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Synthesis of 19,19′-D_6-β-Carotene

JON EIGILL JOHANSEN and SYNNØVE LIAAEN-JENSEN

Organic Chemistry Laboratories, Norwegian Institute of Technology, University of Trondheim, N-7034 Trondheim-NTH, Norway

The total synthesis of 19,19′-D_6-β-carotene (*10*) with two fully deuterated in-chain methyl groups is described. The deuterium was introduced by base-catalyzed deuterium exchange of enolizable hydrogen. Two alternative routes were investigated for optimum deuterium incorporation in the final product.
Spectroscopic and other physical properties of intermediates and products are reported.

Previous reports on the preparation of deuterated carotenoids by reduction methods have just been summarized.[1] In the preceding paper we reported the first synthesis of deuterated carotenoids using the exchange technique on a phosphonium salt to give a deuterated phosphorane.[2]

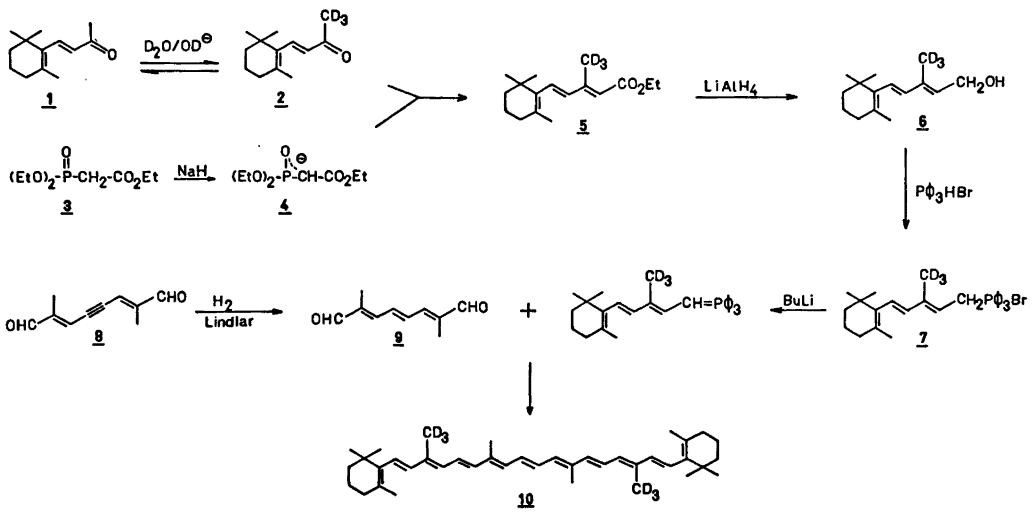
We now report the synthesis of β-carotene with two fully deuterated in-chain methyl groups, involving base-catalyzed deuterium exchange of enolizable hydrogen.

The present work forms part of a larger project comprising synthesis of specifically deuterated carotenoids for mass-spectrometric studies.[3]

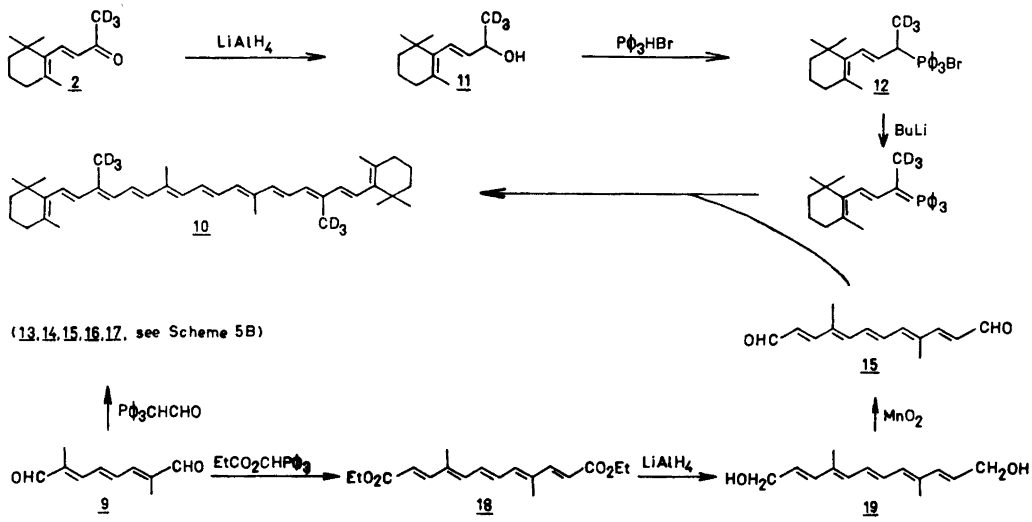
RESULTS AND DISCUSSION

Two alternative approaches were considered for the synthesis of 19,19′-D_6-β-carotene (*10*), shown in Schemes 1 and 2. Both routes involved labelling of β-ionone (*1*) in a base-catalyzed exchange reaction as briefly described by Thomas *et al.*[4]

The shortest, but also least safe route (Scheme 1, route 1), was first pursued. Horner reaction between α,α,α-D_3-β-ionone (*2*, Scheme



Scheme 1.

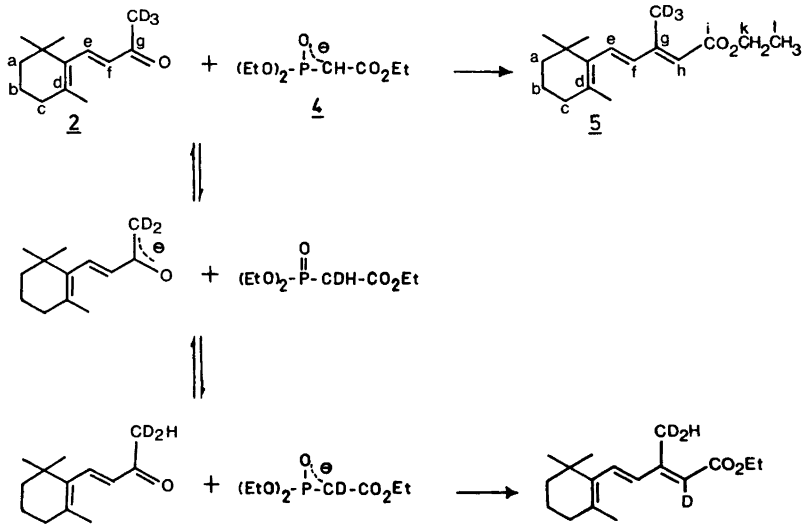


Scheme 2.

2) and triethylphosphonoacetate (*3*) resulted in scrambling of the deuterium. To prevent scrambling *via* enolization of α,α,α-D_3-β-ionone (*2*), route 2 (Scheme 2) involved reduction of the deuterated ketone *2*.

Route 1. Labelled β-ionone (*2*) was obtained by using 0,1 % NaOD in D_2O/pyridine; 1 % NaOD in D_2O/dioxane was employed by Thomas *et al.*[4,5] Also 0.28 N CH_3OLi in CH_3OD effected the same. Maximal incorporation was obtained within 18 min in the NaOD case, while few seconds were sufficient in the latter system. Three deuterium atoms only were incorporated in both cases.[4]

The attempted synthesis of D_3-β-ionylidene acetate (*5*) was performed from α,α,α-D_3-β-ionone (*2*) and triethylphosphonoacetate (*3*).[6] The anion of *3* (*4*) was generated *in situ* with equivalent amount of base (NaH) to prevent enolization of *2*. The resulting ester *5a* was reduced with $LiAlH_4$, and the corresponding alcohol *6a* converted to the phosphonium salt *7a*.



Scheme 3.

Examination of the PMR spectra of the ester *5a* and the alcohol *6a* revealed that some deuterium was lost from the methyl group and present at position *h* (Scheme 3). Thus the phosphonate anion *4* was a sufficiently strong base to effect enolization of α,α,α-D_3-β-ionone (*2*), and served as a deuterium acceptor as shown in Scheme 3. Compounds *5a*, *6a*, and *7a* thus represent mixtures with deuterium in both positions *g* and *h* (Scheme 3; *5*, *6*, *7* and *7*-phosphorane also considered to comprise *cis*-isomers as to the trisubstituted double bond).

The trienedial *9*, obtained by selective, catalytic hydrogenation [7,8] of the corresponding acetylene *8*, was condensed with the phosphorane of the phosphonium bromide *7a* to give deuterated β-carotene (*10a*) with uneven and unsatisfactory deuterium incorporation (D_0:D_1:D_2:D_3:D_4:D_5:D_6:D_7:D_8 = 2:5:12:20:24:21:13:3:0).

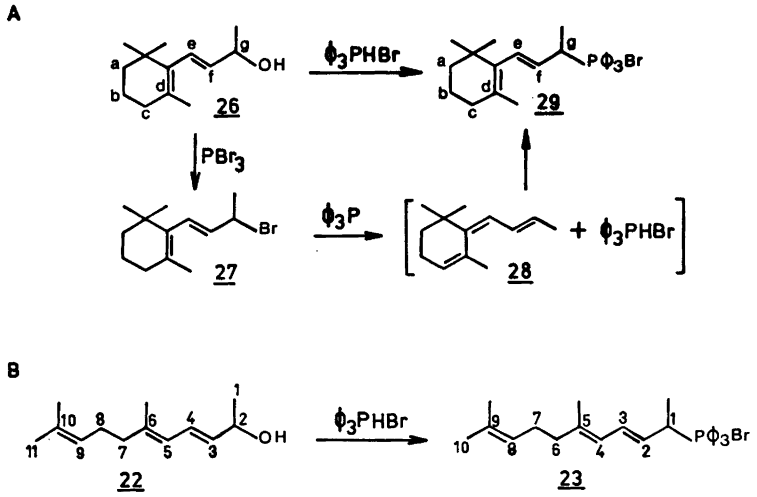
Route 2. On formation of phosphonium salts by S_N2 mechanism primary substrates are favoured.[9] Synthesis of the secondary phosphonium bromide *29* (Scheme 4A) either from the corresponding alcohol *26* [10] or bromide *27* [11] are described in patents only. In the latter case the reaction is presumed to occur *via* the triene *28* intermediate.[12]

As a model was checked the reaction of ψ-ionol (*22*, Scheme 4B) with triphenylphosphonium bromide, which gave the corresponding phosphonium bromide *23* without complications.

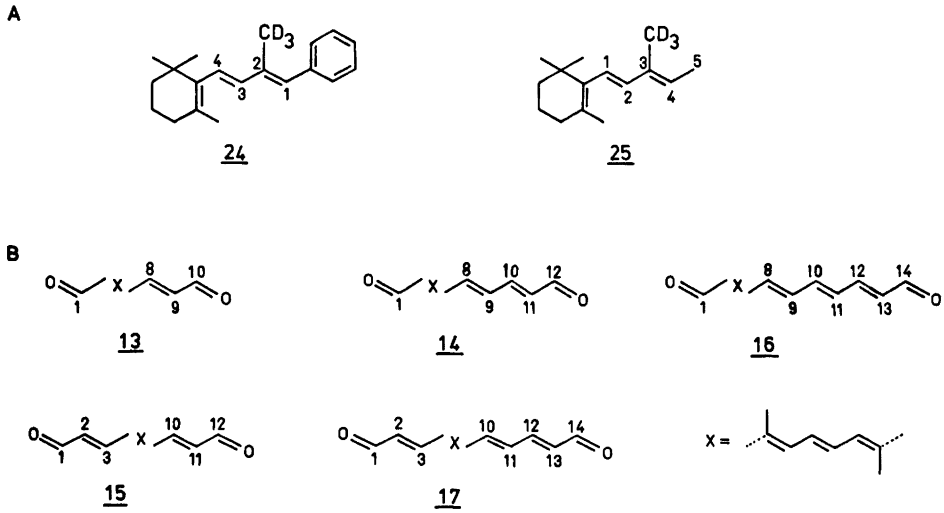
α,α,α-D_3-β-Ionone (*2*) from Route 1 was reduced with $LiAlH_4$, and the corresponding alcohol *11* converted to the phosphonium salt *12* with triphenylphosphonium bromide in like manner and in good yield.

The PMR spectrum of the phosphonium salt *12* showed unexpectedly two singlets at δ 0.70 and 0.88 (6 H), attributed to the *gem.* dimethyl group. Normally the *gem.* dimethyl in an unsubstituted β-end group give rise to a singlet around δ 1.1.[13] The compounds *24* and *25* (Scheme 5A), also prepared, showed singlets at δ 1.02 and 1.05 and δ 1.00 and 1.03, respectively. The abnormal chemical shift of the *gem.* dimethyl group in the phosphonium salt *12* is ascribed to the anisotropic effect of the triphenylphosphonium group, whereas the magnetic non-equivalence may be due to *cis* and *trans* isomerism.

The C_{14}-dialdehyde *15*, used as the central component, was synthesized from the C_{10}-dial *9*. Condensation of the C_{10}-dial *9* with formylmethylene triphenylphosphorane [14] gave a mixture of different products (Schemes 2 and 5B), not readily separable. However, condensation of the C_{10}-dial *9* with carbethoxymethyl triphenylphosphonium bromide to the diethyl ester *18*, followed by reduction with $LiAlH_4$ to the corresponding diol *19*, and allylic oxidation with activated MnO_2 gave the desired C_{14}-dialdehyde *15*.



Scheme 4.



Scheme 5.

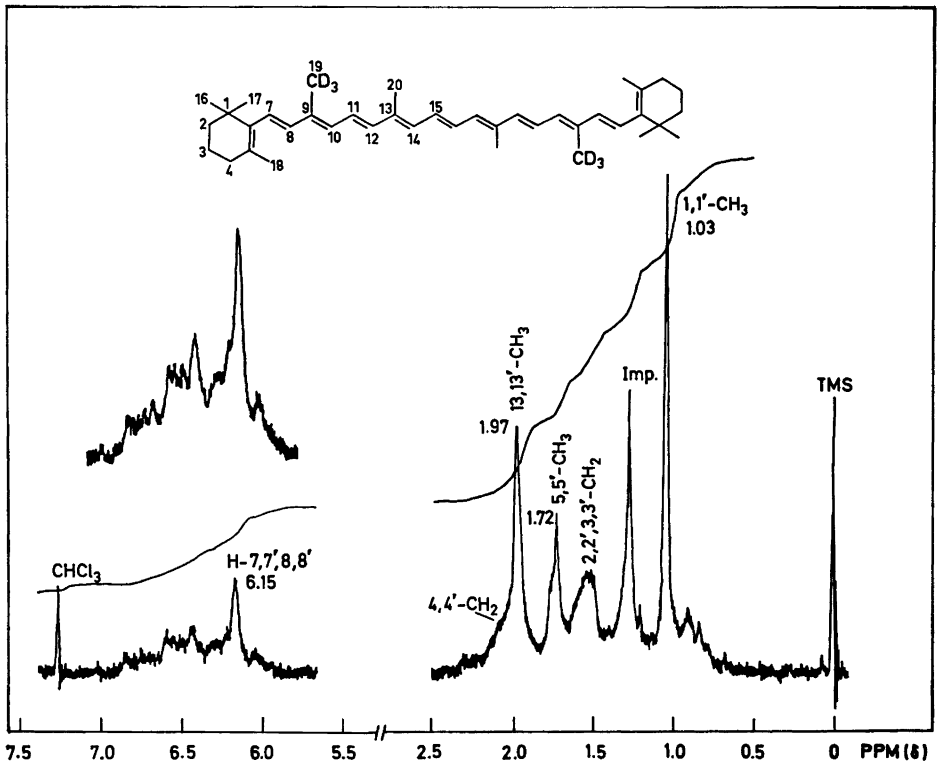


Fig. 1. ^{1}H NMR spectrum ($CDCl_3$) of 19,19'-D_6-β-carotene.

19,19'-D_6-β-Carotene (*10*) was obtained by condensation of the dialdehyde *15* and the phosphorane of the phosphonium bromide *12*. Deuterated β-carotene (*10*) thus prepared had 85 % deuterium incorporation (D_0:D_1:D_2:D_3:D_4:D_5:D_6 = 0:1:2:4:10:42:41). The PMR spectrum of *10* is given in Fig. 1. Specific deuterium incorporation in 19,19' is consistent with the integral for the in-chain methyl signal at δ 1.97 (6 rather than 12 hydrogens). IR absorption at 2110 and 2160 cm^{-1} was ascribed to C–D stretching vibrations.

For the deuterated β-carotene (*10a*), prepared by Route 1, labelled at C-10,10', absorption at 761 cm^{-1} was also observed, compatible with C–D out-of-plane vibration of a trisubstituted double bond (>C=CD–).

The mass spectrum of 19,19'-D_6-β-carotene (*10*) is discussed elsewhere.[3]

EXPERIMENTAL PART

Materials and methods were as described elsewhere.[2,15]

Heavy water was from Norsk Hydro (>99.8 % deuterated). Pyridine *p.a.* (Merck) was distilled and kept over barium oxide. NaH (50 %), delivered in mineral oil, was washed with petroleum ether prior to use. NaOD was from Merck (40 % in D_2O). β-Ionone (Firmenich, synthetic) contained 13 % α-ionone, judged by the ^1H NMR integral.

Complete spectra of the compounds prepared are available elsewhere.[16]

Deuterium incorporation is calculated from the mass spectra, taking naturally occurring isotopes into account, *cf.* Ref. 1.

Route 1

α,α,α-D$_3$-β-Ionone (*2*). β-Ionone (*1*, 9.0 g), D_2O (28.1 g) and pyridine (60 ml) were mixed, 10 drops NaOD added and the mixture stirred at room temperature for 1 h. The product was extracted with ether, washed thoroughly with H_2O (7 times), dried (Na_2SO_4) and evaporated. This gave *2*; yield 8.95 g (98 %); n_D^{20} = 1.5173; λ_{max} (hexane) 281 nm [*E*(1 %, 1 cm) = 400]; ν_{max}(liq.) 3015–2730 (CH), 2227 and 2212 (CD), 1690, 1665 (conj. C=C), 1460–1365 (CH_2,CH_3), 1265, 980 (*trans*-CH=CH), 920 and 735 cm^{-1} (the two last absorptions were absent or very weak in the spectrum of undeuterated β-ionone (*1*)); δ ($CDCl_3$, Scheme 3) 0,87 s and 0.94 s (*gem.* dimethyl in α,α,α-D_3-α-ionone), 1.08 s (6 H, *gem.* dimethyl), 1.77 s (3 H, CH_3-*d*), 1.98–2.13 (2 H, H-*c*), 6.12 d (1 H, J_{e-f} = 16.5 Hz, H-*e*) and 7.31 (1 H, J_{e-f} = 16.5 Hz, H-*f*); *m/e* (130°C) 195 (M), 180 (M–15, 100 %) and 139 (M–56); D_0:D_1:D_2:D_3 = 0:3:21:76; 90 % deuterium incorporation.

Deuterated ethyl β-ionylidene acetate (*5a*). To triethylphosphonoacetate (*3*, 7.5 g) was slowly added NaH (50 %, 1.6 g) in dry ether (20 ml) and the mixture stirred at room temp. for 1 h. *2* (5 g) in dry ether was added during 30 min, and the mixture stirred for 24 h; 80 % conversion judged by TLC. The mixture was transferred to water (1 l), extracted with ether, washed with water, dried (Na_2SO_4) and evaporated; yield 6.12 g *2* and *5a*, plus *ca.* 13 % α-isomers. The reaction was repeated with the product mixture, and the same amount of reagent *4* generated *in situ* as above. The mixture, worked up as above after 2 h, gave *5a*, yield 6.48 g (95 %); n_D^{20} = 1.5361; λ_{max} (hexane) 262 [*E*(1 %, 1 cm) = 550] and (290) nm; ν_{max} (liq.) 3015–2725 (CH), 2210, 2165, 2110, and 2060 (CD), 1715 (C=O), 1605 (conj. C=C), 1455=1360 (CH_2,CH_3), 1235 (C–O), 1215 [not in the undeuterated analogue *20* prepared below, 1150 (C–O), 1080 (not in *20*) and 970 (*trans*-CH=CH); δ (CCl_4), Scheme 3] 0.82 s and 0.92 s (*gem.* dimethyl in the α-isomer), 1.02 s (6 H, *gem.* dimethyl), 1.25 t (3 H, J_{k-l} = 7 Hz, H-*l*), 1.68 s (3 H, CH_3-*d*), 2.29 (*ca.* 1 H, CH_3-*g*), 4.11 k (2 H, J_{k-l} = 7 Hz, H-*k*), 5.66 s (0.7 H, H-h), 6.02 d (1 H, J_{e-f} = 16 Hz, H-*f*) and 6.53 d (1 H, J_{e-f} = 16 Hz, H-*e*); *m/e* (130°C) 266 (M+1), 265 (M), 264 (M–1), 263 (M–2), 262 (M–3), 250 (M–15), 236 (M–29), 220 (M–45), and 59 (100 %); D_0:D_1:D_2:D_3:D_4 = 13:21:31:28:7; 63 % deuterium incorporation (assuming 3 exchangeable H).

Deuterated β-ionylidene ethanol (*6a*). To a mixture of *5a* (5.5 g) in dry ether (10 ml) was added $LiAlH_4$ (0.85 g) in dry ether (50 ml) at 0°C during 30 min. Excess $LiAlH_4$ was destroyed with moist ether and water after 1 h stirring. The mixture was poured into 1 N H_2SO_4 (0°C) and the product extracted with ether. The extract was washed with water, aqueous $NaHCO_3$ solution and water, dried (Na_2SO_4) and evaporated. This gave *6a* plus *ca.* 13 % α-isomer; yield 4.2 mg (91 %); $n_D^{20.5}$ = 1.5363; λ_{max} (hexane) 239 [*E*(1 %, 1 cm) = 560] and (265) nm (reported λ_{max} 237 and 265 in methanol[17]); ν_{max} (liq.) 3320 (OH), 3020–2725 (CH), 2240, 2210, 2155, 2110, and 2065 (CD), 1455–1360 (CH_2, CH_3), 970 (*trans*-CH=CH), 915 and 735 cm^{-1}; δ ($CDCl_3$, reference letters as for *5a* in Scheme 3) 0.82 s and 0.90 s (*gem.* dimethyl in the α-isomer), 1.02 s (6 H, *gem.* dimethyl), 1.68 s (3 H, CH_3-*d*, 2.08 (–OH), 4.27 s and 4.27 d (2 H, J_{h-i} = 7 Hz, H-*i*), 5.62 s and 5.62 t (*ca.* 0.8 H, J_{h-i} = 7 Hz, H-*h*) and 6.07 (2 H, H-*e*, *f*); *m/e*(130°C) 224 (M+1), 223 (M), 222 (M–1), 221 (M–2), 220 (M–3), 179 (M–44), 149 (M–74), 136 (M–87), and 41 (100 %), D_0:D_1:D_2:D_3:D_4 = 14:23:28:27:8; 61 % deuterium incorporation (assuming 3 exchangeable H).

Deuterated β-ionylidene triphenylphosphonium bromide (7a). To triphenylphosphonium bromide (6.15 g) in methanol (65 ml) was added *6a* (4.0 g), and the mixture was stirred for 48 h. The solvent was removed, and the residue washed with ether and ethyl acetate gave *6a* plus *ca.* 13 % α-isomer; yield 5.1 g (51 %). Recrystallization three times from CH_2Cl_2-ethyl acetate gave white, cubic crystals; m.p. 157–158°C (reported 123°C [17]); λ_{max} (methanol) 204, 225, 261, 267, and 274 nm with E(1 %, 1 cm) = 1060, 730, 212, 221, and 208, respectively; ν_{max} (KBr) 3020–2775 (CH), 1440, 1115, 995, 975 (*trans*-CH=CH) and 760–685 (phenyl and bromine); δ ($CDCl_3$, reference letters as for *5a* in Scheme 3) 0.96 (6 H, *gem.* dimethyl), 1.64 (3 H, CH_3-*d*), *ca.* 1.9 (2 H, H-*c*), 4.78 dd (J_{H-P} = 16 Hz, J_{h-i} = 7 Hz, =CH–CH_2P), 4.78 d (J_{H-P} = 16Hz, =CD–CH_2P), 4.78 (total 2 H), 5.29 t (*ca.* 0.6 H, J_{h-i} = 7 Hz, H-*h*), 5.99 (2 H, H-*e,f*) and 7.6-8.1 (15 aromatic H).

2,7-Dimethylocta-2,4,6-triene-1,8-dial (9). 2,7-Dimethylocta-2,6-diene-4-yne-1,8-dial (*8*, 5 g) in ethyl acetate (150 ml) was hydrogenated in the presence of Lindlar catalyst [7] (3.5 g) until one equivalent of hydrogen was absorbed as described by Mildner and Weedon.[8] The catalyst was removed by filtration, the solvent evaporated, and the product crystallized from benzene; *9* had m.p. 133–135°C (reported 135–140°C[8]); λ_{max} (MeOH) 236, 3235 [E(1 %, 1 cm) = 2800] and 334 nm; ν_{max} (KBr) 2810, 2710 (CH), 1655 (C=O), 1600 (conj. C=C), 1435–1330 (CH_3), 1225, 1010, 900, 830, 800, 730, and 670 cm^{-1}; δ($CDCl_3$) 1.95 s (6 H, 2 CH_3), 6.75–7.52 (4 olefinic H, complex coupling) and 9.63 s (2 aldehyde H); *m/e* (75°C) 164 (M).

10,10',19,19'-Deuterated β-carotene (10a). To a suspension of deuterated β-ionylidenethyltriphenyl-phosphonium bromide (*7a*, 0.262 g) in dry ether (20 ml) was added dropwise a solution of 0.06 N BuLi in dry ether (20 ml). Excess BuLi was destroyed by addition of CH_2Cl_2 (3 ml). After 10 min C_{10}-dial (*9*, 33 mg) in CH_2Cl_2 (3 ml) was dropwise added over a period of 20 min, and the mixture stirred at room temp. for 5 h. The solvent was removed and the residue dissolved in 90 % aqueous methanol. The pigments were extracted with petroleum ether, washed with water, dried (Na_2SO_4) and the solvent removed. Chromatography on alumina (Woelm neutral, grade 2 [18]) and elution with benzene gave *10a* yield 15.0 mg (7 %); δ ($CDCl_3$) 0.84 s, 0.92 s (imp. or *gem.* dimethyl in α-carotene), 1.03 s (12 H, CH_3-1,1'), 1.27 s (imp.), 1.49–1.54 (8 H, H-2,2',3,3'), 1.72 s (6 H, CH_3-5,5'), 1.97 s (6 H, CH_3-13,13'), 2.09 (4 H, H-4,4'), 6.14 (H-7,7',8,8'), and 6.0–6.8 (olefinic H). Crystallization from $CHCl_3$-petroleum ether yielded 8.8 mg; m.p. 150–151°C (reported 178–179°C for undeuterated β-carotene [19]), undepressed on admixture with authentic β-carotene; λ_{max} (petroleum ether) 340, 424, *447*, and 474 nm; % D_B/D_{II}[20] = 9.5, % III/II[20] = 42 (reported λ_{max} (petroleum ether, b.p. 80–105°C) *453* and 481 nm[21]); ν_{max} (KBr) 3020–2820 (CH), 2220 (?), 1550 (C=C), 1450 (CH_2), 1395–1360 (CH_3), 1212, 1174, 966 (trans-CH=CH), 761 (>C=CD–?), and 710 cm^{-1}; *m/e* (190°C) 543–536 (M); D_0:D_1:D_2:D_3:D_4:D_5:D_6:D_7:D_8 = 2:5:12:20:24:21:13:3:0; 64 % deuterium incorporation (assuming 6 exchangeable H).

Route 2

α,α,α-D$_3$-β-Ionol (11). α,α,α-D_3-β-ionone (*2*, 3.5 g) in dry ether was reduced with $LiAlH_4$ (0.60 g) in dry ether (50 ml) by the procedure used above for the synthesis of *6a* yield 3.1 g (88 %); n_D^{17} = 1.4923; λ_{max} (hexane) and 233 [E (1 %, 1 cm) = 245]; ν_{max} (liq.) 3300 (OH), 3020–2720 (CH), 2215, 2120 and 2060 (CD), 1445 (CH_2), 1380, 1370 and 1360 (CH_3), 1115, 1045, 1030 (C–O) and 970 cm^{-1} (*trans*-CH=CH); δ (CCl_4, Scheme 4A) 0.80 s and 0.88 s (*gem.* dimethyl in the α-isomer), 0.99 s (6 H, *gem.* dimethyl), 1.64 s (3 H, CH_3-*d*), 2.78 s (1 H, –O*H*), 4.25 d (1 H, J_{f-g} = 6 Hz, H-*g*), 5.40 dd (1 H, J_{f-g} = 6 Hz, J_{e-f} = 16 Hz, H-*f*) and 5.99 d (1 H, J_{e-f} = 16 Hz, H-*e*); *m/e* (110°C) 197 (M), 179 (M–18), 164 (M–33), 141 (M–56), 136 (M–61), 123 (M–74) and 121 (M–76, 100 %); D_0:D_1:D_2:D_3 = 2:5:24:69; 87 % deuterium incorporation.

α,α,α-D$_3$-β-Ionyl-triphenylphosphonium bromide (12). A mixture of α,α,α-D_3-β-ionol (*11*, 2.95 g) and triphenylphosphonium bromide (5.14 g) in methanol (65 ml) was stirred at room temperature for 48 h. The solvent was removed and the residue washed with ether. The product (*12*) yield 6.4 mg (80 %) had λ_{max} (methanol) 207.5, (225), 261, 267, and 274 nm with E(1 %, 1 cm) = 577, 426, 130, 134, and 107, respectively; ν_{max} (KBr) 3050–2830 (CH), 2225 (CD), 1435 (CH_2), 1110, 995, 975 (*trans*-CH=CH), 755, 725 and 695 cm^{-1} (bromide and monosubst. benzene; δ($CDCl_3$, Scheme 4A) 0.70 s and 0.88 s (6 H, *gem.* dimethyl), 1.43 s and *ca.* 1.90 (9 H, H-*a*, *b*, *c*, CH_3-*d*), 4.87–5.37 (1 H, H-*g*, complex coupling), 5.97–7.01 (2 H, H-*e,f*, complex coupling, *cis-trans*?) and 7.6–8.3 (15 aromatic H).

2,7-Dimethyldeca-2,4,6,8-tetraene-1,10-dial (13), 2,7-dimethyldodeca-2,4,6,8,10-pentaene-1,12-dial (14), 4,9-dimethyldodeca-2,4,6,8,10-pentaene-1,12-dial (15), 2,7-dimethyltetradeca-2,4,6,8,10,12-hexaene-1,14-dial (16) and 4,9-dimethyltetradeca-2,4,6,8,10,12-hexaene-1,14-dial (17). A mixture of C_{10}-dial (*9*, 1.52 g) and formylmethylenetriphenylphosphorane (5.69 g) in benzene (300 ml) was refluxed for 22 h as described by Trippett and Walker.[14] An aliquot of the reaction mixture was submitted to TLC on alumina G 254 (20 % acetone in petroleum ether = 25 % APE) giving *8:13:(14+15):(16+17)* = 57:37:5:1, calculated from the electronic spectra using extinction coefficients based on those reported for *9*, *14* and crocetindial.[22]

13 had $R_F = 0.32$; λ_{max} (ether) *ca.* 335, 349 and 369 nm; δ ($CDCl_3$) 1.92 s and 1.94 s (3 H, CH_3-2), 2.05 (3 H, CH_3-7), 6.0–7.5 (6 olefinic H) and 9.0–9.7 (2 H, aldehyde). *14* + *15* had $R_F = 0.28$; λ_{max} (ether) 360, 378, and 401 nm; δ ($CDCl_3$) 1.93 s (CH_3-2 in *14*), 2.05 (CH_3-7 in *14* and CH_3-4,9 in *15*), 6.0–7.5 (8 olefinic H) and 9.0–9.7 (2 H, aldehyde); *14*:*15* = 1:1, calculated from the ^{1}H NMR spectrum. *16* + *17* exhibited $R_F = 0.24$; λ_{max} (ether) 381, 403, and 427 nm; δ ($CDCl_3$) 1.26 (imp.), 1.90 s (CH_3-2 in *16*), 2.02 s (6 H, CH_3-7 in *16* and CH_3-4 in *17*), 6.0–7.5 (10 olefinic H) and 9.5–9.7 (2 H, aldehyde); *16*:*17* = 1:4, calculated from the ^{1}H NMR spectrum.

Diethyl 4,9-dimethyldodeca-2,4,6,8,10-pentaene-1,12-dioate (18). A mixture of C_{10}-dial (*9*, 0.55 g) and carbethoxymethylenetriphenylphosphorane (8.5 g) in $CHCl_3$ (60 ml) was stirred at room temp. for 12 h. Chromatography twice on kieselgel (eluent 25 % benzene in $CHCl_3$) gave *18*; yield 1.02 g (100 %); λ_{max} (ether) 272, 352, *370*, and 392 nm; ν_{max}(KBr) 2980–2850 (CH), 1705 (conj. ester), 1605 (conj. C=C), 1365 (CH_3), 1300, 1175, 1035, 980–970 (*trans*-CH=CH), 850 and 800 cm^{-1}; δ ($CDCl_3$) 1.32 t (6 H, $J = 7$ Hz, 2 CH_3 in ethyl), 1.95 s (6 H, CH_3-4,9), 4.23 q (4 H, $J = 7$ Hz, 2 CH_2 in ethyl) and 5.75–7.60 (8 olefinic H, complex coupling); *m/e* (140°C) 304 (M), 259 (M–45) and 157 (100 %).

4,9-Dimethyldodeca-2,4,6,8,10-pentaene-1,12-diol (19). The C_{14}-diester *18* (1.0 g) in dry ether (50 ml) was reduced with $LiAlH_4$ (0.30 g) in dry ether (50 ml) by the procedure described above for preparation of *6a*. This gave crude *19*; yield 0.47 g (65 %). An analytical amount, purified by TLC on kieselgel (30 % APE), exhibited λ_{max}(ether) 248, 324, 340, and 359 nm; δ ($CDCl_3$) 1.25 (imp.), 1.90 s (6 H, CH_3-4,9) 2.62 s (2 H, -O*H*), 4.23 d (4 H, $J_{1-2(11-12)} = 6$ Hz, H-1,12) and 5.7–6.5 (8 olefinic H, complex coupling); *m/e* (130°C) 220 (M) and 95 (100 %).

4,9-Dimethyldodeca-2,4,6,8,10-pentaene-1,12-dial (15). A mixture of crude *19* (140 mg) and activated MnO_2 (1.40 g) in acetone (75 ml) was kept at room temp. for 12 h. TLC on kieselgel G (20 % APE) gave *15*; yield 41 mg (29 %); λ_{max}(ether) 280, 362, *379*, and 401 nm (previously found λ_{max} (petroleum ether) 358, *378*, and 400 [22]), ν_{max} (KBr) 3040–2710 (CH), 1665 (conj. C=O), 1585 (conj. C=C), 1385 and 1370 (CH_3), 1170, 1125, and 975 cm^{-1} (*trans*-CH=CH); δ ($CDCl_3$) 2.02 s (6 H, $CH_3-4,9$), 6.05–7.35 (8 olefinic H, complex coupling) and 9.64 d (2 H, $J_{1-2(11-12)} = 7.5$ Hz, H-1,12); *m/e* (140°C) 216(M).

19,19′-D_6-β-Carotene (10). To a suspension of α,α,α-D_3-β-ionyl-triphenylphospohonium bromide (*12*, 389 mg) in a dry ether (20 ml) was added dropwise a solution of 0.06 N BuLi in dry ether (30 ml). Excess BuLi was destroyed by addition of CH_2Cl_2 (3 ml). After 10 min was C_{14}-dial (*15*, 40 mg) in CH_2Cl_2 (10 ml) added slowly during 20 min, and the mixture stirred at room temperature for 3 h. The solvent was removed and the residue dissolved in 90 % aqueous methanol. The pigments were extracted with petroleum ether, washed with water, dried (Na_2SO_4) and the solvent removed. Chromatography on alumina (Merck neutral, grade 2 [18]) and elution with 10 % ether in petroleum ether gave *10*; yield 41.2 mg (41 %). Paper chromatography of *10* on Schleicher & Schüll No. 288 paper (1 % ether in petroleum ether) gave two zones: neo a $R_F = 0.61$; λ_{max} (petroleum ether) *442* and 475 nm and all-*trans* $R_F = 0.54$; λ_{max} (petroleum ether) *447* and 471 nm. The *trans* isomer was inseparable from authentic β-carotene, whereas both zones were separated from authentic α- and ε-carotene, also theoretically present. *10* exhibited δ ($CDCl_3$, Fig. 1) 0.85 s (imp.), 0.91 (imp.), 1.03 s (12 H, *gem.* dimethyl), 1.27 s (imp.), 1.5–1.6 (8 H, H-2,2′,3,3′), 1.72 s (6 H, end-of-chain CH_3), 1.97 (6 H, in-chain 13,13′-CH_3), 6.15 (H-7,7′,8,8′) and 6.05–6.85 (14 olefinic H). Crystallization from acetone gave 2.3 mg, *m.p.* 163–164°C (reported 178–179°C for undeuterated β-carotene [19]), undepressed on admixture with authentic β-carotene; λ_{max} (petroleum ether) 339, *447.5* and 474 nm, % D_B/D_{II}[20] = 13, % III/II[20] = 28 (reported λ_{max} in petroleum ether *453* and 481 nm[21]); ν_{max} (KBr) 3020–2820 (CH), 2110 and 2060 (CD), 1705, 1623, 1556 (C=C), 1455 (CH_2), 1395–1360 (CH_3), 967 (*trans*-CH=CH) and 830 (>C=CH–); *m/e* (200°C) 542 (M), 463 (M–79), 450 (M–92), 433 (M–109), 406 (M–136) and 481 (M–161), D_0:D_1:D_2:D_3:D_4:D_5:D_6 = 0:1:2:4:10:42:41; 85 % deuterium incorporation.

Model compounds

Ethyl β-ionylidene acetate (20) was prepared from triethylphosphonoacetate (*3*, 1.5 g), NaH (50 %, 0.32 g) and β-ionone (*1*, 1.0 g) by the same procedure as for *5a* above; conversion 70 %, judged by TLC. Preparative TLC on kieselgel HF 254 + 366 (10 % ether in petroleum ether) gave *5a*, yield 0.65 g (48 %); $n_D^{20.5}$ = 1.5361; λ_{max} (hexane) and ν_{max} (liq.) see *5a* above; δ (CCl_4, Scheme 5A) 2.29 s (3 H, CH_3-*g*) and 5.66 s (1 H, H-*h*), otherwise as for 5a above.

ψ-Ionol (22). A solution of ψ-ionyl acetate [23] (*21*, 8.5 g) in 10 % KOH in methanol (0.5 l) and ether (0.5 l) was stirred for 12 h. Water was added and the product transferred to ether. The ether extract was washed, dried (Na_2SO_4) and the solvent evaporated. This gave *22* yield 6.5 g (93 %); $n_D^{17} = 1.5059$; λ_{max} (hexane) 241 [*E*(1 %, 1 cm) = 1210]; ν_{max} (liq.) 3330, 3020–2725, 1665, 1448, 1375, 1138, 1057, and 965; δ (CCl_4, Scheme 4B) 1.20 d (3 H, $J_{1-2} = 6.5$ Hz, H-1), 1.58 s, 1.65 s and 1.73 s (3 × 3 H, H-11, CH_3-6,10), 2.23 s (1 H, -O*H*), 4.21 dq (1 H, $J_{1-2} = 6.5$ Hz, $J_{2-3} = 6$ Hz, H-2), 5.04 (1 H, H-9), 5.47 dd (1 H, $J_{2-3} = 6$ Hz, $J_{3-4} = 15$ Hz, H-3), 5.71 d (1 H, $J_{4-5} = 10.5$

Hz, H-5) and 6.27 dd (1 H, $J_{3-4}=15$ Hz, $J_{4-5}=10.5$ Hz, H-4); *m/e* (110°C) 194 (M), 176 (M − 18), 151 (M − 43), and 133 (M − 43 − 18).

ψ-Ionyl-triphenylphosphonium bromide (23). A mixture of *ψ*-ionol (*22*, 3.0 g) and triphenylphosphonium bromide (5.3 g) in methanol (40 ml) was stirred at room temp. for 24 h. The solvent was removed and the product washed with ether and water. This gave *23* yield 4.4 g (53 %); λ_{max} (MeOH) 204.5, (225), 261, 267, and 274 [*E*(1 %, 1 cm) = 1050, 630, 192, 184, and 121]; ν_{max}(KBr) 3050 − 2850, 1435, 1375, 1110, 995, 755, 725 and 695 cm^{-1}; δ ($CDCl_3$), Scheme 4B) 1.58, 1.63 (H-10, CH_3-1,5 and 9), 4.70 − 6.50 (H-1,2,3,4, and 8, complex coupling) and 7.60 − 8.20 (aromatic H).

2-D_3-Methyl-1-phenyl-4-(2,6,6-trimethyl-cyclohex-1-enyl)-1,3-butadiene (24). To a mixture of α,α,α-D_3-*β*-ionyl-triphenylphosphonium bromide (*12*, 0.52 g) in dry ether (10 ml) was added 0.06 N BuLi in dry ether (20 ml). Excess BuLi was destroyed by addition of CH_2Cl_2 (3 ml) after 10 min. Freshly distilled benzaldehyde (0.11 mg) was added and the mixture stirred for 2 h at 35°C. TLC twice on kieselgel HF 254 + 366 (petroleum ether) gave *24* (0.11 g, 41 %); λ_{max} (hexane) 288 [*E*(1 %, 1 cm) = 730]; ν_{max} (liq.) 3020 − 2830, 2140, 1595, 1490, 1445 − 1360, 975, 965, 920, 740, and 700; δ ($CDCl_3$, Scheme 5A) 1.02 s and 1.05 s (6 H, *gem.* dimethyl), 1.45 − 1.63 (4 H, H-4′,5′), 1.70 (s?, 3 H, 2′-CH_3), 2.00 m (2 H, H-3′), 6.09 − 6.73 (3 H, H-1,3,4, complex coupling, *cis-trans* around double bonds 1,2 and 3,4?) and 7.22 − 7.37 (5 aromatic H); *m/e* (110°C) 269 (M, 100 %), D_0:D_1:D_2:D_3 = 2:6:21:71; 88 % deuterium incorporation.

3-D_3-Methyl-1-(2,6,6-trimethylcyclohex-1-yl)-1,3-pentadiene (25) was made by the above procedure, using large excess of acetaldehyde (2 ml) instead of benzaldehyde. This gave *25*; yield 0.10 g (48 %); λ_{max} (hexane) 363 [*E*(1 %, 1 cm) = 620]; ν_{max} (liq.) 3020 − 2720, 2230, 2200, 2110, 2060, 1445 − 1360, 970, and 735 cm^{-1}; δ ($CDCl_3$), Scheme 5A) 1.00 s and 1.03 s (6 H, *gem.* dimethyl), 1.72 (s?, CH_3-2′, 1.73 d (H-5, $J_{4-5}=6.5$ Hz), 2.00 m (2 H, H-3′), 5.43 p or dq (1 H, $J_{4-5}=6.5$ Hz, H-4, *cis-trans*?), 6.00 s (H-1,2, *trans*), 6.06 d and 6.50 d ($J_{1-2}=16.5$ Hz, H-1,2, *cis*), *m/e* (110°C) 207 (M), 180 (M − 27), and 46 (100 %), D_0:D_1:D_2:D_3 = 3:9:29:59; 82 % deuterium incorporation.

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