinyl bromide **10**, and **7** and the *E*-allyl alcohol **11**. The relevant diagnostic ^{13}C NMR chemical shift data for each of these isomers are collected on structures **12**, **13**, **14** and **15** (Fig. 1).

Bromination of the 2*Z*-trienynol **8**, using dibromotetrachloroethane in the presence of triphenylphosphine,[12] next gave the 2*Z*-allyl bromide **9**, which was immediately reacted with triphenylphosphine leading to the corresponding phosphonium salt **4**. The salt **4** was obtained as colourless crystals, which were very hygroscopic (Scheme 1). A Wittig reaction between molar equivalents of the phosphonium salt **4** and the C_{10} triene dial **5**,[13] using aq NaOH as base

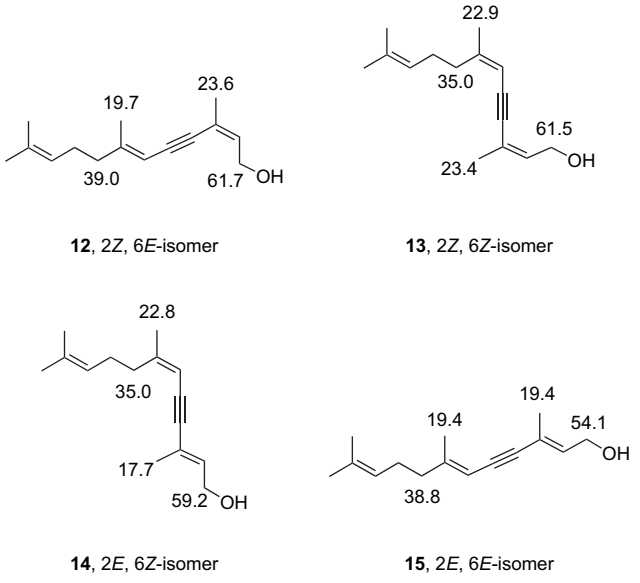
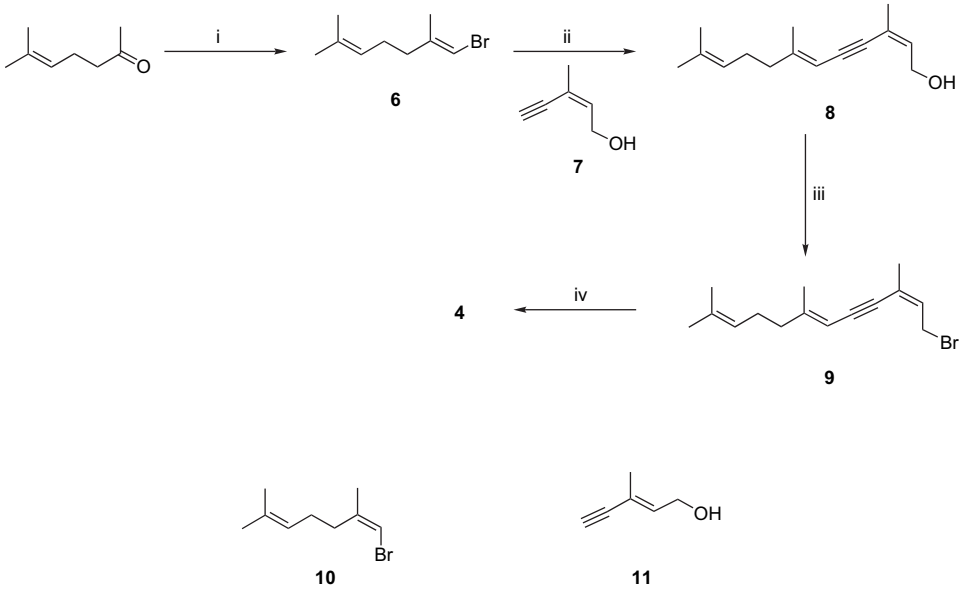
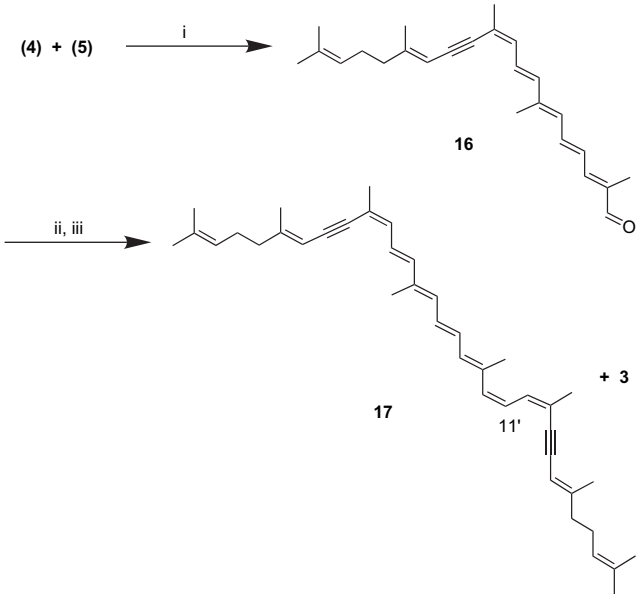


Figure 1. Pertinent ^{13}C NMR chemical shift data for the four isomers of the substituted 2,4,10-trien-4-yn-1-ol (**8**).



Scheme 1. Reagents and conditions: (i) $BrCH_2\overset{+}{P}Ph_3\bar{B}r$, $KOBu^t$, THF, −60 °C, 81%, 3:1 *E*/*Z* mixture; (ii) $(PPh_3)_4Pd$, $PrNH_2$, then **7**, CuI, 70%; (iii) $BrCl_2CCCl_2Br$, PPh_3, Et_2O, 0 °C, 98% and (iv) PPh_3, C_6H_6, 25 °C, 85%.

in $ClCH_2CH_2Cl$, followed by chromatography, led cleanly to the 9*Z*-heptenynal **16** (Scheme 2). The geometry of **16** followed from analysis of its CMR spectroscopic data[14] and comparison with similar data recorded for the related 9*Z*- and 9*E*-polyenynals **18** and **19**,[15] respectively (Fig. 2).† A second Wittig reaction between the salt **4** and the 9*Z*-heptenynal **16**, using aq NaOH in $ClCH_2CH_2Cl$, then gave the symmetrical 9,9′-*Z* isomer of the bis-acetylene **3**, which was obtained as a deep red solid. HPLC analysis demonstrated that the bis-acetylene **3** was produced as a mixture of two 11′*Z*,*E*-isomers in the ratio 2:1, identified as the required 9*Z*,11*E*,9′*Z*,11′*E*-isomer **3** (major product) and the isomeric 9*Z*,11*E*,9′*Z*,11′*Z* compound **17**.

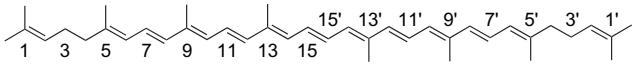


Scheme 2. Reagents and conditions: (i) aq NaOH, $ClCH_2CH_2Cl$, 25 °C, 36%; (ii) **4**, aq NaOH, $ClCH_2CH_2Cl$, 25 °C, then **16**, 61%, 2:1 mixture of **3** and **17** and (iii) I_2, C_6H_6, 90%.

Rather than separating the two isomers at this stage, a solution containing a mixture of the isomers in hexane was treated with a very dilute solution of iodine in benzene, and the progress of the isomerisation of the 9*Z*,11*E*,9′*Z*,11′*Z*-isomer **17** to the isomer **3** was monitored by HPLC analysis. After washing with aqueous sodium thiosulfate solution, work up and crystallisation gave the symmetrical 9,9′-*Z* isomer of the bis-acetylene **3** as minute orange crystals, mp 110 °C.

Consistent with its symmetrical structure only 20 carbon signals were observed in the CMR spectrum of **3**, which also showed diagnostic resonances at *δ* 39.0 and *δ* 19.7 (5*E* and 5′*E* double bonds), *δ* 23.6 (9*Z* and 9′*Z* double bonds) and at *δ* 12.8 (11*E* and 11′*E* double bonds). Pertinent ^{13}C and ^{1}H NMR data are collected on structures **20** and **21** (Fig. 3). Several years after we had published a preliminary communication,[5] Hengartner et al.[6] published an identical synthetic approach to the same 9,9′-*Z* isomer of the bis-acetylene **3**, on large scale.

† The system of numbering carotenoids recommended by I.U.P.A.C. is used throughout this paper, i.e., lycopene.



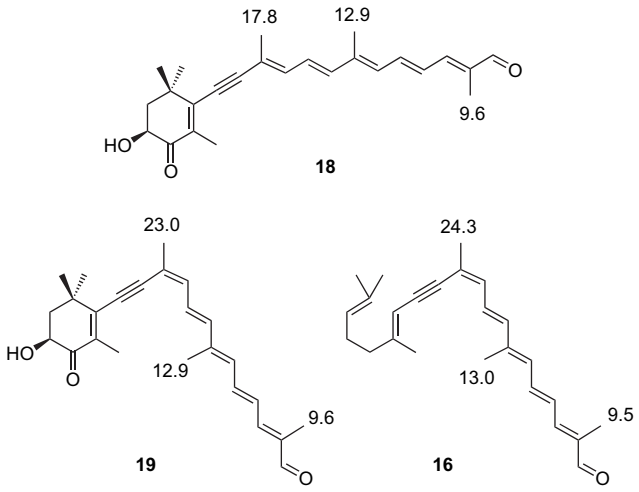


Figure 2. Pertinent ^{13}C NMR chemical shift data for the C-9*Z* polyenal **16** and the related C-9*E*- and C-9*Z*-analogues **18** and **19**, respectively.

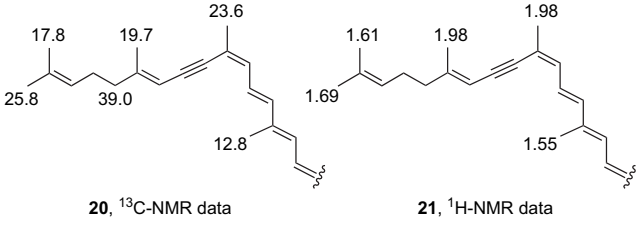


Figure 3. Pertinent ^{13}C and ^{1}H NMR chemical shift data for the 9*Z*- and 9′*Z*-bis-acetylene **3**.

All that now remained to complete our synthesis of natural prolycopene **2** was to carry out a semi-hydrogenation of the bis-acetylene **3** in the presence of Lindlar's catalyst. This was no trivial task especially in view of the limited amounts of **3** that were available. After considerable experimentation, using alternative polyenyne substrates as models, different microhydrogenator designs and various Lindlar catalyst cocktails, we successfully hydrogenated the bis-acetylene **3** on 10 mg scale to produce prolycopene **2**, which was purified by HPLC and obtained in ca. 15% yield. The synthetic material did not separate from naturally derived prolycopene in HPLC analysis and their PMR spectroscopic and mass spectrometric data were closely identical. Hengartner et al.[6] later carried out the same semi-hydrogenation of the bis-acetylene **3** on 10 times the scale we had been able to use, but also in the presence of Lindlar's catalyst, and secured a 44% yield of crystalline prolycopene.

3. Experimental

3.1. General details

Melting points of polyenes were determined in evacuated capillary tubes using a Gallenkamp melting point apparatus.

Infrared spectra were recorded as liquid films, unless stated otherwise, on a Phillips P.U. 9706 spectrophotometer. ^{1}H NMR spectra were determined on a Bruker WM 250 PFT or AM 400 PFT spectrometer and ^{13}C NMR spectra were obtained on the same instruments at 63.0 and 100.0 MHz,

respectively. Samples were dissolved in deuterated chloroform ($CDCl_3$), which provided the deuterium lock for the spectrometers. Tetramethylsilane or residual chloroform was used as an internal standard. Mass measurements were determined on either an AEI MS 902 or a VG 707E spectrometer. Elemental analyses were carried out on a Perkin Elmer 240B elemental analyser.

Due to their sensitivity, strict methods of handling polyenes were adhered to throughout the experimental work. Thus, all solutions of polyenes were handled under a nitrogen blanket in subdued light or in darkness, and all columns and TLC chambers used in chromatographic separations were wrapped in aluminium foil. Transfers of polyenes were carried out rapidly under a blanket of nitrogen and at no time were solutions containing polyenes heated above room temperature; all polyenes were stored under nitrogen at −12 °C. All solvents were distilled before use. Solutions were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure.

Analytical HPLC analyses were carried out on a Zorbax, Silica, 250×4.6 mm column using a Waters 6000 or 6000A pump connected to a Cecil C212 variable wavelength monitor or a Waters Model 440 absorbance detector. Preparative HPLC work was carried out on a C-18 column using a Waters Prep LC/System 500 pump fitted with an integral refractive index detector.

Capillary GLC analysis was performed on a Perkin Elmer Sigma 2 instrument using a Carbowax 50 m column. Preparative GLC was carried out on a 76 cm×8 mm silicone oil (15%) on diatomite column using an Aerograph Auroprep Model A-700 instrument.

3.1.1. (*E*,*Z*)-1-Bromo-2,6-dimethyl-1,5-heptadiene (6). Freshly prepared potassium tertiary butoxide (7.2 g, 6.4 mmol) was added, all at once, to a stirred suspension of bromomethyltriphenylphosphonium bromide (31 g, 7.1 mmol) in dry THF (500 ml) at room temperature under a nitrogen atmosphere, and the resulting mixture was then stirred at room temperature for 30 min. The deep yellow solution of the corresponding ylide was cooled to −60 °C and then 6-methylhept-5-en-2-one (3.0 g, 2.4 mmol) in dry THF (20 ml) was added over 10 min. The mixture was stirred at −60 °C for 1 h, and then allowed to warm to room temperature where it was stirred for a further 24 h. The mixture was evaporated to dryness in vacuo and the residue was then triturated with petrol (bp 40–60 °C) (4×100 ml). The combined organic extracts were evaporated to leave a brown oil. Chromatography followed by distillation gave a 3:1 mixture of *E*- and *Z*-isomers of the vinyl bromide (3.9 g, 81%) as a colourless oil, bp 56 °C at 0.6 mmHg. The *E*- and *Z*-isomers were separated by preparative GC to give: (i) *E*-1-bromo-2,6-dimethyl-1,5-heptadiene,[10] ν_{max} 2920, 1630, 825, 720 cm^{-1}, δ_H 5.9 (1H, q, *J*=1, =C*H*Br), 5.06 (1H, br, =C*H*), 2.08–2.16 (4H, m), 1.8 (3H, d, *J*=1, =CMe), 1.68 (3H, s, Me), 1.60 (3H, s, Me) ppm; δ_C 141.5 (s, =C), 132.2 (s, =C), 123.3 (d, =CH), 101.4 (d, =CH), 38.5 (t, CH_2), 26.4 (t, CH_2), 25.7 (q, CH_3), 19.2 (q, CH_3), 17.7 (q, CH_3) ppm and (ii) *Z*-1-bromo-2,6-dimethyl-1,5-heptadiene, ν_{max} 2980, 2920, 1635, 780, 730 cm^{-1}, δ_H 5.86 (1H, q, *J*=1.5, =C*H*Br), 5.14 (1H, tqn, *J*=7 and 1.5, =C*H*), 2.07–2.37 (4H, m), 1.79 (3H, d, *J*=1.5, =CMe), 1.70 (3H, d, *J*=1.1, =CMe), 1.63 (3H, s, Me) ppm; δ_C 141.5 (s, =C), 132.3 (s, =C), 123.6 (d, =C), 100.9 (d, =C), 34.6 (t, CH_2), 25.6 (q, CH_3), 22.3 (q, CH_3), 17.7 (q, CH_3) ppm.

3.1.2. (2*Z*,6*E*)-3,7,11-Trimethyldodeca-2,6,10-trien-4-yn-1-ol (8). *E*-1-Bromo-2,6-dimethyl-1,5-heptadiene (**6**) (0.54 g, 2.7 mmol) was added to a stirred suspension of tetrakistriphenylphosphine palladium(0) (0.20 g, 0.17 mmol) in freshly distilled, degassed propylamine (5.0 ml) under a nitrogen atmosphere in the dark, and the resulting mixture was then stirred at room temperature for 20 min. *Z*-2-Methylpent-2-en-4-yn-1-ol (0.26 g, 2.7 mmol) followed by freshly purified copper (I) iodide (0.14 g, 0.74 mmol) were added, and the resulting deep brown viscous mixture was then stirred at room temperature for a further 17 h. The mixture was evaporated in vacuo to leave a brown oil, which was dissolved in ether (50 ml). The ether solution was washed with saturated ammonium chloride solution (4×100 ml) and water (2×100 ml), then dried and evaporated in vacuo to leave the crude trienynol as a brown oil. Chromatography [silica G, ether/petrol ether (bp 40–60 °C), 1:2], followed by bulb-to-bulb distillation gave the 2*Z*,6*E* alcohol (0.41 g, 70%) as a colourless liquid, bp 150 °C at 0.3 mmHg. Found: C, 82.5; H, 10.9%. $C_{15}H_{22}O$ requires: C, 82.5; H, 10.2%; λ_{max} (EtOH) 264 inf (14,000), 272 (16,700), 286 inf (11,600) nm; ν_{max} 3320, 2920, 2190, 1615, 835 cm^{-1}, δ_H 5.83 (1H, tq, *J*=6.5 and 1.4, =C*H*CH_2OH), 5.43 (1H, =C*H*C), 5.08 (1H, br, Me_2C=C*H*), 4.35 (2H, d, *J*=6.5, CH_2OH), 3.20 (1H, br, –OH), 2.12–2.17 (4H, m), 1.92 (6H, 2×=CMe), 1.69 (3H, =CMe), 1.61 (3H, =CMe) ppm; δ_C 152.8 (s, =C), 134.2 (d, =CH), 132.4 (s, =C), 123.5 (d, =CH), 121.7 (s, =C), 104.9 (t, =CH), 93.1 (s, ≡C), 90.2 (s, ≡C), 61.7 (t, CH_2), 39.0 (t, CH_2), 26.5 (t, CH_2), 25.9 (q, CH_3), 23.6 (q, CH_3), 19.9 (q, CH_3), 17.9 (q, CH_3) ppm; *m*/*z* 218.1667; $C_{15}H_{22}O$ requires *M* 218.1671.

3.1.3. (2*Z*,6*Z*)-3,7,11-Trimethyldodeca-2,6,10-trien-4-yn-1-ol (13). *Z*-1-Bromo-2,6-dimethyl-1,5-heptadiene (0.19 g, 0.94 mmol) and *Z*-2-methylpent-2-en-4-yn-1-ol (0.09 g, 0.95 mmol) were reacted together in an identical manner to that described for the preparation of the corresponding 2*Z*,6*E* alcohol. The product (0.13 g, 63%) was obtained as a colourless oil. Found: C, 82.6; H, 10.6%. $C_{15}H_{22}O$ requires: C, 82.5; H, 10.2%; λ_{max} (EtOH) 263 inf (11,700), 272 (13,900), 285 inf (9750) nm; ν_{max} 3320, 2920, 2190, 1615, 830 cm^{-1}, δ_H 5.82 (1H, tq, *J*=6.6 and 1.4, =C*H*CH_2OH), 5.42 (1H, d, *J*=1.4 =C*H*C), 5.14 (1H, tqn, *J*=6.3 and 1.4, Me_2C=C*H*), 4.32 (2H, d, *J*=6.6, CH_2OH), 2.73 (1H, br, –OH), 2.33 (2H, t, *J*=7.6, CH_2C=CH_2), 2.13 (2H, q, *J*=7.6, CH_2CH_2), 1.91 (3H, d, *J*=1.2, =CMe), 1.83 (3H, d, *J*=1.4, =CMe), 1.69 (3H, d, *J*=0.8, =CMe), 1.62 (3H, Me) ppm; δ_C 152.9 (s, =C), 134.0 (d, =CH), 132.2 (s, =C), 123.7 (d, =CH), 121.8 (s, =C), 105.4 (d, =CH), 92.8 (s, ≡C), 89.7 (s, ≡C), 61.5 (t, CH_2), 35.2 (t, CH_2), 26.4 (t, CH_2), 25.8 (q, CH_3), 23.4 (q, CH_3), 22.9 (q, CH_3), 17.8 (q, CH_3) ppm; *m*/*z* 218.1673; $C_{15}H_{22}O$ requires *M* 218.1671.

3.1.4. (2*E*,6*Z*)-3,7,11-Trimethyldodeca-2,6,10-trien-4-yn-1-ol (14) and (2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trien-4-yn-1-ol (15). A 3:1 mixture of *E*- and *Z*- isomers of 1-bromo-2,6-dimethyl-1,5-heptadiene (**6**) (0.54 g,

2.7 mmol) was added to a stirred suspension of tetrakis-triphenylphosphine palladium(0) (0.20 g, 0.17 mmol) in freshly distilled, degassed *n*-propylamine (5.0 ml) under a nitrogen atmosphere in the dark, and the resulting mixture was then stirred at room temperature for 20 min. *E*-2-Methylpent-2-en-4-yn-1-ol (0.26 g, 2.7 mmol) followed by freshly purified copper (I) iodide (0.14 g, 0.74 mmol) were added, and the resulting deep brown viscous mixture was then stirred at room temperature for a further 17 h. The mixture was evaporated in vacuo to leave the crude mixture of trienynol isomers as a brown oil. Chromatography [silica G, ether/petrol ether (bp 40–60 °C), 1:2], followed by bulb-to-bulb distillation gave a 3:1 mixture of the *E*-2 and the *E*-6 isomers (0.27 g, 46%) as a colourless oil (bp 150 °C at 0.3 mmHg). The two isomers were separated by preparative reverse phase HPLC to give: (i) the (2*E*,6*E*)-isomer (**15**), Found: C, 82.5; H, 10.4%. $C_{15}H_{22}O$ requires: C, 82.5; H, 10.2%; λ_{max} (EtOH) 262 inf (13,300), 271 (16,000), 284 inf (11,500) nm; ν_{max} 3320, 2925, 2200, 1615, 740, 700 cm^{-1}, δ_H 5.97 (1H, tq, *J*=6.8 and 1.4, =C*H*CH_2OH), 5.38 (1H, =C*H*C), 5.08 (1H, br, Me_2C=C*H*), 4.21 (2H, d, *J*=6.8, CH_2OH), 2.24 (1H, br, –OH), 2.11–2.12 (4H, m), 1.9 (3H, d, *J*=1, =CMe), 1.86 (3H, d, *J*=0.7, =CMe), 1.68 (3H, =CMe), 1.60 (3H, =CMe) ppm; δ_C 152.1 (s, =C), 134.1 (d, =CH), 132.1 (s, =C), 123.5 (d, =CH), 121.4 (s, =C), 104.8 (d, =CH), 94.3 (s, ≡C), 86.1 (s, ≡C), 59.1 (t, CH_2), 38.8 (t, CH_2), 26.3 (t, CH_2), 25.7 (q, CH_3), 19.4 (q, CH_3), 17.7 (q, CH_3) ppm and (ii) the (2*E*,6*Z*)-isomer (**14**), Found: C, 82.5; H, 10.4%. $C_{15}H_{22}O$ requires: C, 82.5; H, 10.2%; λ_{max} (EtOH) 262 inf (11,000), 271 (13,000), 286 (9820) nm; ν_{max} 3320, 2925, 2195, 1615, 1005, 833 cm^{-1}, δ_H 5.96 (1H, tq, *J*=6.9 and 1.3, =C*H*CH_2OH), 5.38 (1H, =C*H*C), 5.15 (1H, tt, *J*=7.1 and 1.3, Me_2C=C*H*), 4.23 (2H, d, *J*=6.9, CH_2OH), 2.32 (2H, t, *J*=7.5, CH_2CH_2), 2.14 (2H, q, *J*=7.5, CH_2CH_2), 1.86 (3H, d, *J*=0.6, =CMe), 1.86 (3H, d, *J*=1.4, =CMe), 1.70 (3H, Me), 1.63 (3H, Me) ppm; δ_C 152.5 (s, =C), 133.8 (d, =CH), 132.1 (s, =C), 123.8 (d, =CH), 121.6 (s, =C), 105.3 (d, =CH), 93.7 (s, ≡C), 86.0 (s, ≡C), 59.2 (t, CH_2), 35.0 (t, CH_2), 26.4 (t, CH_2), 25.7 (q, CH_3), 17.7 (q, CH_3), 17.4 (q, CH_3) ppm; *m*/*z* 218.1663; $C_{15}H_{22}O$ requires *M* 218.1671.

3.1.5. (2*Z*,6*E*)-1-Bromo-3,7,11-trimethyldodeca-2,6,10-trien-4-yne (9). A solution of 1,2-dibromotetrachlorethane (0.21 g, 0.64 mmol) in dry ether (5 ml) was added over 5 min to a stirred solution of (2*Z*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trien-4-yn-1-ol (**8**) (0.82 g, 3.8 mmol) and triphenylphosphine (0.17 g, 0.65 mmol) in dry ether (5 ml) at 0 °C under a nitrogen atmosphere in the dark, and the mixture was then stirred at this temperature for 10 min. The mixture was warmed to room temperature and the stirring was then continued for a further 20 min, by which time a colourless precipitate of triphenylphosphine oxide had formed. The precipitate was filtered off, and the ether was then evaporated to leave a brown oil. Chromatography [silica G, ether/petrol ether (bp 40–60 °C), 1:3] gave the 2*Z*,6*E*-alkyl bromide (0.12 g, 98%) as a colourless oil, which showed λ_{max} (EtOH) 283 (13,000) nm; ν_{max} 2920, 2190, 1610, 835, 780, 755 cm^{-1}, δ_H 5.87 (1H, tq, *J*=8.0 and 1.3, =C*H*CH_2Br), 5.47 (1H, =C*H*C=), 5.09 (1H, br, Me_2C=C*H*), 4.25 (2H, d, *J*=8.0, CH_2Br), 2.15 (4H, m), 1.94 (6H, 2×=CMe), 1.69 (3H, Me), 1.61 (3H, Me) ppm; δ_C 153.3 (s, =C), 132.2 (s, =C), 130.12 (d, =CH), 124.7 (s, =C), 123.3 (d, =CH), 104.8 (d, =CH), 95.1 (s, ≡C), 89.3 (s, ≡C), 38.9 (t, CH_2), 30.8 (t, CH_2), 25.7 (q, CH_3), 23.3 (q, CH_3), 19.6 (q, CH_3), 17.7 (q, CH_3) ppm; *m*/*z* 280.0836; $C_{15}H_{21}{}^{79}Br$ requires *M* 280.0826.

3.1.6. (2*Z*,6*E*)-3,7,11-Trimethyldodeca-2,6,10-trien-4-ynyl-triphenylphosphonium bromide (4). Triphenylphosphine (0.26 g, 0.99 mmol) was added to a solution of freshly prepared (2*Z*,6*E*)-1-bromo-3,7,11-trimethyldodeca-2,6,10-trien-4-yne (**9**) (0.279 g, 0.99 mmol) in dry benzene (15 ml) and the mixture was then stirred in the dark, overnight under a nitrogen atmosphere. The benzene was evaporated leaving a sticky pale brown solid, which was triturated with dry ether (6×10 ml). The ether was evaporated leaving the phosphonium salt (0.46 g, 85%) as an extremely hygroscopic, flaky colourless solid, which showed λ_{max} ($CHCl_3$) 230 (36,300), 277 (18,640), 268 (17,830), 303 (13,500) nm; ν_{max} ($CHCl_3$ solution) 3380, 2900, 2480, 2200, 1615, 1010 cm^{-1}, δ_H 7.70–7.90 (15H, m), 5.65 (1H, br, =C*H*CH_2), 5.21 (1H, =C*H*C=), 5.04 (1H, br, Me_2C=C*H*), 4.94 (2H, dd, *J*=6 and 12, CH_2PPh_3), 2.07–2.12 (4H, m), 1.83 (3H, d, *J*=6, =CMe), 1.72 (3H, =CMe), 1.69 (3H, =CMe), 1.60 (3H, =CMe) ppm; δ_C 153.4 (s, =C), 135.0 (d, =CH), 133.8 (d, *J*=9.5, =CH), 132.3 (s, =C), 130.3 (d, *J*=12.2, =CH), 128.9 (d, *J*=13.8, =CH), 123.2 (d, =CH), 118.5 (d, *J*=10.5, =CH), 118.1 (d, *J*=85.5, =CH), 104.3 (d, =CH), 94.8 (s, ≡C), 89.3 (s, ≡C), 38.6 (t, CH_2), 27.0 (t, *J*=50.1, CH_2), 26.1 (t, CH_2), 25.6 (q, CH_3), 23.5 (q, CH_3), 19.5 (q, CH_3), 17.7 (q, CH_3) ppm; FAB mass spectrum *m*/*z* 463 (M−Br) (73%), 262 (53%), 183 (57%), 69 (94%), 55 (100%).

The corresponding 2*E*,6*E*-triphenylphosphonium salt was prepared in a similar manner from the 2*E*,6*E*-alcohol (**15**), and was obtained as a very hygroscopic flaky colourless solid, which showed λ_{max} (EtOH) 200 (31,000), 231 inf (10,800), 267 (5560), 275 (6180), 287 inf (4940), 303 inf (4630) nm; ν_{max} 2920, 2440, 2200, 1610, 920 cm^{-1}, δ_H 7.69–7.91 (15H, m), 5.66 (1H, q, *J*=7.4 =C*H*CH_2), 5.21 (1H, =C*H*C=), 5.04 (1H, br, Me_2C=C*H*), 4.79 (2H, dd, *J*=16 and 8, CH_2PPh_3), 2.10 (4H, m), 1.84 (3H, =CMe), 1.67 (3H, =CMe), 1.59 (3H, =CMe), 1.54 (3H, d, *J*=4.0, =CMe) ppm; δ_C 153.5 (s, =C), 135.2 (d, =CH), 133.9 (d, *J*=9.6, =CH), 132.2 (s, =C), 130.4 (d, *J*=12.4, =CH), 128.9 (d, *J*=13.8, =CH), 123.2 (d, *J*=10.9, =CH), 117.8 (d, *J*=85.5, =CH), 104.3 (d, =CH), 93.2 (s, ≡C), 88.3 (s, ≡C), 38.7 (t, CH_2), 26.2 (t, CH_2), 25.7 (q, CH_3), 25.4 (t, *J*=47.8, CH_2), 19.5 (q, CH_3), 18.7 (q, CH_3), 17.8 (q, CH_3) ppm.

3.1.7. (10*Z*)-2,7,11,15,19-Pentamethyleicosa-2,4,6,8,10,14,18-hepten-12-yn-1-al (16). Aqueous 2 M sodium hydroxide (2 ml, 4 mmol) was added to a stirred solution of (2*Z*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trien-4-ynyl-triphenylphosphonium bromide (**4**) (0.4 g, 0.74 mmol) in 1,2-dichloroethane (200 ml) and the mixture was then stirred under an argon atmosphere, at room temperature, in the dark for 10 min. A solution of the C_{10}-triene dialdehyde (**5**) (0.483 g, 2.9 mmol) in 1,2-dichloroethane (40 ml) was added to the stirred deep red coloured solution of the ylide over a period of 10 min and stirring was then continued at room temperature for a further 2 h. Glacial acetic acid (2 ml, 35 mmol)

was added, followed by ether (200 ml) and the mixture was then washed with water (4×100 ml). The combined aqueous washings were re-extracted with ether (2×100 ml), and the combined ether solutions were then dried and evaporated leaving a viscous orange oil. Purification by preparative thin layer chromatography [silica G, ether/petrol ether (bp 40–60 °C), 1:2] gave the (*Z*-10) C_{25} aldehyde (0.092 g, 36%) as a bright orange-red oil. λ_{max} (hexane) 391 inf (26,800), 411 (32,000), 434 (24,300) nm; ν_{max} ($CHCl_3$ solution) 2920, 1660, 1560, 985 cm^{-1}, δ_H 9.45 (1H, C*H*O), 6.29–6.72 (7H, m, =CH), 5.53 (1H, =CH), 5.10 (1H, br, =CH), 2.17 (4H, m), 2.02 (3H, Me), 2.00 (3H, Me), 1.99 (3H, Me), 1.70 (3H, Me), 1.62 (3H, Me) ppm; δ_C 39.0 (t, CH_2), 26.6 (t, CH_2), 25.7 (q, CH_3), 23.8 (q, CH_3), 19.7 (q, CH_3), 17.8 (q, CH_3), 13.1 (s), 9.7 (q, CH_3) ppm; *m/z* 348.2454; $C_{25}H_{32}O$ requires *M* 348.2453.

3.1.8. (9*Z*,9′*Z*)-7,8,7′,8′-Tetradehydrolycopene (3). Aqueous 2 M sodium hydroxide (1 ml, 2 mmol) was added to a stirred solution of (2*Z*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trien-4-ynyl-triphenylphosphonium bromide (**4**) (0.286 g, 0.53 mmol) in 1,2-dichloroethane (20 ml), and the mixture was then stirred under an argon atmosphere, at room temperature, in the dark for 10 min. A solution of the (10*Z*) C_{25}-aldehyde (**16**) (0.092 g, 0.026 mmol) in 1,2-dichloroethane (30 ml) was added and the mixture was stirred at room temperature for a further 2 h. Glacial acetic acid (1 ml, 17.5 mmol) was added, followed by ether (200 ml) and the mixture was then washed with water (4×50 ml). The combined aqueous washings were re-extracted with ether (2×100 ml), and the ether solutions were then dried and evaporated leaving a deep red solid. The solid was purified by preparative thin layer chromatography [silica G, 10% acetone in *n*-hexane] to give the tetradehydro C_{40} compound (0.05 g, 61%) as a deep red solid. HPLC analysis showed that the solid consisted of a 2:1 mixture of the desired 9*Z*,11*E*,9′*Z*,11′*E*-isomer (**3**) and the 9*Z*,11*E*,9′*Z*,11′*Z*-isomer (**17**).

A very dilute solution of iodine in benzene (0.5 ml) was added to a solution of the tetrahydrolycopene isomers (0.08 g, 0.015 mmol) in *n*-hexane (10 ml) under a nitrogen atmosphere. The solution was stirred under a nitrogen atmosphere at room temperature for 3.5 h by which time HPLC analysis showed that only the 9*Z*,11*E*,9′*Z*,11′*E*-isomer of the tetrahydrolycopene was present. The solution was washed thoroughly with 1 M sodium thiosulfate solution (4×3 ml) and water (2×10 ml), then dried and evaporated to leave a deep red solid (0.075 g). Crystallisation from hexane/ethanol gave the (9*Z*,9′*Z*) tetrahydrolycopene as minute orange crystals, mp 100 °C, which showed λ_{max} (*n*-hexane) 419 (37,000), 443 (55,600), 472 (49,100) nm; ν_{max} ($CHCl_3$ solution) 1600, 980, 930, 880 cm^{-1}, δ_H 6.80 (2H, dd, *J*=15 and 11, C11, C11′-*H*), 6.60 (AA′ of AA′BB′ spin system, C15, C15′-*H*), 6.35 (2H, d, *J*=15, C12, C12′-*H*), 6.29 (2H, d, *J*=11, C10, C10′-*H*), 6.25 (BB′ of AA′BB′ spin system, C14, C14′-*H*), 5.52 (2H, C6, C6′-*H*), 5.10 (2H, br, C2, C2′-*H*), 2.16 (8H, m, 4×CH_2), 1.98 (12H, 4×=CMe), 1.95 (6H, 2×=CMe), 1.69 (6H, 2×=CMe), 1.61 (6H, 2×=CMe) ppm; δ_C 152.1 (s, =C), 137.3 (d, =CH), 136.6 (s, =C), 135.7 (d, =CH), 133.1 (d, =CH), 132.3 (s, =C), 130.2 (d, =CH), 127.2 (d, =CH), 123.5 (d, =CH), 119.9 (s, =C), 105.4 (d, =CH), 94.9 (s, ≡C), 92.4 (s, ≡C), 39.0 (t, CH_2), 26.4 (t, CH_2), 25.8 (q, CH_3), 23.6 (q, CH_3), 19.6 (q, CH_3), 17.8 (q, CH_3), 12.8 (q, CH_3) ppm; *m/z* 532.4058; $C_{40}H_{52}$ requires *M* 532.4069.

3.1.9. Prolycopene (2). Lindlar's catalyst (10 mg) was added to freshly distilled, degassed ethyl acetate (5 ml) in a microhydrogenator in the dark, and the system was then flushed out three times with hydrogen. A solution of the tetrahydrolycopene (**3**) (10 mg, 0.019 mmol) in ethyl acetate (2 ml) was added and hydrogen uptake started immediately. After 30 s hydrogen uptake had ceased! The catalyst was filtered off and the ethyl acetate was then evaporated in vacuo to leave a bright orange oil. Analysis by HPLC showed that the oil was a mixture of compounds, the major one of which was isoretentive with authentic prolycopene. The prolycopene was separated by HPLC to give a red solid (<1 mg), which showed λ_{max} (*n*-hexane) 417, 438, 468 nm; δ_H 6.62–5.95 (16H, m), 5.07 (2H, br), 2.05–2.07 (8H, m), 1.98 (6H, 2×CH_3), 1.87 (6H, 2×CH_3), 1.78 (6H, 2×CH_3), 1.65 (6H, 2×CH_3), 1.56 (6H, 2×CH_3) ppm; *m/z* 536.4388; $C_{40}H_{56}$ requires *M* 536.4382. The synthetic prolycopene did not separate from authentic, naturally derived prolycopene in chromatographic analysis and their visible absorption, PMR spectroscopic data, together with mass spectrometry data were closely identical.

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